All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Methoxy polyethylene glycol-epoetin beta (Mircera®▼)

Roche Products Limited

Advice No: 1809 – October 2009

Recommendation of AWMSG

Methoxy polyethylene glycol-epoetin beta (Mircera®) is recommended as an option for use within NHS Wales for the treatment of adults with symptomatic anaemia associated with chronic kidney disease.

AWMSG is of the opinion that methoxy polyethylene glycol-epoetin beta (Mircera®▼) is suitable for shared care within NHS Wales.

This report should be cited as:

ABBREVIATIONS

AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CKD	Chronic Kidney Disease
C.E.R.A	Continuous Erythropoietin Receptor Activator
EPO	Erythropoietin
ESA	Erythropoiesis Stimulating Agent
Hb	Haemoglobin
ITT	Intention-to-treat
IV	Intravenous
K/DOQI	Kidney Disease Outcomes Quality Initiative
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMG	New Medicines Group
PRCA	Pure Red Cell Aplasia
QoL	Quality of Life
SC	Subcutaneous
SPC	Summary of Product Characteristics
WMP	Welsh Medicines Partnership

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 14th October 2009

The recommendation of AWMSG is:

Methoxy polyethylene glycol-epoetin beta (Mircera®▼) is recommended as an option for use within NHS Wales for the treatment of adults with symptomatic anaemia associated with chronic kidney disease.

AWMSG is of the opinion that methoxy polyethylene glycol-epoetin beta (Mircera®▼) is suitable for shared care within NHS Wales.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Methoxy polyethylene glycol-epoetin beta (Mircera®▼) is licensed for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD). The safety and efficacy of Mircera®▼ therapy in other indications has not been established[1].

2.2 Dosing

Treatment with Mircera®▼ has to be initiated under the supervision of a physician experienced in the management of patients with renal impairment[1].

For patients not currently treated with an erythropoiesis stimulating agent (ESA) the recommended starting dose is 0.6 microgram/kg body weight, administered once every two weeks as a single intravenous (IV) or subcutaneous (SC) injection in order to increase haemoglobin levels to greater than 10g/dL (6.21mmol/L). It is recommended that haemoglobin is monitored every two weeks until stabilised and periodically thereafter[1].

Haemoglobin variability should be addressed through dose management, with consideration for the haemoglobin target range of 10g/dL (6.21mmol/L) to 12g/dL (7.45mmol/L). A sustained haemoglobin level of greater than 12g/dL (7.45mmol/L) should be avoided; guidance for appropriate dose adjustment for when haemoglobin values exceed 12g/dL (7.45mmol/L) are outlined in the Summary of Product Characteristics (SPC)[1].

If a haemoglobin concentration above 10g/dL (6.21mmol/L) is reached for the individual patient, Mircera®▼ may be administered once-monthly using the dose equal to twice the previous once-every-two-weeks dose[1].

Patients currently treated with an ESA can be switched to Mircera®▼ administered once a month as a single IV or SC injection. The starting dose of Mircera®▼ is based on the calculated previous weekly dose of ESA at the time of substitution (as described in the SPC)[1].

Supplementary iron therapy is recommended for all patients with serum ferritin values below 100 micrograms/L or with transferrin saturation below 20%. To ensure effective erythropoiesis, iron status has to be evaluated for all patients prior and during treatment.

2.3 Market authorisation date

20 July 2007[1,2]

2.4 UK Launch date

24 September 2007[3]

3.0 DECISION CONTEXT

Anaemia is a common complication in patients with chronic renal failure, and although its pathogenesis is multifactorial, the loss of peritubular cells in the kidney responsible for the synthesis and secretion of erythropoietin (EPO) is considered the key etiologic factor[4]. The main impact of anaemia on organ function is reduced oxygen delivery to tissues leading to debilitating symptoms such as: fatigue, exercise intolerance, impaired cognitive function, sleep disorder, altered haemostasis, and depressed immune function[4,5]. Anaemia is also associated with a high prevalence of cardiovascular disease in renal patients, and their consequent increased morbidity and mortality[4,5]. It has been reported that cardiovascular disease accounts for more than 50% of deaths in these patients[4].

It is known from epidemiological data that the prevalence of anaemia increases as the glomerular filtration rate declines, and that anaemia develops relatively early during the course of CKD[6]. A UK study highlighted in guidance published by the National Institute for Health and Clinical Excellence (NICE) in 2008, has demonstrated that the prevalence of anaemia rises sharply from CKD stage 3B onwards[6]. In the UK, the age-standardised prevalence of stage 3-5 CKD has been estimated to be 10.6% for females and 5.8% for males[7,8].

EPO is the hormone responsible for maintaining the proliferation and differentiation of erythroid progenitor cells in the bone marrow, and thus renal anaemia can be regarded as a hormone deficiency state[4]. Exogenous replacement therapy of EPO by recombinant hormone epoetin is a well accepted therapy for the treatment of anaemia in patients with CKD[5] and is reported to be effective in about 90-95% of such patients[4]. Clinical practice guidelines for the management of CKD have been produced in the UK (NICE Guidelines), Europe (European best practice Guidelines), and the USA (National Kidney Foundation Kidney Disease Outcomes Quality Initiative [K/DOQI] Guidelines)[6,9,10]. Separate to these guidelines there is current NICE guidance specifically on anaemia management in CKD; recommending that the management of anaemia should be considered if the haemoglobin ≤11g/dL (or 10g/dL if under two years of age)[7]. Treatment should be aimed to maintain stable haemoglobin levels between 10.5 and 12.5g/dL for adults and children older than two years of age[7].

The original recombinant human EPOs (epoetin alfa and epoetin beta) have now been in clinical use for nearly 20 years[11-13]. Other biosimilar products have recently become available (e.g. epoetin alfa [Binocrit®▼], epoetin zeta [Retacrit®▼])[14]. These have a relatively short acting circulating half-life and require two or three injections per week. Longer acting ESAs have now been developed including darbepoetin alfa (Aranesp®), and more recently continuous erythropoetin receptor activator (C.E.R.A)[11]; allowing less frequent dosing regimens of once every two weeks, and in some cases once monthly.

NICE guidance recommends that the choice of ESA should be dependent on the patient's dialysis status, the most appropriate route and frequency of administration, and the local availability and cost[7]. Not all of the EPOs currently available however are included in this guidance as they were not licensed at the time.

Methoxy polyethylene glycol-epoetin beta, the active substance of Mircera®▼, is a continuous erythropoetin receptor activator[1]. Mircera®▼ shows a different activity at the receptor level; its reduced affinity for the receptor and longer interaction in the receptor environment allows continuous stimulation of erythropoiesis in contrast to shorter-acting EPOs[1].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

Evidence highlighted in the company submission for the use of Mircera®▼ in the treatment of symptomatic anaemia associated with CKD, includes four published open-label, multicentre, randomised, parallel-group, phase III studies; a phase III randomised, open-label study provided in abstract and two 'real-life' studies which are also provided in abstract form.

Two of the phase III studies were designed to establish the comparative efficacy and safety of Mircera®▼ in haemoglobin correction versus epoetin (AMICUS) and darbepoetin alfa (ARCTOS). The remaining two studies (MAXIMA and PROTOS) were designed to demonstrate non-inferiority of Mircera®▼ in haemoglobin maintenance versus epoetin alfa and epoetin beta. These phase III studies concluded that Mircera®▼ was non-inferior to the comparators used in terms of correcting haemoglobin levels and maintaining haemoglobin levels within pre-defined ranges, although in the AMICUS study this conclusion was based on post hoc analyses, as this study was not designed for formal comparisons of the ESAs.

Mircera®▼ has been directly compared to the only other long-acting ESA, darbepoetin alfa, in the maintenance of haemoglobin levels (PATRONUS study). However this randomised open-label study has yet to be published and has been provided in abstract only. Evidence of the efficacy of Mircera®▼ in maintaining haemoglobin levels in non-dialysis patients has not been presented. The adverse events reported during the clinical trials showed a similar adverse event profile for Mircera®▼ compared to the comparator ESAs (i.e. epoetin alfa, epoetin beta, and darbepoetin alfa).

4.2 Review of the evidence on cost-effectiveness

The company's submission describes a cost minimisation analysis of Mircera®▼ compared with the ESAs epoetin alfa (Eprex®), epoetin beta (NeoRecormon®) and darbepoetin alfa (Aranesp®). The company considers that Mircera®▼ is at least as clinically effective as the comparator ESAs in terms of efficacy and safety on the basis of results from several phase III clinical trials powered for non-inferiority.

Three separate patient groups are considered in the analysis: dialysis patients switched from an alternative ESA, dialysis patients who are ESA-naïve, and non-dialysis patients who are ESA-naïve. Drug acquisition costs are derived from three of the phase III trials that best represent these patient groups. There are some uncertainties in relation to the ESA dose levels, which may bias the model in favour of Mircera®▼ in some of the analyses. Administration costs for dialysis are derived from a time and motion study, and in non-dialysis patients are based primarily on expert opinion.

The results indicate that, in each of the three patient groups, the overall costs of treatment with IV Mircera®▼ are lower compared with using other ESAs. In dialysis patients, the use of Mircera®▼ is estimated to be less expensive in terms of both drug administration costs and drug acquisition costs, with the exception of IV epoetin alfa in dialysis patients switched from an alternative ESA (switch / dialysis patients), which

has a lower drug acquisition cost than Mircera®▼. However, the extent to which these analyses adequately reflect the use of ESAs in peritoneal dialysis patients, or in those haemodialysis patients in whom the SC route is preferred, is uncertain. In non-dialysis patients, the drug acquisition costs are greater with SC Mircera®▼ than with all comparator ESAs, but these are more than offset by the estimated lower administration costs in each patient group.

5.0 LIMITATIONS OF DECISION CONTEXT

- There is no evidence of the efficacy of Mircera®▼ in maintaining haemoglobin levels in those patients who are not yet receiving renal replacement therapy (i.e. dialysis).
- There appears to be relatively few peritoneal dialysis patients in the phase III clinical trials compared with in Welsh practice (see section 7.2 for further details).
- Non-inferiority of Mircera®▼ compared to other ESAs was demonstrated for surrogate endpoints of correction and maintenance of haemoglobin levels, but not for more clinically relevant outcomes of mortality, quality of life (QoL) and adverse events.
- In the company product information, Mircera®▼ is not recommended for use in children and adolescents below 18 years of age due to a lack of safety and efficacy data[1].
- In the cost minimisation analyses in dialysis patients it is assumed that all ESAs are administered via the IV route. WMP-sought expert opinion indicates that, for haemodialysis patients, the preferred route of administration currently varies across specialist renal centres, and for peritoneal dialysis patients the preferred route is SC. The extent to which these analyses adequately reflect the use of ESAs in peritoneal dialysis patients, or in those haemodialysis patients in whom the SC route is preferred, is uncertain.
- A cost minimisation analysis requires evidence on therapeutic equivalence in all dimensions of health outcome (e.g. health-related quality of life and safety parameters), whereas the trials upon which these analyses are based, are powered for non-inferiority (relative to comparator) of changes in haemoglobin level.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy

Four published phase III studies[16] have been used to establish the comparative efficacy and safety of Mircera®▼ in haemoglobin correction (AMICUS and ARCTOS)[17,18] and in haemoglobin maintenance (MAXIMA and PROTOS)[19,20]; versus epoetin alfa, epoetin beta, and darbepoetin alfa. In addition the company have highlighted a randomised open-label superiority study (Mircera®▼ versus darbepoetin alfa [PATRONUS])[21] and two 'real-life' studies all which have been presented in abstract or poster form[22,23]. Further details regarding the trials summarised below can be found in Table 1, in Appendix 1.

6.1.1 The AMICUS (AdMinistration Intravenously for anaemia Correction and sUStained maintenance in dialysis) study[17]

This was an open-label, multicentre, randomised, parallel-group, phase III study to determine whether Mircera®▼ was as effective and as well tolerated as epoetin (alfa or beta) for anaemia correction in adults patients (aged ≥18 years) with CKD stage 5

receiving haemodialysis or peritoneal dialysis. A total of 181 adults were randomised in a 3:1 ratio (stratified for geographic region) to receive IV Mircera®▼ 0.4 micrograms/kg once every two weeks as a starting dose (n=135) or IV epoetin alfa or beta (n=5 [alfa], n=41, [beta]) three times weekly (at a mean starting dose of 120IU/kg per week) for 24 weeks. Participants had to have a baseline haemoglobin of 8-11g/dL and an adequate iron status. During correction, Mircera®▼ and epoetin doses could be adjusted (no more frequently than once every four weeks) to achieve individual patient haemoglobin levels of ≥11.0g/dL and an increase ≥1.0g/dL compared to baseline.

The primary efficacy endpoint was haemoglobin response rate in the intention-to-treat (ITT) population, based on weekly measurements and defined as an increase in haemoglobin from baseline of ≥1.0g/dL and a single haemoglobin concentration ≥11.0g/dL without blood transfusion during the 24 weeks after the first dose.

Results from the 24-week study period show 93.3% (126/135) in the Mircera®▼ group (95% confidence interval [CI]: 87.72 to 96.91, p<0.0001[16]) and 91.3% (42/46) from the epoetin group (95% CI: 79.21 to 97.58, p<0.0001[16]) responded. There were no significant differences between the treatment groups in secondary outcomes including haemoglobin change from baseline over time or incidence of red blood cell transfusions. The median time to response however was 57 days (95% CI: 50 to 64 days) in the Mircera®▼ group compared to 31 days (95% CI: 27 to 38 days) in the epoetin group[17].

6.1.1.1 Points to note

- Since the lower limit of the confidence interval reported was greater than the predefined response rate (60%) (p<0.001[17]), it can be concluded that Mircera®▼ once every two weeks effectively corrected anaemia.
- Non-inferiority was based on post hoc analyses, as this study was not designed for formal comparisons of ESAs.
- Similar proportions of patients administered Mircera®▼ (28.1%) and epoetin (30.4%) had previously received an ESA, and all had discontinued treatment at least 12 weeks before the first study drug administration.
- In the first eight weeks of treatment haemoglobin values greater than 13g/dL were experienced by 8.2% in the Mircera®▼ group and 17.4% in the epoetin group (p=0.1, not significant). In the correction period, approximately 60% of patients in both treatment groups experienced maximum haemoglobin values greater than 13g/dL (p=0.9, not significant)[17]. These results are based on *post hoc* analysis and this study was not originally designed to compare treatments therefore these results should be viewed with caution.
- The company suggest in their submission that the lower starting dose of 0.4 micrograms/kg might have been reflected in the time to response reported in the trial. The median dose at the time of haemoglobin response for the Mircera®▼ treated group was 0.6 micrograms/kg once every two weeks (which is the initial starting dose as per the SPC).
- Quality of life data using the 36-Item Short-Form Health Survey (SF-36 questionnaire) was reported in the published paper by Klinger and colleagues. It was acknowledged that this data may be biased due to the open nature of the study.

6.1.2 The ARCTOS (Administration of C.E.R.A. in CKD patients to treat anaemia with a Twice-mOnthly Schedule) study[18]

This was an open-label, multicentre, darbepoetin alfa-controlled, parallel-group phase III study to determine whether SC Mircera®▼ administered every two weeks, was as effective and well tolerated as once weekly SC darbepoetin alfa for anaemia correction in ESA-naïve patients. Eligible patients were aged ≥18 years, had stage 3 or 4 CKD, were not on dialysis and had haemoglobin 8-11g/dL at baseline, plus adequate iron status. A total of 324 participants were randomly assigned 1:1 (stratified by geographic location) to receive starting doses of SC Mircera®▼ 0.6 micrograms/kg every two weeks or SC darbepoetin alfa 0.45 micrograms/kg once every week. The study consisted of an 18-week correction period, a 10-week evaluation period for efficacy assessments, followed by an extension to 52 weeks. Dosage adjustment was allowed every four weeks.

The first primary efficacy endpoint was haemoglobin response rate (see AMICUS study section 6.1.1. for definition) within the first 28 weeks. In the ITT population response rates in the Mircera®▼ and darbepoetin alfa groups were 97.5% (158/162 [95% CI: 93.80 to 99.32], p<0.0001[16]) and 96.3% (156/162 [95% CI: 92.11 to 98.63], p<0.0001[16]), respectively. The second primary endpoint was an assessment of non-inferiority of the difference between treatments in mean change in haemoglobin concentration between baseline and the evaluation period in all randomised patients without major protocol violation (i.e. per-protocol population, n=283). After adjustment for covariates (baseline haemoglobin level and geographic region), the mean change in haemoglobin from baseline to the evaluation period in the per-protocol population was 2.15g/dL with Mircera®▼ (n=139) and 2.00g/dL with darbepoetin alfa (n=144). The mean difference in the change in haemoglobin between the two groups was 0.16g/dL (95% CI: -0.05 to 0.35).

There were no significant differences in the secondary endpoints of haemoglobin change over time or red blood cell transfusions. The median time to response for those receiving Mircera®▼ was longer compared to those receiving darbepoetin alfa, 43 and 29 days, respectively; p<0.0001.

6.1.2.1 Points to note

- Since the lower limit of the confidence interval reported was greater than the predefined response rate (60%) (p<0.0001), it can be concluded that Mircera®▼ once every two weeks effectively corrected anaemia. In addition Mircera®▼ met the criteria for non-inferiority to darbepoetin alfa as the lower limit of the 95% CI (-0.05) for the mean difference in the change in haemoglobin between the two treatment groups was above the prespecified limit of -0.75g/dL.
- 12.4% of patients taking Mircera®▼ and 33.5% of patients receiving darbopoetin alfa experienced at least one haemoglobin value of greater than 13g/dL during the first eight weeks (p<0.0001, significant). In the correction and evaluation period (weeks 1 to 28) 67.7% of patients receiving Mircera®▼ and 80.6% of patients receiving darbopoetin experienced at least one haemoglobin value above 13g/dL (P<0.0082, significant)[18]. These results are based on *post hoc* analysis and should be viewed with caution.
- The dose of darbepoetin alfa used in this trial was 0.45 micrograms/kg once weekly; however the SPC for darbepoetin alfa suggests an alternative initial SC dose of 0.75 micrograms/kg once every two weeks in non-dialysis patients[24].

6.1.3 The MAXIMA (Maintenance of haemoglobin eXcels with IV adMinistration of C.E.R.A) trial and the PROTOS (Patients Receiving C.E.R.A. Once a month for the mainTenance Of Stable haemoglobin) trial[19,20]

Both of theses studies were open-label, randomised, multicentre, parallel group phase III studies. They were carried out to assess the efficacy of maintenance therapy with Mircera®▼ in dialysis patients with anaemia related to CKD who had been receiving epoetin alfa or beta. The studies followed the same design, except that the study drugs were administered IV in the MAXIMA study (n=673) and SC in the PROTOS study (n=572). Eligible patients (aged ≥18 years) were randomised to 1:1:1 ratio to continue to receive epoetin alfa or beta at their current weekly dose and dosing interval (i.e. one to three times weekly), to change to receive Mircera®▼ once every two weeks, or to receive Mircera®▼ once every four weeks. Eligible patients had received the same type of dialysis for at least 12 weeks before screening, had a stable baseline haemoglobin level between 10.5g/dL and 13.0g/dL and had received the same dose of epoetin for at least eight weeks before screening.

A period of 28 weeks after the first dose of study drug was used for dose titration and stabilisation of haemoglobin concentration; followed by an eight-week evaluation period to assess the primary efficacy endpoint. After the evaluation period, patients continued on their treatment until week 52 to assess long-term safety. The initial dose of Mircera®▼ was based on the epoetin dose administered the week prior to randomisation. The dose of Mircera®▼ was then adjusted to maintain individual patient's haemoglobin within a target range of ±1.0g/dL of their baseline haemoglobin and between 10.0g/dL and 13.5g/dL throughout the dose titration/evaluation period. Dose adjustment was not allowed more frequently than once every four weeks.

The primary efficacy endpoint in both studies was the mean change in the haemoglobin concentration between baseline and the evaluation period. Baseline haemoglobin was taken as the mean of all haemoglobin values between weeks -4 and 1 during the run-in period. Mircera®▼ would be considered non-inferior to epoetin if the lower limit of the two-sided 97.5% CI for the difference between the treatment groups was above -0.75g/dL.

Details of all the primary results from both studies can be found in Appendix 1, Table 1. For the per protocol population in the MAXIMA trial, the lower limit of 97.5% CI for the mean difference in haemoglobin between baseline and evaluations periods between Mircera®▼ IV once-monthly (n=172) and epoetin (n=180) groups was -0.173g/dL. Since this lower limit was greater than that pre-specified (-0.75g/dL), the Mircera®▼ group was regarded as non-inferior to the epoetin group. Indicating that conversion from epoetin to Mircera®▼ did not compromise clinical efficacy. Similar results were demonstrated in the PROTOS study for Mircera®▼ administered SC (see appendix 1, Table 1). In both studies analyses performed in the ITT population confirmed these findings.

6.1.3.1 Points to note

- In both studies participants were required to have a baseline haemoglobin concentration between 10.5g/dL and 13.0g/dL; in the titration and evaluation periods, the dosage of Mircera®▼ was adjusted to maintain patients' haemoglobin between 10.0g/dL and 13.5g/dL based on recommended European targets at the time of the studies. It should be noted that NICE now recommend a narrower range between 10.5g/dL and 12.5g/dL due to an increased risk of mortality at higher concentrations[7].

6.1.4 Other Studies

The company have also provided a poster of the PATRONUS (comPArator sTudy of C.E.R.A. and darbepOetin alfa in patieNts Undergoing dialySis) study[21], which was presented in May 2009 at the Word Congress of Nephrology. The purpose of this randomised, open-label, parallel, controlled phase III study was to test the superiority of IV Mircera®▼ at a once-monthly dosing interval over darbepoetin alfa in 490 haemodialysis patients initially on a stable regimen of IV darbepoetin alfa once-weekly. The primary endpoint of the study was the response rate for both Mircera®▼ and darbepoetin alfa regimens defined as the proportion of patients who maintained an average haemoglobin ≥10.5 g/dL, with a maximum haemoglobin decrease from baseline of 1.0g/dL during the evaluation period (weeks 50-53). The secondary endpoint was the difference in average dose between week 27 and months 11 and 12 for the two groups. AWMSG have noted that darbepoetin alfa is not currently licensed for once-monthly intravenous administration in haemodialysis patients; also the benefit of once-monthly dosing in patients already receiving regular haemodialysis is unclear and is discussed under section 7.2.

In addition two 'real-life' studies presented in abstract/poster format at the American Society of Nephrology, Renal week during 2008[22,23] were also highlighted in the company submission.

AWMSG are of the opinion that in order to fully assess these studies, further detail of the design and outcomes involved would be required.

6.2 Safety

The safety data for Mircera®▼ are pooled from four phase II, and six phase III studies (four of which have been discussed in section 6.1). The adverse events, which may or may not be related to the study medications, reported during the clinical trials showed a similar adverse event profile for Mircera®▼ compared to the comparator ESA (i.e. epoetin alfa, epoetin beta, and darbepoetin alfa)[16]. The overall incidence of adverse events considered by the investigators as related to treatment was 7% in the Mircera®▼ group and 5% in the comparator groups. Serious adverse events occurred in 47% of Mircera®▼ recipients compared with 54% in the comparator groups. Serious upper gastrointestinal haemorrhage was reported more frequently in the Mircera®▼ group (3% versus 2%) but when all serious haemorrhagic events were pooled, the frequency was similar across groups (7% versus 6%). Pulmonary embolism was reported in nine patients in the Mircera®▼ group and none in the reference group, but none of these were considered related to Mircera®▼ as assessed by the investigator. The rate of early discontinuation due to adverse events, regardless of relation to the study medication, was 3% in patients treated with Mircera®▼ and 2% in patients who received reference treatment[5].

The main adverse event during treatment with Mircera®▼ was hypertension which is known to occur with other ESAs[1]. Blood pressure should therefore be adequately controlled in all patients before, at initiation of, and during treatment with Mircera®▼[1]. In both groups the most common adverse events other than hypertension, were diarrhoea, nasopharyngitis, headache and upper respiratory tract infection[16].

During treatment with Mircera®▼, a slight decrease in platelet counts remaining within the normal range was observed in clinical studies. Platelet counts below 100 X 10^9/L were observed in 7% of patients treated with Mircera®▼ and 4% of patients treated with other ESAs. Pure Red Cell Aplasia (PRCA) caused by anti-erythropoetin antibodies has been reported in association with ESAs[1,5]. These antibodies have been shown to cross-react with all ESAs, and patients suspected or confirmed to have antibodies to erythropoietin should not be switched to Mircera®▼[1]. To date, no patients treated with Mircera®▼ had newly developed detectable anti-Mircera®▼ or anti-erythropoetin antibodies in any of the clinical trials[16].

In CKD patients, maintenance of haemoglobin concentration should not exceed the upper limit of the target haemoglobin concentration recommended[1]. In clinical trials an increased risk of death and serious cardiovascular events was observed when ESAs were administered to target a haemoglobin level of greater than 12g/dL[1]. A post hoc analysis was performed to determine the rate of haemoglobin decline when treatment of Mircera®▼ was withheld in patients whose haemoglobin exceeded 14g/dL. When treatment was stopped temporarily, the rate of haemoglobin decline was found to be comparable in patients treated with Mircera®▼ and those treated with other ESAs[16]; therefore suggesting there is no higher risk from exceeding haemoglobin targets with Mircera®▼ compared to other ESAs.

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

Short acting:

- Epoetin alfa (Eprex®, Binocrit®▼)
- Epoetin beta (NeoRecormon®)
- Epoetin zeta (Retacrit®▼)

Longer acting:

- Darbepoetin alfa (Aranesp®)

None of the currently available ESAs are licensed for extended dosing up to once a month in the treatment of dialysis patients with anaemia associated CKD[12,13, 24-26]. Darbepoetin alfa is longer acting, but has a limited licence for one monthly dosing (in the maintenance phase), only for patients not on dialysis[24].

7.2 Comparative effectiveness

- Mircera®▼ has been directly compared with darbepoetin alfa, in the maintenance of haemoglobin in patients undergoing haemodialysis (PATRONUS study), although the full detail of the trial data has yet to be published[16,21].
- There would appear to be relatively few peritoneal dialysis patients in the phase III clinical trials compared with in Welsh practice (based on the fact that only the AMICUS correction study[17] and the PROTOS maintenance study[20] included peritoneal dialysis patients). In the AMICUS study, 2.2% of patients in the Mircera®▼ arm were peritoneal dialysis patients and none in the epoetin arm[4]. In the PROTOS study, 7.3% of Mircera®▼ recipients and 10.5% of the epoetin recipients were peritoneal dialysis patients[5,17,20]. This compares with UK Renal Registry data which estimates 1,065 haemodialysis and 344 peritoneal dialysis patients are currently in Wales[27]. Approximately a quarter of patients receiving renal replacement therapy are receiving peritoneal dialysis.

- Health-related quality of life was assessed in the phase III correction studies using the SF-36 questionnaire[17,18]. Clinically meaningful changes from baseline scores (defined as a change of five points or more) were observed in several domains for both Mircera®▼ and the comparators, but the extent to which these differ between Mircera®▼ and the comparator for each of the domains is not formally reported or compared.
- Mircera®▼can be used either IV or SC at once-monthly dosing in the maintenance phase in all CKD patients (dialysis or non dialysis). Although darbepoeitin alfa has a once-monthly licence, this is restricted to SC administration and to only those patients who are not receiving dialysis. It could be argued however that the main advantage of a reduction in the frequency of EPO administration relates more to those not on regular haemodialysis (as these patients would not already be regularly attending a renal unit anyway).
- Mircera®▼ has a much longer storage life once removed from the fridge. It can be left at room temperature (≤30^{o}C) for a single period of up to one month which may offer convenience for transportation of the product (e.g. patients travelling on holiday). Once removed from the fridge it should be used within this one month period[1]. The company considers the need for only once monthly injections have benefits in terms of reduced storage needs, injection burden and district nurse visits and patient convenience[16].
- Darbepoetin alfa is licensed for use in both adults and children for the treatment of anaemia associated with CKD; Mircera is only licensed for use in adults[1,24].
- In the AMICUS and ARCTOS studies, Mircera®▼ took longer to increase haemoglobin concentration than epoetin or darbepoetin. This was statistically significant for both correction studies ($p<0.0001$). Nevertheless CHMP did not consider this was relevant for the management of this clinical situation[5].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for consideration

The key economic issues for AWMSG to consider are whether any additional benefits offered by methoxy polyethylene glycol-epoetin beta over the relevant comparator justify the additional costs and if so, whether the total budgetary impact of supporting the use of methoxy polyethylene glycol-epoetin beta is acceptable.

8.2 Description and critique of the company's submission

The company's submission[2] describes a cost-minimisation analysis of Mircera®▼ compared with the ESAs epoetin alfa (Eprex®), epoetin beta (NeoRecormon®) and darbepoetin alfa (Aranesp®). Biosimilar epoetin products (Binocrit®▼ or Retacrit®▼[14]) are not considered as comparators, as the company reports that these are not currently used in Wales[16]. The company considers that Mircera®▼ is not clinically inferior to the comparator ESAs in terms of efficacy and safety on the basis of results from four phase III non-inferiority clinical trials[17-20]. It should be noted that the application of cost minimisation analysis may not be valid where the clinical evidence is from trials other than those powered for equivalence[28].

Three patient groups are considered: dialysis patients switched from an alternative ESA, dialysis patients who are ESA-naïve, and non-dialysis patients who are ESA-naïve. The company submission makes no distinction between haemodialysis and peritoneal dialysis patients. The analyses in patients undergoing dialysis relate to IV administration of ESAs and, as AWMSG-sought expert opinion indicates that IV administration is rarely used in patients who are undergoing peritoneal dialysis, it may not be appropriate to apply the results of these analyses to peritoneal dialysis patients.

Drug acquisition costs are derived from three of the phase III trials that best represent the modelled patient groups[17-19]. There are some uncertainties in relation to the ESA doses, which may bias the model in favour of Mircera®▼ in some of the analyses. Administration costs for dialysis are derived from a time and motion study, and in non-dialysis patients, are based primarily on expert opinion.

These results indicate that, in each of the three patient groups, the overall costs of treatment with Mircera®▼ is lower compared with using other ESAs. In dialysis patients, the use of Mircera®▼ is estimated to be less expensive in terms of both drug administration costs and drug acquisition costs, with the exception of epoetin alfa in switch / dialysis patients, which has a lower drug acquisition cost than Mircera®▼. In non-dialysis patients, the drug acquisition costs are greater with Mircera®▼ than with all comparator ESAs, but these are more than offset by the estimated lower administration costs in each patient group[16].

The model has been provided to AWMSG.

8.3 Population

The analysis considers three patient groups[16]:

i) Dialysis patients switched from an alternative ESA (switch / dialysis) – these patients are assumed to receive ESA via the IV route.
ii) Dialysis patients who are ESA-naïve (naïve / dialysis) – these patients are assumed to receive ESAs via the IV route
iii) Non-dialysis patients who are ESA-naïve (naïve / non-dialysis) – these patients are assumed to receive ESAs via the SC route.

In ESA-naïve patients, treatment is assumed to involve a haemoglobin correction period, followed by haemoglobin maintenance. For patients switching from an alternative ESA to Mircera®▼, treatment is assumed to involve only maintenance of haemoglobin.

No distinction is made between patients who are undergoing haemodialysis or peritoneal dialysis. WMP-sought expert opinion indicates that local administration practices vary for haemodialysis patients, with some centres mainly using IV administration, and other favouring SC administration. For peritoneal dialysis patients, ESAs would normally be administered via the SC route. It is, therefore, uncertain that the results of these analyses in dialysis patients, where ESAs are assumed to be administered exclusively via the IV route, can be applied to peritoneal dialysis patients. The company submission states that a switch / non-dialysis group is not specifically considered in the analyses due to there being no trial data specifically in this patients group and the fact that this is the patient group that Mircera®▼ is least likely to be used in due to smaller patient numbers and shorter duration of treatment.[16].

8.4 Perspective and time horizon

The analysis was conducted from the perspective of NHS Wales. A one-year time horizon of analysis has been used in patients who switch from an alternative ESA to Mircera®▼, even though treatment with all ESAs is likely to be long-term. The company considers that this is justified on the basis that results of the cost-minimisation analysis are unlikely to be different beyond one year[16].

For dialysis patients who are ESA-naïve, the time horizon is the period of time required to achieve haemoglobin correction and is assumed to be unlikely to ever exceed one year. In the Mircera®▼ arm of the AMICUS trial upon which this analysis is based, time to correction to target haemoglobin level was 8.1 weeks, compared with 4.4 weeks in the epoetin arm[17]. A maintenance phase is not included in this analysis as the results can be inferred from the analysis in switch / dialysis patients. For non-dialysis patients who are ESA-naïve, a one year period of analysis is assumed, composed of a haemoglobin correction period and a haemoglobin maintenance period[16].

8.5 Comparators

The comparators are other ESAs that company-conducted market research is reported to indicate are currently used in Wales. These are epoetin alfa (Eprex®), epoetin beta (NeoRecormon®) and darbepoetin alfa (Aranesp®). The analysis does not consider Binocrit®▼ or Retacrit®▼ which are biosimilar epoetins[14], as company-sought research reportedly indicates that these agents are not currently used in Wales[16].

8.6 Clinical inputs

8.6.1 Efficacy data

The basis of the cost minimisation approach is assumed therapeutic equivalence between Mircera®▼ and the comparator ESAs. The company submission details four phase III clinical trials – two correction studies in ESA-naïve patients (AMICUS[17] and ARCTOS[18]), and two maintenance studies in patients already taking ESAs (MAXIMA[19] and PROTOS[20]), as discussed in section 6 and Appendix 1. Briefly, all studies concluded that Mircera®▼ was non-inferior to the comparators used in terms of correcting Hb levels and maintaining Hb levels within pre-defined ranges, although in the AMICUS study this conclusion was based on post hoc analyses, as this study was not designed for formal comparisons of the ESAs[17]. In both of the correction studies, the time to achieve target haemoglobin levels was significantly longer with Mircera®▼ than with the comparator ESAs. The median time to reach target haemoglobin was 57 and 43 days after Mircera®▼ treatment, compared with 31 and 29 days after epoetin and darbepoetin treatment, respectively ($p<0.0001$ for both comparisons)[27]. The CHMP considered that this was not clinically relevant in the context of long term treatment of these patients with ESAs[5].

The AMICUS correction study compared IV Mircera®▼ given every two weeks at an initial dose of 0.4 micrograms/kg against IV epoetin given three times per week[17]. The Mircera®▼ SPC indicates a starting dose of 0.6 micrograms/kg every two weeks in ESA-naïve patients[1], and this dose was used in the ARCTOS correction study, which compared SC Mircera®▼ against SC darbepoetin alfa given at a dose of 0.45 micrograms/kg once weekly in non-dialysis patients[18]. It should be noted that the SPC for darbepoetin alfa suggests an alternative initial SC dose of 0.75 micrograms/kg once every two weeks in non-dialysis patients[24], although WMP-sought expert opinion suggests that once-weekly dosing of darbepoetin alfa is more commonly used unless there are individual issues with injection frequency.

The MAXIMA maintenance study compared IV Mircera®▼ given once every two weeks or once monthly against epoetins administered once to three times per week[19], and the PROTOS study compared SC Mircera®▼ given once every two weeks or once monthly against SC epoetins administered once to three times per week[20], both in dialysis patients stabilised on epoetins. The initial dose of Mircera®▼ was based on the epoetin dose in the previous week.

The company submission suggests that haemodialysis and peritoneal dialysis typically involve differing ESA doses, but does not distinguish between these types of dialysis in the analyses that are provided, stating that the clinical trials recruited patients from both groups and there is no reason to suggest there would be any difference in the relative drug utilisation requirements for alternative ESAs across the two groups[16]. It should be noted that only the AMICUS correction study[17] and the PROTOS maintenance study[18] included peritoneal dialysis patients. In the AMICUS study, 2.2% of patients in the Mircera®▼ arm were receiving peritoneal dialysis and none in the epoetin arm[17]. In the PROTOS study, around 7.3% of Mircera®▼ recipients were on peritoneal dialysis and around 10.5% of patients in the epoetin arm[5,20].

8.6.1.1 Drug dosing in switch / dialysis patients

The MAXIMA study is used to provide the mean weekly drug doses of ESAs used for the cost minimisation analysis in switch / dialysis patients[16]. As recommended in the Mircera®▼ SPC[1], it is assumed that Mircera®▼ is administered once monthly in this patient group, and so the mean dose of Mircera®▼ from the once-monthly Mircera®▼ arm has been used in the base case analysis, derived from the entire post-randomisation period rather than simply the efficacy evaluation period of the study. These data are derived from the MAXIMA clinical study report (commercial in confidence)[16].

As the MAXIMA study did not include a darbepoetin alfa arm, the dose of darbepoetin alfa for use in the cost minimisation analysis has been approximated by dividing the reported mean weekly epoetin arm doses by 200, based on the suggested conversion factor in the darbepoetin alfa SPC[24]. The darbepoetin alfa SPC notes that, due to individual variability, individual dose titration is required[24]. Furthermore, in a scenario analysis presented in the company submission, it is acknowledged that the conversion factors presented in the SPCs for darbepoetin alfa and Mircera®▼ are broad, starting dose categories and it is uncertain that these adequately reflect equipotent doses in clinical practice[16](see section 8.10.3). It would appear that this approach is associated with some uncertainty. Sensitivity analysis has explored the impact of variation in dose conversion by +/-10%[16]. In the maintenance phase, it is assumed that darbepoetin is administered once every two weeks.

The PROTOS study was not considered in the company submission to be appropriate to use due to the fact that this study used the SC route of administration in a population that consisted largely (over 90%)[5] of haemodialysis patients. The company submission acknowledges that when epoetin is administered via the SC route, relatively lower doses can be used with the same efficacy compared with IV administration, but considers that patients undergoing (haemo)dialysis are likely to receive their ESA via the IV route[16]. It should be noted that over 90% of patients in the PROTOS study were receiving haemodialysis[27] and would have ready IV access, yet all patients received ESAs via the SC route. WMP-sought expert opinion indicates that, currently, practice varies in haemodialysis patients attending specialist renal centres in Wales, with some centres using SC administration for all patients, and others using mainly IV administration.

8.6.1.2 Drug dosing in naïve / dialysis patients

The AMICUS study is used to provide the mean weekly drug doses of ESAs in naïve / dialysis patients during haemoglobin correction[16]. Only dose information from the efficacy evaluation phase of the study is used for the correction phase, which was significantly longer in the Mircera®▼ arm than the epoetin arm[27]. The mean dose per week per kg for each ESA is derived from the AMICUS clinical study report (commercial in confidence). The mean average patient weight in the AMICUS trial has then been used to calculate a mean dose per patient per week, which is multiplied by the respective length of the correction phase. It should be noted that the initial dose of Mircera®▼ in the AMICUS trial (0.4 micrograms/kg every two weeks) was lower than that recommended in the SPC (0.6 micrograms/kg every two weeks)[1]. The time to achieve target Hb was longer with Mircera®▼ than epoetin in this study, but it was also longer with Mircera®▼ than with darbepoetin alfa in the ARCTOS study, which used the SPC-recommended initial Mircera®▼ dose[18]. The use of the lower initial Mircera®▼ starting dose from the AMICUS study in the cost minimisation analysis in naïve / dialysis patients may, therefore, bias the analysis in favour of Mircera®▼.

The AMICUS study informally compared Mircera®▼ against epoetin, and so darbepoetin alfa doses are estimated using the approach described above in 8.6.1.1. It is assumed that the time to haemoglobin correction with darbepoetin alfa is the same as for epoetin, and that darbepoetin alfa is administered once weekly[16], as per the SPC[24]. No maintenance phase of treatment is included in this analysis, as it is assumed the results during the maintenance phase can be inferred from the analysis in switch / dialysis patients.

8.6.1.3 Drug dosing in naïve / non-dialysis patients

The ARCTOS study is used to provide the mean weekly drug doses of ESAs in naïve / non-dialysis patients. For the correction of haemoglobin phase of treatment, the approach described above in 8.6.1.2 for naïve / dialysis patients is used. For the maintenance phase of treatment up to a total of 52 weeks, the mean dose per kg observed in the last week of the study (week 28) is used and is assumed not to change for the remainder of the year. The ARCTOS clinical study report (commercial in confidence) has been used to derive mean weekly ESA doses per kg. As the ARCTOS study compared Mircera®▼ against darbepoetin alfa, the doses for epoetin used in the cost minimisation analysis are estimated using the approximate conversion factor in the darbepoetin alfa SPC[24].

In this analysis, darbepoetin alfa is assumed to be administered once weekly during the correction phase, and either once weekly or once every two weeks during the maintenance phase[16]. Reportedly based on company-sought expert opinion, it is assumed that 60% of patients would receive darbepoetin alfa once weekly and 40% once every two weeks (average of 0.8 weekly administrations) during the maintenance phase. The SPC for darbepoetin alfa suggests an alternative initial SC dose of 0.75 micrograms/kg once every two weeks in non-dialysis patients, and suggests that once the target haemoglobin level has been achieved the dose interval may be increased to once monthly administration[24]. Sensitivity analysis has explored doses within the range +/-10%, although this does not capture the difference in weekly dose equivalents that would be possible with darbepoetin alfa if it was to be administered once every two weeks in the correction phase and once monthly in the maintenance phase.

8.6.2 Adverse events

Adverse events are not considered in the analysis as these are assumed to be comparable between the available ESAs[16]. The CHMP concluded that the overall adverse event profile was similar between Mircera® and the comparators across the pooled clinical trials[5]. The overall incidence of adverse events considered by the investigators as related to treatment was 7.0% in the Mircera®▼ group and 5% in the comparator groups. Serious adverse events occurred in 47% of Mircera®▼ recipients compared with 54% in the comparator groups. Serious upper gastrointestinal haemorrhage was reported more frequently in the Mircera®▼ group (3% versus 2%) but when all serious hemorrhagic events were pooled, the frequency was similar across groups (7% versus 6%). Pulmonary embolism was reported by nine patients in the Mircera®▼ group and none in the reference group, but none of these were considered related to Mircera®▼ as assessed by the investigator. The rate of early discontinuation due to adverse events, regardless of relation to the study medication, was 3% in patients treated with Mircera®▼ and 2% in patients who received reference treatment[5].

8.6.3 Utility weights

Utility weights are not incorporated into the cost minimisation analysis due to the assumption of therapeutic equivalence. Health-related quality of life was assessed in the phase III correction studies using the SF-36 questionnaire[17,18]. Clinically meaningful changes from baseline scores (defined as a change of five points or more) were observed in several domains for both Mircera®▼ and the comparators, but the extent to which these differ between Mircera®▼ and the comparator for each of the domains is not formally reported or compared. Visual inspection of graphical respresentations of the results suggest that, in the AMICUS study, SF-36 scores were improved by more than five points with IV Mircera®▼ administered once every two weeks compared with IV epoetin administered three times per week in several domains when measured at 13 weeks and at 25 weeks[17]. In the ARCTOS study in non-dialysis patients receiving ESA via the SC route, visual inspection suggests that only in one domain, role physical, and only when measured at 29 weeks, was there a difference between SF-36 scores greater by more than five points in the Mircera®▼ every two weeks group compared with the darbepoetin alfa once weekly group[17]. Given the lack of detail around these analyses, these results should be interpreted with caution.

8.7 Healthcare resource utilisation and cost

8.7.1 Drug costs

ESA acquisition costs are based on the average cost per microgram (for Mircera®▼ or darbepoetin alfa) or per IU (for epoetin alfa and beta) as listed in the current British National Formulary (BNF)[14]. These are then used to cost the average weekly dose equivalents for the ESAs, which are estimated as discussed in section 8.6.1. No rounding of doses to the use of the nearest suitable pre-filled syringes is considered, which based on WMP-sought expert opinion is usual in practice for all ESAs.

The company highlights in its submission that, although the list prices are appropriately used in the cost minimisation analyses, there are various discount schemes and contracts in place for the ESAs, which would reduce the acquisition cost estimates for the ESAs[16].

8.7.2 Adverse event costs

Not applicable as the analysis assumed equivalence.

8.7.3 Other resource use and costs

8.7.3.1 Administration costs in dialysis patients

A time and motion study was conducted in 2006 to estimate resource use and costs associated with ESA administration in dialysis patients in 12 German and UK dialysis centres[29]. This involved timed observations and estimated from dialysis staff in relation to activities and disposables. The 2005/6 cost per IV ESA dose has been inflated, resulting in a cost of £2.66 per IV ESA dose[16].

8.7.3.2 Administration costs in non-dialysis patients

Based on company-sought expert opinion, it is assumed that most non-dialysis patients would self-administer ESAs via SC injection, which would incur no costs to the NHS[16]. However, it is assumed that 15% of patients require assistance at home with ESA administration, and that 10% have their ESA administered by a healthcare professional at GP surgery or in the hospital. It is further assumed that 25% of those who require ESA administration via a healthcare professional also require NHS transport[16]. Based on published unit costs, the average cost per ESA administration in non-dialysis patients is estimated to be £7.60[16].

8.7.3.2 Societal costs

An analysis has been provided to estimate societal cost impact of the use of Mircera®▼ compared with other ESAs. As dialysis patients are assumed to receive their ESAs at the same time undergoing dialysis, the societal costs in this group of patients are considered negligible. In non-dialysis patients, the impact of self administration or administration by a healthcare professional is explored in terms of time impact and productivity losses[16]. This involves a range of assumptions in relation to the proportion of patients who are in full-time employment and their (in)ability to self-administer ESAs via SC injection. Whilst serving to highlight an important aspect of the burden of chronic kidney disease and its management, the results of this analysis should be interpreted with caution. Results of this analysis are presented in Appendix 2.

8.8 Discounting

Costs have not been discounted due to a maximum time horizon of analysis of one year[16].

8.9 Results

8.9.1 Base-case analysis

The overall NHS costs (drug acquisition costs + drug administration costs) for Mircera®▼ and the incremental costs compared with other ESAs are presented in Table A.

These results indicate that, in each of the three patient groups, the overall costs of treatment with Mircera® is lower compared with using other ESAs. A breakdown in terms of incremental drug costs and incremental administration costs is presented in Appendix 2, Table 2 and Table 3. In dialysis patients, the use of Mircera®▼ is estimated to be less expensive in terms of both drug administration costs and drug acquisition costs, with the exception of epoetin alfa in switch / dialysis patients, which has a lower drug acquistion cost than Mircera®▼. In non-dialysis patients, the drug acquisition costs are greater with Mircera®▼ than with all comparator ESAs, but these are more than offset by the estimated lower administration costs in each patient group[16].

Table A. Overall per patient NHS costs for Mircera® and the incremental costs compared with other ESAs[16]

	Switch / dialysis patients (one year treatment)	Naïve / dialysis patients (*Hb correction period only)	Naïve / non-dialysis patients (*Hb correction + maintenance = one year)
Mircera®▼ costs (£)	4732.52	210.49	2039.63
Incremental costs of Mircera versus Comparator ESAs (£)			
Epoetin alfa	-66.68	-64.51	-561.46
Epoetin beta	-1110.84	-122.03	-173.01
Darbepoetin alfa	-765.12	-98.50	-37.77

*Hb=haemoglobin

8.10 Sensitivity/scenario analyses

8.10.1 One-way sensitivity/scenario analyses

One-way sensitivity analyses explored the impact of varying the relative drug utilisation, the darbepoetin conversion factor and the drug administration costs in the range +/-10% of the base case values. These suggest that the model is most sensitive to relative drug utilisation (relative dose levels). There were substantial changes in the incremental costs with the use of Mircera®▼ across all comparators when explored within the +/-10% range for dose levels, and it is uncertain that this range adequately captures the difference in dose requirements for ESAs when administered via the IV versus the SC route. However, only in the switch / dialysis patients when epoetin alfa was the comparator ESA was the overall NHS cost of Mircera®▼ estimated to be greater than the comparator.

8.10.2 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was not conducted.

8.10.3 Scenario analysis

The company submission considers an alternative way of estimating the doses of Mircera®▼ and other ESAs for the switch / dialysis patient group, rather than basing this on the MAXIMA phase III clinical trial[16]. Based on the 2008 UK Renal Registry report[27], the mean weekly dose of epoetin in Wales is 9,296 IU. This is estimated to be equivalent to a monthly Mircera®▼ dose of 200 micrograms (i.e. 50 micrograms weekly equivalent) and a weekly darbepoetin alfa dose of 46.48 micrograms, based on the conversion factors in the Mircera®▼ and darbepoetin alfa SPCs, respectively[1,24]. Using the drug administration costs as in the base case analysis, the incremental overall NHS costs of Mircera®▼ compared with the comparator ESAs are as presented in Table B.

This analysis suggests that the overall costs of treatment with Mircera®▼ are lower compared with epoetin treatment, but are greater compared with darbepoetin alfa treatment. The company submission highlights a number of limitations to this analysis, including that fact that this approach has little internal validity compared with the trial-derived analyses that involve direct comparisons of the ESAs. In addition, the company submission suggests that the conversion factors suggested in the SPCs for darbepoetin alfa and Mircera®▼ are broad, starting dose categories and it is uncertain that these adequately reflect equipotent doses in clinical practice[16]. This analysis should be interpreted with caution. It is noteworthy that the base case analysis also uses the conversion factor approach for estimating darbepoetin alfa doses from epoetin doses, and vice versa.

Table B. Incremental costs of Mircera®▼ versus other ESAs, based on doses of epoetin used in clinical practice in Wales

	Incremental Mircera®▼ drug acquisition costs (£)	Incremental Mircera®▼ drug administration costs (£)	Incremental Mircera®▼ total NHS costs (£)
Epoetin alfa	-299.15	-379.72	-678.87
Epoetin beta	-1343.19	-379.72	-1722.91
Darbepoetin alfa	+285.32	-34.52	+250.80

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of Mircera®▼.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

UK renal registry data is used to provide incidence and prevalence data for patients undergoing dialysis treatment, and the proportions currently using ESAs. The incidence and prevalence of anaemic pre-dialysis patients is based on estimates listed in the 2006 NICE clinical guideline on the management of anaemia in patients with CKD. The proportion of these patients estimated to be eligible for ESA treatment has simply been assumed by the company in the absence of other estimates. For simplicity, the comparator ESA in dialysis patients is assumed to be IV epoetin alfa, and for non-dialysis patients it is assumed to be SC darbepoetin alfa. The drug acquisition costs are estimated to be greater for Mircera®▼ treatment, but these are offset by lower drug administration costs, resulting in net cost savings being estimated for the use of Mircera®▼.

Drug and administration costs are derived directly from the cost minimisation analysis, and the uncertainties associated with drug doses and administration frequencies are carried through to the budget impact analysis. The company estimates should be interpreted in that context.

9.2 Perspective and time horizon

The analysis considers direct costs from the perspective of NHS Wales over a five year period 2009-13[16].

9.3 Data sources

9.3.1 Incident and prevalent cases

Incidence and prevalence data for patients undergoing renal replacement therapy (CKD stage 5) are derived from the 2007 UK Renal Registry data[11]. These indicate that, in 2007 there were 416 incident cases and between 2002-2007 the incidence rate increased by 8.1%, which is assumed to be equivalent to an increase of 1.6% per year. On this basis, the incident number of patients in 2008 is estimated to be 423. There were 2,377 prevalent cases in 2007, and prevalence increased by 5.4% on average each year[27]. Therefore, the company estimates that there were 2,505 patients undergoing renal replacement therapy in 2008[16].

The 2007 UK renal registry data indicate that in the UK there were 96.8 deaths per 1000 prevalent renal replacement therapy patients[27]. Assuming that the death rate remains constant, this is equivalent to 242 deaths in 2008. The net number of renal replacement therapy patients in 2009 is therefore calculated to be 2,686[16].

Incidence data for pre-dialysis renal patients (CKD stage 2-4) are reported to be lacking[16]. From the information contained within the 2006 NICE clinical guideline on the management of anaemia on CKD[7], the company estimates that stage 2/3 CKD prevalence is around 4.3% and stage 3/4 CKD prevalence is around 0.2%, with anaemia prevalence being 1% and 9%, respectively[16]. Based on the current adult population of Wales (2,423,500), the company estimates that there are 1,042 anaemic CKD stage 3 patients, and 436 anaemic CKD stage 4 patients[16]. The company estimates that the number of pre-dialysis patients being treated with an ESA is increasing by 5% per annum[16], although the basis of this estimate is unclear.

The number of haemodialysis and peritoneal dialysis patients in Wales is estimated from 2007 UK Renal Registry data, adjusted upwards by 5.4%. This results in an estimated 1,065 haemodialysis and 344 peritoneal dialysis patients currently in Wales. The same data set indicates that 87% of haemodialysis patients and 77% of peritoneal dialysis patients are treated with an ESA. The number of ESA-eligible renal replacement therapy patients in Wales is therefore estimated to be 1,192[16].

As data for pre-dialysis patients are lacking, the company assumes that 50% and 75% of anaemic patients at CKD stages 3 and 4, respectively, receive ESAs. This equates to 521 CKD stage 3 and 327 CKD stage 4 patients eligible for ESA treatment. The combined total of ESA-eligible patients is therefore 2,040[16].

9.3.2 Projected rate of adoption and market share

The company simply assumes that all ESA-eligible patients would be eligible for Mircera®▼ treatment, on the basis of its non-inferiority to other ESAs and the convenience of its once monthly administration[16]. It is assumed that there will be a 5% increase in all patient numbers in each of the next five years. Therefore, the numbers of dialysis and non-dialysis patients in 2009 are 1,192 and 848, rising to 1,449 and 1031, respectively, in 2013.

9.3.3 Costs and resource use

For dialysis patients, the drug costs and administration costs are assumed to be the same as those estimated in the cost minimisation analysis for the switch / dialysis group for one year (see section 8). For simplicity, the company has compared Mircera®▼ only against epoetin alfa (assumed to be Eprex® and not the biosimilar product Binacrit®) on the basis that this is the primary ESA used in this population[16].

For non-dialysis patients, the drug costs and administration costs are assumed to be the same as those estimated in the cost minimisation analysis for the naïve / non-dialysis group, which includes both the correction and the maintenance phases of treatment for up to one year (see section 8)[16]. For simplicity, the company has compared Mircera®▼ only against darbepoetin alfa on the basis that this is the primary ESA used in this population[16].

It should be noted that the uncertainties in relation to the estimation of drug and acquisition costs in the cost minimisation analysis apply equally to the budget impact analysis. As highlighted by the company in the cost minimisation analysis, there are various discount schemes and contracts in place for the ESAs, which would reduce the acquisition cost estimates for the ESAs.

9.4 Results

The company estimates net cost savings from the use of Mircera®▼ instead of alternative ESAs, as presented in Table C. The drug acquisition costs for Mircera®▼ are greater than for epoetin alfa and darbepoetin alfa in dialysis and non-dialysis patients, respectively. However, these additional costs are more than offset by the estimated administration cost savings. The use of Mircera®▼ is estimated to result in overall costs savings of around £112,000 in 2009, rising to around £136,000 in 2013. Any deviation in the assumed use of alternative ESAs, or the frequency of their administration, in dialysis and non-dialysis patients could potentially change these estimates substantially. This is not explored in the budget impact analysis, and the company estimates should be interpreted in that context.

Table C. Company estimates of budget impact from the use of Mircera®▼ instead of epoetin alfa and darbepoetin alfa[16]

	2009	2010	2011	2012	2013
Dialysis patients					
No. patients	1,192	1,252	1,314	1,380	1,449
Drug cost versus Epoetin alfa (£)	+373,144	+391,801	+411,391	+431,960	+453,558
Administration costs versus Epoetin alfa (£)	-452,626	-475,258	-499,020	-523,971	-550,170
Net cost impact (£)	-79,483	-83,457	-87,630	-92,011	-96,612
Non-dialysis patients					
No. patients	848	890	935	982	1,031
Drug cost versus Darbepoetin alfa (£)	+147,747	+155,134	+162,891	+171,036	+179,587
Administration costs versus Darbepoetin alfa (£)	-179,776	-188,765	-198,203	-208,113	-218,519
Net cost impact (£)	-32,029	-33,630	-35,312	-37,078	-38,931
Total Net cost impact (£)	-111,512	-117,087	-122,941	-129,089	-135,543

9.5 Sensitivity analysis

No sensitivity analysis was conducted for the budget impact analysis.

9.6 Comparator costs

The annual costs of relevant comparators, based on stable haemoglobin maintenance achieved at a Mircera®▼ dose of 200 micrograms once monthly, and assuming the Mircera®▼ SPC suggested dose conversions[1] and BNF list prices[14], are presented in Table D.

Table D. Examples of relevant annual ESA comparator costs

ESA	Example maintenance dose	Annual cost of example maintenance dose (£)
Mircera®▼	200 micrograms once monthly	3,740
Darbepoetin alfa (Aranesp®)	40-80 micrograms once weekly	3,242 – 6,484
Epoetin alfa (Eprex®)	8,000-16,000IU weekly in three divided doses	2,615 – 5,230
Biosimilar Epoetin alfa (Binocrit®▼)	8,000-16,000IU weekly in three divided doses*	2,118 – 4,236
Epoetin beta (NeoRecormon®)	8,000-16,000IU once weekly	3,242 – 6,484
Epoetin zeta (Retacrit®▼)	8,000-16,000IU weekly in three divided doses*	2,353 – 4,706
This table does not imply therapeutic equivalence of drugs or the stated doses Prices based on pre-filled syringes, no rounding of doses and no vial wastage assumed *Based on being biosimilar epoetins		

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- In 2006 NICE published guidance on the management of anaemia in patients with CKD which has been highlighted previously in section 3.0[7].
- The UK Renal Registry (established by the Renal Association) provides a focus for the collection and analysis of data on the incidence, clinical management and outcome of renal disease. Currently there is a concentration of data concerning renal replacement therapy, including transplantation, but the Registry will extend to other forms of treatment of renal disease in the future. It is considered a source of comparative data, for audit/benchmarking, planning, clinical governance and research; providing data for bodies such as NHS Trusts, and commissioning authorities[30].
- AWMSG are of the opinion that Mircera®▼ may be suitable for shared care arrangements within NHS Wales. Existing shared care protocols for current ESAs may need to be reviewed in light of this decision.

10.2 Related advice

- In September 2008, NICE published guidelines on the early identification and management of CKD in adults in primary and secondary care[6].
- In 2004, the European Best Practice Guidelines Working Group revised their guidelines for the management of anaemia in patients with chronic renal failure[9].
- In 2006, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines and Clinical Practice recommendations were published in the US for anaemia in CKD[10].
- The UK Renal Association current guidelines relating to CKD include specific sections of the National Service Framework for Renal Services and the latest Quality and Outcomes Framework of the General Medical services contract for general practitioners. They are intended to provide clear guidance for the management of patients with CKD and associated audit measures which can be used to assess performance against a nationally agreed set of outcome measures[31].

10.3 Previous AWMSG advice

- Epoetin delta (Dynepo®) was originally recommended in February 2008 for use in patients on dialysis (and in patients not on dialysis) within NHS Wales for the treatment of anaemia in patients with chronic renal failure. In March 2009 the European Commission (EC) issued a decision to withdraw the marketing authorisation for Dynepo® (epoetin delta). This decision follows a letter from the marketing authorisation holder (MAH) responsible for Dynepo® (Shire Pharmaceutical Contract Limited) informing the EC that the company had decided to voluntarily withdraw the marketing authorisation for commercial reasons [32].
- Epoetin alfa (Eprex®), epoetin beta (NeoRecormon®), and darbepoetin alfa (Aranesp®) were all appraised in December 2003 for their use in the correction of anaemia in cancer patients. All three were not supported for use within NHS Wales for this indication[33].

10.4 Ongoing studies

The company have highlighted in their submission that published results from the PATRONUS study (see section 6.1.4) will be available within the next six to 12 months[16].

10.5 Patient organisation information

A patient organisation submission by The National Kidney Federation was provided to AWMSG members.

10.6 Medical expert/Clinical expert summary

Medical/Clinical expert views were provided to AWMSG members.

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Appendix 1. Additional Clinical Information

Table 1. Prospective studies of Mircera®▼ in the treatment of symptomatic anaemia associated with CKD

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
AMICUS study[17]	Randomised open-label, multi-centre, parallel-group, two arm study 24-week correction period	ITT population of 181 patients and PP population of 155 patients	**Inclusion criteria:** Patients aged ≥18 years with anaemia related to CKD stage 5 receiving HD maintenance or PD ≥two weeks before screening and during the screening period Dialysis adequacy as measured by Kt/V ≥1.2 or urea reduction ratio ≥65% for HD patients or weekly Kt/V ≥1.8 for PD patients Baseline Hb concentration 8–11 g/dL determined from the mean of two screening values Adequate iron status defined as serum ferritin ≥100ng/mL or TSAT ≥20% (or percentage of hypochromic red blood cells <10%) (mean of two screening values) **Exclusion criteria:** Previous ESA therapy within 12 weeks prior to screening. Ongoing EPO treatment could not be discontinued to allow participation in the trial. Patients were also excluded if they had: • CRP > 30mg/L; • temporary dialysis access catheter; • High likelihood of early withdrawal or interruption of the study (e.g. myocardial infarction, severe or unstable coronary artery disease, stroke, severe liver disease within the 12 weeks before screening or during the screening period); • Life expectancy <12 months.	**Mircera®▼ (n=135) versus epoetin (n=46)** Male (%):61 versus 70 Mean age, years (SD): 54.7 (14.4) versus 53.4 (15.2) Mean Hb, g/dL (SD): 9.39 (0.88) versus 9.40 (0.82) HD/PD: 132/3 versus 46/0 Median time on dialysis (days): 166 versus 113	Patients were randomised in a 3:1 ratio to receive either Mircera®▼ 0.4 mcg/kg IV once every fortnight or to a reference group receiving epoetin alfa (n=5) or epoetin beta (n=41) IV, three times weekly.	**Primary efficacy endpoint:** **The Hb response rate in the ITT population during the 24-week study period:** 126 patients (93%) were responders, and the lower limit of the 95% CI for the response rate was higher than 60% (95% CI 87.7-96.9, p<0.0001). **Secondary endpoints:** **Hb values and change from baseline over time:** Changes were similar for both treatment arms (graph provided in peer-reviewed publication[17]) Mean Hb levels at end of correction period: Mircera®▼ : 12.09+1.35g/dL Epoetin: 11.96+1.11g/dL **Time to Hb response:** 57 days in the Mircera®▼ group versus 31 days in the epoetin group **Incidence of RBC transfusions:** Seven patients (5.2%) in the Mircera®▼ group versus two patients (4.3%) in the epoetin group received RBC transfusions during the study period.

Table 1 Continued

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
ARCTOS study[18]	Randomised open-label, multi-centre, parallel-group, two-arm study 18 week correction period 10 week evaluation period.	Randomised 324 ITT: 324 PP: 283 (Mircera®▼: 139 darbepoetin alfa: 144)	**Inclusion criteria:** Patients aged ≥18years with anaemia related to CKD stage 3 (Creatinine Clearance (CrCl) 30-59 mL/min) or stage 4 (CrCl 15-29 mL/min) not requiring dialysis Anaemia defined as baseline Hb concentration between 8 and 11g/dL, determined from the mean of two screening values Adequate iron status defined as serum ferritin ≥ 100ng/mL or TSAT ≥20% (or percentage of hypochromic RBCs <10%); from the mean of two screening values **Exclusion criteria:** Dialysis therapy expected within 6 months or rapid progression of CKD (CrCl decrease of more than 20% within 12 weeks) Previous therapy with ESA within 12 weeks prior to screening. Patients were also excluded if they had: • CRP > 15mg/L; • High likelihood of early withdrawal or interruption of the study (e.g. myocardial infarction, severe or unstable coronary artery disease, stroke, severe liver disease within the 12 weeks before screening or during the screening/baseline period)	**Mircera®▼ (n=162) versus darbepoetin alfa (n=162)** Male (%) : 43 versus 49 Mean age, years (SD): 63.9 (14.1) versus 66.9 (12.8) Mean Hb, g/dL (SD): 10.22 (0.60) versus 10.15 (0.69)	Patients were randomised 1:1 to receive Mircera®▼ 0.6 mcg/kg/ SC once every two weeks or darbepoetin alfa 0.45 mcg/kg SC once weekly.	**Primary efficacy endpoints:** **The Hb response rate in the ITT population during the 28-week study period:** 158 (97.5%) Mircera®▼ patients achieved the target Hb response. The lower limit of this CI was higher than 60% (95% CI 93.8%-99.3%, p<0.0001). 156 (96.3%) darbepoetin alfa patients were responders (95% CI 92.1%-98.6%, p<0.0001). **Mean change in Hb concentration between the baseline and evaluation periods in the PP population:** Mircera®▼:2.12g/dL Darbepoetin alfa: 2.02g/dL When adjusted for covariates (baseline Hb levels and geographic region): Mircera®▼:2.15g/dL Darbepoetin alfa: 2.00g/dL Mean difference between the two groups: 0.16g/dL (95% CI: -0.005-0.35). **Secondary endpoints:** **Hb values and change from baseline over time:** Changes were similar for both treatment arms (graph provided in peer-reviewed publication[18]) **Time to Hb response:** 43 days in the Mircera®▼ group versus 29 days in the darbepoetin alfa group. **Incidence of RBC transfusions:** Four patients (2.5%) in the Mircera®▼ group and eleven patients (6.8%) in the darbepoetin alfa group received RBC transfusions during the study period.

Table 1 Continued

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
MAXIMA study[19]	Randomised, controlled, open-label, multi-centre parallel group, three arm, non-inferiority study 28 week period for dose titration and stabilisation of Hb concentration. Followed by an 8-week evaluation period. Patients continued on their treatment until week 52 to assess the long-term safety.	Radomised: 673 ITT: 673 PP: 540 (Mircera®▼ once every two weeks: 188; Mircera®▼ once every month: 172 epoetin alfa/beta: 180)	**Inclusion criteria:** Patients ≥18 years with anaemia related to CKD on regular long-term HD or PD therapy ≥12 weeks before screening and during the screening/baseline period Dialysis adequacy (Kt/V≥1.2 or URR≥65% for HD or weekly Kt/V≥1.8 for PD patients). Baseline Hb concentration:10.5-13g/dL Stable baseline [Hb] (≤1g/dL difference between the mean Hb in weeks -4 and -3 and in weeks -2 and -1) Continuous IV maintenance epoetin therapy for ≥8weeks before screening and during the screening/baseline period Stable IV maintenance epoetin therapy during screening/baseline period (a maximum of one weekly dose change which should not exceed 25% of the weekly dose preceding screening) Adequate iron status (serum ferritin ≥100ng/mL or TSAT ≥20% [or % of hypochromic RBCs <10%]) **Exclusion criteria:** • Temporary dialysis access catheter; • poorly controlled hypertension necessitating interruption of epoetin treatment in the 6 months before screening; • life expectancy <12 months	**Mircera once every two weeks (n=223):** Male (%): 60Mean age, years(SD): 59.0 (15.2) Mean Hb, g/dL (SD): 11.97 (0.65) Median dialysis duration (months): 33.9 **Mircera once monthly (n=224):** Male(%): 56 Mean age, years(SD): 59.0 (15.0) Mean Hb, g/dL (SD): 11.85 (0.65) Median dialysis duration (months): 40.0 **Epoetin three times weekly - once weekly (n=226)** Male (%):59 Mean age, years(SD): 58.6 (15.1) Mean Hb, g/dL (SD): 11.91 (0.64) Median dialysis duration (months): 36.3	Randomised in a 1:1:1 ratio to continue IV epoetin alfa or beta at their current weekly dose and dosing interval or to change to IV Mircera®▼ administered at intervals of either every two weeks or once monthly.	**Primary efficacy endpoint (PP population):** **Difference in the mean change in Hb concentration (g/dL) between baseline and evaluation period.** A non inferiority analysis was performed to analyse this difference between the Mircera®▼ and epoetin treated groups. Adjusted mean change (Mircera®▼ once-monthly versus epoetin) in PP population: -0.025 versus -0.075g/dL (Difference=0.051), 97.5% CI: -0.173 to 0.275, p<0.0001). **Secondary efficacy endpoints (ITT population):** **The number of patients maintaining average Hb concentration during the evaluation period within +1g/dL of their baseline values:** 127 patients (67.6%) in the Mircera®▼ once-monthly treatment group, and 138 patients (67.3%) in the epoetin group **The incidence of RBC transfusions during the dose titration and evaluation periods:** 7.3% in the Mircera®▼ once-monthly group, and 7.6% in the epoetin group

Table 1 Continued

Ref	Study type	No. of patients	Inclusion/exclusion criteria	Baseline characteristics	Treatment regimen	Outcome
PROTOS study[20]	Randomised, controlled, open-label, multi-centre, parallel group, three arm, non-inferiority study 28 week period for dose titration and stabilisation of Hb concentration. Followed by an 8-week evaluation period. Patients continued on their treatment until week 52 to assess the long-term safety	Radomised: 572 ITT: 572 PP: 474 (Mircera®▼ once every two weeks: 154; Mircera®▼ once every month: 153 epoetin alfa/beta: 167)	**Inclusion criteria:** Patients ≥18 years with anaemia related to CKD on regular long-term HD or PD therapy ≥12 weeks before screening and during the screening/baseline period Dialysis adequacy (Kt/V≥1.2 or URR≥65% for HD or weekly Kt/V≥1.8 for PD patients). Baseline [Hb]:10.5-13g/dL. Stable baseline [Hb] (≤1g/dL difference between the mean Hb in weeks -4 and -3 and weeks -2 and -1) Continuous IV maintenance epoetin therapy for ≥8weeks before screening and during the screening/baseline period Stable IV maintenance epoetin therapy during screening/baseline period (a maximum of one weekly dose change which should not exceed 25% of the weekly dose preceding screening) Adequate iron status (serum ferritin ≥100ng/mL or TSAT ≥20% [or % hypochromic RBCs, 10%]). **Exclusion criteria:** • Temporary dialysis access catheter; • poorly controlled hypertension necessitating interruption of epoetin treatment in the 6 months before screening; • life expectancy <12 months	**Mircera once every two weeks (n=190):** Male (%): 57 Mean age, years(SD): 60.5 (15.4) Mean Hb, g/dL (SD): 11.70 (0.72) Median dialysis duration (months): 33.5 **Mircera once monthly (n=191):** Male (%): 61 Mean age, years(SD): 62.3 (15.4) Mean Hb, g/dL (SD): 11.66 (0.71) Median dialysis duration (months): 40.4 **Epoetin three times weekly - once weekly (n=191)** Male (%): 58 Mean age, years(SD): 60.4 (14.7) Mean Hb, g/dL (SD): 11.65 (0.70) Median dialysis duration (months): 33.9	Randomised in a 1:1:1 ratio to continue SC epoetin alfa or beta at their current weekly dose and dosing interval or to change to SC Mircera®▼ administered at intervals of either every two weeks or once monthly	**Primary efficacy endpoint (PP population): Difference in the mean change in Hb concentration (g/dL) between the baseline and evaluation periods.** A non inferiority analysis was performed to analyse this difference between the Mircera®▼ and epoetin treated groups. Adjusted mean change (Mircera®▼ once-monthly versus epoetin) in PP population: -0.131 versus -0.109 (Difference =0.022, 95% CI: -0.262 to 0.217, p<0.0001) **Secondary efficacy endpoints (ITT population):** **The number of patients maintaining average Hb concentration during the evaluation period within +1g/dL of their average baseline Hb concentration:** 111 patients (66.1%) in the Mircera®▼ once-monthly treatment group, and 127 patients (72.2%) in the epoetin group **The incidence of RBC transfusions during the dose titration and evaluation periods:** 10.5% in the Mircera®▼ once-monthly group, and 9.9% in the epoetin group

CI: Confidence interval; CKD: Chronic kidney disease; CrCl: creatinine clearance; CRP: C-reactive protein; ESA: erythropoiesis stimulating agent; EPO: erythropoietin; Hb: haemoglobin; HD: haemodialysis; ITT: intention to treat; IV: intravenous; mcg: micrograms; PD: peritoneal dialysis; PP: Per protocol; RBCs: red blood cells; SC: subcutaneous; SD: standard deviation; TSAT: transferrin saturation.

Appendix 2. Additional Health Economic data

Table 2. Mircera®▼ drug acquisition costs and incremental drug acquisition costs compared with other ESAs

	Switch / dialysis patients (one year treatment)	**Naïve / dialysis patients** (Hb correction period only)	**Naïve / non-dialysis patients** (Hb correction + maintenance = one year)
Mircera®▼ drug costs (£)	4663.88	199.68	2016.45
Incremental drug costs of Mircera®▼ versus comparator ESAs (£)			
Epoetin alfa	+313.04	-40.05	+513.75
Epoetin beta	-731.12	-97.57	+174.12
Darbepoetin alfa	-730.60	-97.55	+174.23

Table 3. Mircera®▼ drug administration costs and incremental drug administration costs compared with other ESAs

	Switch / dialysis patients (one year treatment)	**Naïve / dialysis patients** (Hb correction period only)	**Naïve / non-dialysis patients** (Hb correction + maintenance = one year)
Mircera®▼ drug costs (£)	34.32	10.81	110.39
Incremental drug costs of Mircera®▼ versus comparator ESAs (£)			
Epoetin alfa	-379.72	-24.47	-1075.21
Epoetin beta	-379.72	-24.47	-347.13
Darbepoetin alfa	-34.52	-0.95	-212.00

Societal (patient) burden in ESA-naïve non-dialysis patients

The time required for each naïve non-dialysis ESA administration has been calculated based on 90% of patients self-administering at home (assumed to take 5 minutes) and 10% of patients having ESA administered by healthcare professional (assumed to take 5 minutes for administration plus 24 minutes return journey plus 15 minutes waiting time). This results in an average ESA administration time of 8.9 minutes. Based on the assumed number of administrations per year described in section 8, the company estimates the total time saved per year by each patient with the use of Mircera®▼ is approximately 21 hours compared to administration with epoetin alfa, 6 hours compared to epoetin beta and 4 hours compared to administration with darbepoetin alfa[2].

Based on the relative administration frequency for the comparator ESAs and Mircera®▼ the company estimates that, over the course of a year, non-dialysis maintenance patients will need on average 144 less administrations with Mircera®▼ compared to epoetin alfa, 40 less administrations compared to epoetin beta, and 30 fewer administrations compared to darbepoetin alfa[2].

Assuming that all patients who attend their local GP clinic for administration (10%) who do not require NHS transport (75%) are employed, a total of 7.5% of non-dialysis patients may in practice lose half a work day each time they need an ESA administration in Wales. The number of workdays gained from using Mircera®▼ relative to the comparator ESAs is therefore calculated as the number of administrations avoided per year multiplied by 7.5% of patients requiring a half a day off work divided by 2 (representing the half day lost). Over one year, the productivity cost savings associated with Mircera®▼ are estimated to be £541.93 compared to epoetin alfa, £150.54 compared to epoetin beta, and £111.40 compared to darbepoetin alfa[2].

The company highlights that, when these savings are combined with the NHS cost savings, the benefits of treatment with Mircera®▼ increase further[2]. There are a range of assumptions employed in this analysis which are not supported. Whilst serving to highlight an important aspect of the burden of chronic kidney disease and its management, the results of this analysis should be interpreted with caution. The uncertainties in relation to dose frequencies outlined in section 8 also apply to this analysis.