ADIS DRUG EVALUATION

Drugs 2008; 68 (8): 1139-1156
0012-6667/08/0008-1139/$53.45/0

© 2008 Adis Data Information BV. All rights reserved.

Methoxy Polyethylene Glycol-Epoetin Beta

A Review of its Use in the Management of Anaemia Associated with Chronic Kidney Disease

Monique P. Curran and *Paul L. McCormack*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Various sections of the manuscript reviewed by:

A.L.M. de Francisco, Servicio de Nefrologia, Hospital Universitario Valdecilla, Santander, Spain; ***N.W. Levin***, Renal Research Institute, New York, New York, USA; ***F. Locatelli***, Department of Nephrology and Dialysis, Alessandro Manzoni Hospital, Lecco, Italy; ***I.C. Macdougall***, Department of Renal Medicine, King's College Hospital, London, United Kingdom; ***R. Provenzano***, Department of Nephrology, St John Hospital and Medical Center, Detroit, Michigan, USA; ***B. Spinowitz***, New York Hospital Queens, Cornell University Medical Center, Flushing, New York, USA.

Data Selection

Sources: Medical literature published in any language since 1980 on 'methoxy polyethylene glycol-epoetin beta' or 'R-744', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'R-744' or 'methoxy polyethylene glycol-epoetin beta' or 'CERA'. Searches were last updated 30 April 2008.

Selection: Studies in patients with anaemia associated with chronic kidney disease who received methoxy polyethylene glycol-epoetin beta. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Methoxy polyethylene glycol-epoetin beta, CERA, anaemia, chronic kidney disease, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary

Abstract

Methoxy polyethylene glycol-epoetin beta (Mircera®) is a continuous erythropoietin receptor activator, with a long half-life (approximately 130 hours). In patients with anaemia associated with chronic kidney disease (CKD), both on and not on dialysis, who had not previously received an erythropoiesis-stimulating agent (ESA), methoxy polyethylene glycol-epoetin beta administered intravenously or subcutaneously once every 2 weeks resulted in a smooth and steady rise in haemoglobin levels. The response rates were high (up to 97.5%) in these patients at the end of the correction period; response rates with the comparator ESAs (epoetin alfa or beta, or darbepoetin alfa) were up to 96.3%. Moreover, patients with CKD on dialysis who had previously been treated with an ESA maintained stable haemoglobin levels (within ±1 g/dL of baseline and within a range of 10–13.5 g/dL) when directly converted to methoxy polyethylene glycol-epoetin beta administered intravenously or subcutaneously once every 2 or 4 weeks. Methoxy polyethylene glycol-epoetin beta is generally well tolerated, with most adverse events being of mild to moderate severity, consistent with the co-morbidities known to occur in this patient group and those reported with other ESAs.

In conclusion, in patients with anaemia associated with CKD, subcutaneous or intravenous methoxy polyethylene glycol-epoetin beta achieved a high haemoglobin response rate (ESA-naive patients) when administered once every 2 weeks and maintained stable haemoglobin levels (patients previously treated with ESAs) when administered once monthly.

Pharmacological Properties

Methoxy polyethylene glycol-epoetin beta is a continuous erythropoietin receptor activator, with a slower association with, but slightly faster dissociation from, the erythropoietin receptor than epoetin beta. Cell stimulation studies demonstrated that this agent has a reduced *in vitro*, but an increased *in vivo*, specific activity compared with epoetin beta.

Subcutaneous or intravenous administration of methoxy polyethylene glycol-epoetin beta produced a dose-dependent reticulocyte response in patients with CKD that was independent of the frequency of administration.

Following subcutaneous administration of methoxy polyethylene glycol-epoetin beta to anaemic patients with CKD, both on and not on dialysis, maximum serum concentrations (C_{max}) occurred after a median 72.0 and 94.5 hours. Times to C_{max} after intravenous administration of this agent were 2.0 and 0.25 hours. After subcutaneous administration, absolute bioavailabilities were 62% and 54%, respectively. Haemodialysis had no effect on the serum concentrations of methoxy polyethylene glycol-epoetin beta. Clearance was low (0.49–1.67 mL/h/kg) and the mean terminal elimination half-life was long (77–142 hours) following subcutaneous or intravenous administration.

Therapeutic Efficacy

Six phase III trials have demonstrated the efficacy of methoxy polyethylene glycol-epoetin beta administered subcutaneously or intravenously once every 2 weeks or once every 4 weeks in patients aged ≥18 years with anaemia associated with CKD, both on and not on dialysis.

© 2008 Adis Data Information BV. All rights reserved.

In two phase III correction trials in ESA-naive patients with CKD on dialysis (AMICUS study) or not on dialysis (ARCTOS study), haemoglobin response rates in the correction/evaluation period were high (up to 97.5%) in recipients of methoxy polyethylene glycol-epoetin beta administered intravenously (AMICUS) or subcutaneously (ARCTOS) once every 2 weeks. The corresponding response rates were 91.1% with epoetin alfa or beta in AMICUS and 96.3% with darbepoetin alfa in ARCTOS. Methoxy polyethylene glycol-epoetin beta treatment resulted in a smooth and steady rise in haemoglobin levels, with the median time to response being 57 (AMICUS) and 43 (ARCTOS) days in methoxy polyethylene glycol-epoetin beta recipients, 31 days in epoetin alfa recipients (AMICUS) and 29 days in darbepoetin alfa recipients (ARCTOS).

In four phase III maintenance studies (MAXIMA, PROTOS, STRIATA, RUBRA) in patients with CKD on dialysis previously treated with other ESAs (epoetin alfa or beta, or darbepoetin alfa), methoxy polyethylene glycol-epoetin beta administered intravenously (MAXIMA, STRIATA, RUBRA) or subcutaneously (PROTOS, RUBRA) once every 2 or 4 weeks maintained haemoglobin levels within ±1 g/dL of baseline and within a range of 10–13.5 g/dL. The adjusted mean change in haemoglobin level between baseline and the evaluation period (weeks 29–36) in recipients of both methoxy polyethylene glycol-epoetin beta and the comparators was close to zero, demonstrating that little change in haemoglobin levels had occurred. The majority of methoxy polyethylene glycol-epoetin beta recipients (66–76%) and comparator recipients (67–72%) maintained an average haemoglobin level within ±1 g/dL and within a range of 10–13.5 g/dL during the evaluation period. Blood transfusions were required by few recipients of methoxy polyethylene glycol-epoetin beta (6–12%) or the comparator ESAs (8–11%) during the titration/evaluation period.

Pharmacoeconomics

Data obtained from an observational time and motion study conducted in the UK and Germany were used to estimate the potential time and costs saved by converting from comparator ESAs to methoxy polyethylene glycol-epoetin beta in a hypothetical dialysis centre of 100 patients with CKD. With 100% conversion to methoxy polyethylene glycol-epoetin beta, the estimated annual time savings were 37–43 days and annual costs (excluding drug acquisition costs) were estimated to be reduced by up to 59%.

Tolerability

In a pooled analysis of phase II and III trials in patients with anaemia associated with CKD, treatment-related adverse event rates occurred in 6% of methoxy polyethylene glycol-epoetin beta recipients, with hypertension, diarrhoea and nasopharyngitis being the most commonly reported adverse events. Most adverse events were mild to moderate in severity, and were consistent with the comorbidities known to occur in this patient group. Serious adverse events occurred in a similar percentage of recipients of methoxy polyethylene glycol-epoetin beta and comparator ESAs (37% vs 40%). The proportion of patients who died in the randomized phase III population was 5.7% in the methoxy polyethylene glycol-epoetin beta group and 6.1% in the comparator group.

Platelet levels were lower with methoxy polyethylene glycol-epoetin beta than comparator treatment, but remained within the normal range. Platelet counts $<100 \times 10^9$/L were reported in 7% of methoxy polyethylene glycol-epoetin beta recipients and 4% of recipients of the comparators.

No clinically relevant changes in vital signs, iron levels or laboratory parameters were reported during the phase III studies. No antibodies to methoxy

© 2008 Adis Data Information BV. All rights reserved.

polyethylene glycol-epoetin beta were detected during the clinical trial programme.

1. Introduction

Anaemia is a common complication in patients with chronic kidney disease (CKD). Anaemia is typically associated with poor concentration, loss of cognitive function and debilitating fatigue. If left untreated, chronic anaemia may seriously impair the patient's health-related quality of life (HR-QOL) and increase the risk of cardiac complications.[1,2]

Although the pathogenesis of anaemia in patients with CKD is multifactorial, the most probable reason for a decline in haemoglobin levels is a decrease in erythropoietin production.[2] Erythropoietin is produced in the kidney and released into the blood stream in response to hypoxia. Erythropoietin then interacts with erythroid progenitor cells to increase red blood cell production.[2]

Erythropoiesis-stimulating agents (ESAs) are standard therapy for renal anaemia patients and have been associated with improved HR-QOL and survival.[1-3] However, conventional ESAs, such as epoetin (recombinant human erythropoietin) alfa and beta, have short half-lives, and require frequent administration in order to maintain haemoglobin levels within the target range. Effective management of renal anaemia is often labour intensive and time consuming, with patients receiving ESA treatment up to three times a week.

Methoxy polyethylene glycol-epoetin beta (Mircera®)[1] is an ESA with a long half-life (about 130 hours) and can be administered intravenously or subcutaneously, allowing predictable stimulation of erythropoiesis and a prolonged dosing interval. It is often referred to by the descriptive name 'continuous erythropoietin receptor activator' (C.E.R.A.).

This review focuses on the clinical use of methoxy polyethylene glycol-epoetin beta (administered intravenously or subcutaneously) in adult patients with anaemia associated with CKD, including those on and not on dialysis.

2. Pharmacodynamic Properties

Methoxy polyethylene glycol-epoetin beta is a covalent conjugate of epoetin beta (produced by recombinant DNA technology) and methoxy polyethylene glycol.[4,5] The resultant molecule has a molecular weight (approximately 60 kDa) that is twice that of epoetin and differs from recombinant epoetin by integration of an amide bond between methoxy polyethylene glycol-butanoic acid and either the N-terminal amino group or the ε-amino group of lysine (predominantly lysine-52 or lysine-45) present in epoetin beta.[4]

2.1 Binding Studies

Methoxy polyethylene glycol-epoetin beta has a slower association with, but a slightly faster dissociation from, the erythropoietin receptor than epoetin beta.

In competitive binding assays in UT-7 cells (a human acute myeloid leukaemia cell line),[6] the concentration of half-maximal inhibition of binding of ^{125}I-epoetin-beta to UT-7 cell erythropoietin receptor sites was 200 nmol/L for methoxy polyethylene glycol-epoetin beta and 1.5 nmol/L for epoetin beta.[6] In a surface plasmon resonance study, the dissociation equilibrium constants for methoxy polyethylene glycol-epoetin beta and epoetin-β were 140 and 2.9 nmol/L.[6] Closer analysis of the equilibrium binding curves indicated that the difference in affinity between the two agents was mainly due to a slower association of methoxy polyethylene glycol-epoetin beta than epoetin beta with the erythropoietin receptor.[5,6] Methoxy polyethylene glycol-epoetin beta dissociation from the receptor was ≈1.5-fold faster than epoetin beta.[6]

2.2 *In Vivo* and *In Vitro* Cell Proliferation Studies

Cell stimulation studies show that methoxy polyethylene glycol-epoetin beta has a reduced *in vitro*,

1 The use of trade names is for product identification purposes only and does not imply endorsement.

© 2008 Adis Data Information BV. All rights reserved.

but an increased *in vivo*, specific activity compared with epoetin beta.

The effective concentrations required to stimulate half-maximal cellular proliferation with methoxy polyethylene glycol-epoetin beta, compared with epoetin beta, were approximately 10-fold higher in UT-7 cells and approximately 43-fold higher in CD34+ cells.[7] However, the level of maximal stimulation of both the UT-7 and CD34+ cells was similar for both agents.[7] Stimulation of cellular proliferation was specific for erythroid precursors, as the differentiation of white blood cells and megakaryocytes was not affected by methoxy polyethylene glycol-epoetin beta or epoetin beta.[7]

In contrast, *in vivo* studies have demonstrated that methoxy polyethylene glycol-epoetin beta is a more potent stimulator of erythropoiesis than epoetin both in the duration and magnitude of the response. A single subcutaneous injection of methoxy polyethylene glycol-epoetin beta 20 μg/kg in mice resulted in an increase in mean reticulocytes (an early marker of erythropoiesis) that was almost twice that with the same dose of epoetin, with a duration of response that was about 3 days longer.[8] Administration of methoxy polyethylene glycol-epoetin beta 0.75 μg/kg once weekly for 12 weeks to rats with surgically induced renal insufficiency produced increases in mean reticulocyte count that were significantly different to those with saline control ($p < 0.05$).[9]

2.3 Clinical Studies

Methoxy polyethylene glycol-epoetin beta produced dose-dependent reticulocyte responses in healthy volunteers[10,11] or in patients with CKD including those on and not on dialysis.[5,12]

In phase I trials in healthy male volunteers (n = 108),[10] single doses of intravenous methoxy polyethylene glycol-epoetin beta 0.4–3.2 μg/kg or the subcutaneous formulation of this agent 0.8–3.2 μg/kg induced dose-dependent increases in reticulocyte response that peaked within 10 days of administration and returned to baseline values by day 20.[10] At the highest dose administered, the mean increase in reticulocytes was 334% with intravenous administration and 262% with subcutaneous administration.[10] In healthy volunteers (n = 42), subcutaneous administration of this agent in the arm, thigh or abdomen (3.0 μg/kg) increased mean reticulocyte count relative to baseline by 258%, 273% and 269%, respectively.[11]

Similarly, in patients with CKD on peritoneal dialysis (n = 16),[5] a single subcutaneous (0.8 μg/kg) or intravenous (0.4 μg/kg) dose of methoxy polyethylene glycol-epoetin beta induced a reticulocyte response that peaked at a median of 8 days after administration and returned to baseline values by day 20. There was no difference in the time course for reticulocyte counts between the two routes of administration. In multiple-dose studies in patients with CKD on (n = 61) or not on (n = 65) dialysis,[12] subcutaneous or intravenous methoxy polyethylene glycol-epoetin beta (0.15–0.60 μg/kg) administered once weekly, once every 2 weeks or once every 3 weeks produced dose-dependent reticulocyte responses, with the response being independent of the frequency of administration.

3. Pharmacokinetic Properties

This section will focus on the pharmacokinetics of methoxy polyethylene glycol-epoetin beta in anaemic patients with CKD, including those on and not on dialysis[4,13] (summarized in table I). The pharmacokinetics of this agent have also been studied in healthy volunteers.[11,14] Data from the US prescribing information,[15] the Summary of Product Characteristics (SPC)[4] and the scientific discussion from the review of the marketing application by the European Medicines Agency (EMEA)[13] have been included in this section.

Following subcutaneous administration of methoxy polyethylene glycol-epoetin beta to anaemic patients with CKD on and not on dialysis, maximum serum concentrations (C_{max}) of this agent occurred after a median 72.0 and 94.5 hours (table I). Time to C_{max} with intravenous administration was 2.0 and 0.25 hours. With subcutaneous administration, absolute bioavailability values (based on the area under the concentration-time curve from day 1 to last measurement) were 62% and 54%.[4,13]

Haemodialysis had no effect on the serum concentrations of methoxy polyethylene glycol-epoetin beta, according to data from a study in 41 patients

© 2008 Adis Data Information BV. All rights reserved.

Table I. Pharmacokinetic parameters of a single dose of methoxy polyethylene glycol-epoetin beta in anaemic patients with chronic kidney disease; mean values are presented unless otherwise indicated[13]

Population	Study design	Dose (μg/kg)	C_{max} (ng/mL)	t_{max} (h)[a]	AUC_{last} (ng • h/mL)	$t_{½β}$ (h)	CL (mL/h/kg)	Bioavailability (%)
Patients on dialysis	r, op, co	IV 0.4	9.05	2.0	1028	134	0.49	100
(n = 16)		SC 0.8	4.6	72.0	1106	139	0.90	62
Patients not on dialysis	r, op, pl	IV 0.8	16.0	0.25	949	77	0.93	100
(n = 24)		SC 1.2	3.19	94.5	771	142	1.67	54

a Median value.

AUC_{last} = area under the concentration-time curve from day 1 to the last measurement; **C_{max}** = maximum serum concentration; **CL** = clearance; **co** = cross-over; **IV** = intravenous; **op** = open-label; **pl** = parallel; **r** = randomized; **SC** = subcutaneous; **t_{max}** = time to maximum serum concentrations; **$t_{½β}$** = terminal elimination half-life.

with CKD intravenously administered this agent before and after haemodialysis.[4,15]

Following single-dose intravenous or subcutaneous administration of methoxy polyethylene glycol-epoetin beta in patients with CKD on or not on dialysis (table I), clearance was low (0.49–1.67 mL/h/kg) and the mean terminal elimination half-life ($t_{½}β$) was long (77–142 hours).[4,13]

Clearance, volume of distribution and bioavailability of methoxy polyethylene glycol-epoetin beta remained stable with long-term (up to 21 weeks) administration of this agent to patients with CKD.[12,15] For example, mean clearance of this agent was 0.798 L/day after an initial dose, 0.718 L/day after 9 weeks of administration and 0.710 L/day at week 19 or 21.[12]

According to an analysis of 126 patients with CKD, there was no difference in the pharmacokinetic parameters between patients on and not on dialysis.[4]

The pharmacokinetic profile of methoxy polyethylene glycol-epoetin beta was unaffected by the site of administration of a subcutaneous dose. In a study in 42 healthy volunteers who were administered a subcutaneous injection of methoxy polyethylene glycol-epoetin beta 3.0 μg/kg to the abdomen, arm and thigh, mean C_{max} values were 15.7, 14.2 and 16.5 ng/mL, median time to maximum serum concentration values were all 96 hours and mean $t_{½}β$ values were similar (160–164 hours).[11]

Population pharmacokinetic analyses of methoxy polyethylene glycol-epoetin beta demonstrated that the co-variates of sex, race and peritoneal dialysis status did not effect the population pharmacokinetics of this agent. Although bodyweight increased clearance and volume of distribution, these effects were not considered to be clinically relevant.[13]

No pharmacokinetic studies have been conducted in the elderly or paediatric patients. There are no data available regarding the metabolism of methoxy polyethylene glycol-epoetin beta, and the interaction of this agent with other drugs has not been investigated in clinical studies.

4. Therapeutic Efficacy

Four dose-finding phase II[16-19] and six phase III[20-25] randomized, open-label, parallel-group, multicentre trials (see table II for trial acronym definitions) have investigated the efficacy of methoxy polyethylene glycol-epoetin beta in patients aged ≥18 years with anaemia associated with CKD, including those on and not on dialysis. This section will focus on data from the phase III studies.

4.1 Phase III Correction Studies

Two phase III correction studies (table III) investigated the efficacy of intravenous[20] or subcutaneous[21] methoxy polyethylene glycol-epoetin beta administered once every 2 weeks in ESA-naive patients with anaemia associated with CKD who were either on dialysis (AMICUS)[20] or not on dialysis (ARCTOS).[21]

Both studies consisted of an initial 2-week run-in period, after which the patients were randomized to methoxy polyethylene glycol-epoetin beta or comparator (epoetin alfa or beta [AMICUS[20]] or darbepoetin alfa [ARCTOS[21]]). In the AMICUS study,[20] patients then entered a 24-week correction period. In the ARCTOS study,[21] patients entered an

© 2008 Adis Data Information BV. All rights reserved.

18-week correction period followed by a 10-week evaluation period.

Study drugs were adjusted to achieve a haemoglobin response (defined as a haemoglobin level ≥11 g/dL and an increase ≥1.0 g/dL from the patient's baseline haemoglobin level).[20,21] Following achievement of a response in the ARCTOS trial,[21] doses were adjusted to maintain the patient's haemoglobin within ±1 g/dL of the response level and within a target range of 11–13 g/dL. Dose adjustments were performed no more frequently than once monthly. The median dose of methoxy polyethylene glycol-epoetin beta at the time of response was 0.6 μg/kg administered once every 2 weeks.[21]

Patients had CKD stages 3 or 4 (ARCTOS)[21] or stage 5 (AMICUS)[20] and a baseline haemoglobin level of 8–11 g/dL and adequate iron status (serum ferritin ≥100 ng/mL or transferrin saturation ≥20% [or hypochromic red blood cells <10%]). Patients were excluded if they had received an ESA within the last 12 weeks or had a red blood cell transfusion or a gastrointestinal bleed within the last 8 weeks. Patients had no evidence of infection or inflammation as determined by history and laboratory data, including C-reactive protein (>15[21] or >30[20] mg/L).

A primary endpoint in both studies was the haemoglobin response rate during the correction (AMICUS) or correction/evaluation (ARCTOS) period in the intent-to-treat (ITT) population.[20,21] In addition, a coprimary endpoint in the ARCTOS study was the change in haemoglobin levels between baseline and the evaluation period in the per-protocol (PP) population.[21]

Table II. Acronyms of phase III trials involving methoxy polyethylene glycol-epoetin beta

Acronym	Full trial name
AMICUS	C.E.R.**A.** ad**M**inistered **I**ntravenously for anemia **C**orrection and s**US**tained maintenance in dialysis
ARCTOS	**A**dministration of C.E.**R.**A. in **C**KD patients to treat anemia with a **T**wice-monthly **S**chedule
MAXIMA	**M**aintenance of h**A**emoglobin e**X**cels with **I**V ad**M**inistration of C.E.R.**A.**
PROTOS	**P**atients **R**eceiving C.E.R.A. **O**nce a month for the main**T**enance **O**f **S**table haemoglobin
RUBRA	Ta**R**geting s**U**stained haemoglo**B**in in dialysis with IV and SC C.E.**R**.A **A**dministration
STRIATA	**S**tabilizing haemoglobin **Ta**r**G**ets in dialysis following **I**V C.E.R.**A. T**reatment of **A**naemia

4.1.1 Study Results

Haemoglobin response rates were high (93.3%[20] and 97.5%[21]) in recipients of methoxy polyethylene glycol-epoetin beta administered subcutaneously (ARCTOS) or intravenously (AMICUS) once every 2 weeks in both studies during the correction[20] or correction/evaluation[21] period (see table III). In both studies, the lower limit of the 95% confidence interval (CI) for the response rate with methoxy polyethylene glycol-epoetin beta was well above the predefined value of 60% ($p < 0.0001$), demonstrating that methoxy polyethylene glycol-epoetin beta administered once every 2 weeks corrected anaemia.

According to covariate analysis of the ARCTOS data (see table III),[21] the mean difference in the change in haemoglobin between the recipients of methoxy polyethylene glycol-epoetin beta and darbepoetin alfa was 0.16 g/dL (95% CI −0.05, +0.35; $p < 0.0001$). The lower limit of the two-sided 95% CI for the between-group difference was above the pre-specified level of −0.75 g/dL, thus establishing the noninferiority of methoxy polyethylene glycol-epoetin beta to darbepoetin alfa in the correction of anaemia.

Haemoglobin levels increased smoothly and steadily with both treatments in the AMICUS and ARCTOS studies.[20,21] The median times to treatment response were 57 (AMICUS) and 43 (ARCTOS) days with methoxy polyethylene glycol-epoetin beta, 31 days with epoetin alfa (AMICUS) and 29 days in darbepoetin alfa (ARCTOS).[20,21]

Fewer recipients of methoxy polyethylene glycol-epoetin beta than recipients of the comparator had at least one haemoglobin level >13 mg/dL during the first 8 weeks of the ARCTOS trial (12.4% vs 33.5%; $p < 0.001$).[21] However, the between-group difference was not significant in the AMICUS trial (8.2% vs 17.4%).[20]

Red blood cell transfusions were required by 2.5% of methoxy polyethylene glycol-epoetin beta recipients and 6.8% of darbepoetin alfa recipients in the ARCTOS study,[21] and by 5.2% of methoxy polyethylene glycol-epoetin beta recipients and

© 2008 Adis Data Information BV. All rights reserved.

Table III. Outcomes from phase III correction trials of methoxy polyethylene glycol-epoetin beta (C.E.R.A.) in adult patients (pts), aged ≥18 years, with anaemia associated with chronic kidney disease not previously treated with erythropoiesis-stimulating agents.[20,21] Trials were randomized, open-label, multicentre, parallel-group studies and involved a 2-week run-in period, a 24-week correction period[20] or an 18-week correction period and a 10-week evaluation period[21]

Trial	Drug (μg/kg) regimen	No. of pts	Mean baseline Hb level (g/dL)	Hb response rate[a] (% pts) [95% CI]	Mean change in Hb level[b] (g/dL)
Pts on dialysis					
Klinger et al.[20]	IV C.E.R.A. 0.4 q2w[c]	135	9.39	93.3 [87.7, 96.9][d]	2.70
(AMICUS)	IV epoetin alfa or beta according to label tiw	46	9.40	91.3 [79.2, 97.6][d]	2.56
Pts not on dialysis					
Macdougall et al.[21]	SC C.E.R.A. 0.6 q2w	162	10.22	97.5 [93.8, 99.3][d]	2.15[d]
(ARCTOS)	SC darbepoetin alfa 0.45 qw	162	10.15	96.3 [92.1, 98.6][d]	2.00[d]

a An increase ≥1 g/dL vs baseline and a concentration ≥11 g/L without blood transfusion in the intent-to-treat population; Hb levels were to be within the targeted range of 11–13 g/dL.

b Mean change between baseline and the correction[20] or correction/evaluation[21] period in the per-protocol population; adjusted for baseline Hb levels and geographic region.

c C.E.R.A was initiated at a dosage of 0.4 μg/kg q2w, with up-titration to a median dosage of 0.6 μg/kg q2w at the time of response.

d Primary or coprimary endpoint. Assessed at end of the correction period (24 weeks)[20] or at the end of the correction/evaluation period (28 weeks).[21]

Hb = haemoglobin; **IV** = intravenous; **q2w** = once every 2 weeks; **qw** = once every week; **SC** = subcutaneous; **tiw** = three times per week.

4.3% of epoetin beta recipients in the AMICUS trial.[20]

4.2 Phase III Maintenance Studies

The four phase III maintenance studies (MAXIMA,[22] PROTOS,[23] STRIATA,[24] RUBRA[25]; see table IV) investigated the efficacy of intravenous[22,24,25] or subcutaneous[23,25] methoxy polyethylene glycol-epoetin beta in maintaining stable haemoglobin levels in patients with anaemia associated with CKD on dialysis who had been directly converted from another ESA (epoetin alfa or beta,[22,23,25] or darbepoetin alfa[24] administered at a consistent interval for ≥8 weeks).

After a 4-week run-in period during which patients continued with their previous ESA, patients were randomized to methoxy polyethylene glycol-epoetin beta administered every second[22-25] or fourth[22,23] week or to continue with their current ESA dose, schedule and route of administration (see table IV). The initial methoxy polyethylene glycol-epoetin beta dose was determined by the patient's previous weekly ESA dose (see table V). Patients then entered a 28-week titration period, followed by an 8-week evaluation period during which the dose of the active agents was adjusted to maintain the patient's haemoglobin level within 10–13.5 g/dL and within ±1 g/dL of the baseline haemoglobin value. Dose adjustments were allowed no more frequently than once every 4 weeks.

Patients had been receiving haemodialysis or peritoneal dialysis for ≥12 weeks and had a stable baseline haemoglobin of 10.5–13.0 g/dL and an adequate iron status (defined as serum ferritin ≥100 ng/mL or transferrin saturation ≥20% or hypochromic red blood cells <10%). Patients were excluded if they had active infection or inflammation (C-reactive protein >30 mg/L), poorly controlled hypertension, a life expectancy <12 months, or had experienced severe disease within the last 12 weeks, had received a red blood cell transfusion or had a gastrointestinal bleed within the last 8 weeks.[22-25]

The primary endpoint in all studies was the mean change in haemoglobin levels between baseline and the evaluation period (week 29–36) in the PP population.[22-25]

4.2.1 Study Results

The phase III maintenance studies demonstrated that methoxy polyethylene glycol-epoetin beta administered once every 2 or 4 weeks was noninferior to epoetin alfa, epoetin beta (MAXIMA, PROTOS,

© 2008 Adis Data Information BV. All rights reserved.

RUBRA) or darbepoetin alfa (STRIATA) in maintaining stable haemoglobin levels over the evaluation period (weeks 29–36; table IV).[22-25]

The adjusted mean change in haemoglobin level between baseline and evaluation in recipients of both methoxy polyethylene glycol-epoetin beta and the comparators was close to zero, demonstrating that little change in haemoglobin levels had occurred (see table IV).[22-25] In all studies, mean haemoglobin levels during the evaluation period were 11.5–12.1 g/dL.

The lower limit of the two-sided 97.5%[22,23] or 95%[24,25] CI for the between-group difference in the adjusted mean change in haemoglobin level was greater than the prespecified limit of −0.75 g/dL, confirming the noninferiority of methoxy polyethylene glycol-epoetin beta administered intravenously or subcutaneously once every 2 or 4 weeks to its comparators ($p < 0.0001$ for all studies; see table IV). Similar data were obtained in the ITT population.

During the evaluation period, 66–76% of methoxy polyethylene glycol-epoetin beta recipients and 67–68% of recipients of epoetin alfa or beta maintained an average haemoglobin level within ±1 g/dL of baseline values during the evaluation period (see figure 1 for data from MAXIMA, PROTOS and RUBRA).[22,23,25]

During the titration and evaluation period, blood transfusions were required by 6–12% of patients treated with methoxy polyethylene glycol-epoetin beta and 8–11% of patients treated with the comparator.[22-25]

Table IV. Outcomes from phase III maintenance trials of methoxy polyethylene glycol-epoetin beta (C.E.R.A.) in adult patients (pts), aged ≥18 years, with anaemia associated with chronic kidney disease previously treated with other erythropoiesis-stimulating agents (ESAs).[22-25] Trials were randomized, open-label, parallel-group, multicentre studies and involved a 4-week screening period followed by a 28-week titration period and an 8-week evaluation period. The per-protocol analysis data are presented

Trial	Initial drug (μg) regimen	No. of pts	Mean baseline Hb level (g/dL)	Mean change in Hb level (g/dL)[a,b]	Difference between C.E.R.A. vs comparator in mean change in Hb level[a] (g/dL) [97.5%[22,23] or 95%[24,25] CI][c]
Levin et al.[22]	IV C.E.R.A. 60, 100 or 180 q2w[d]	188	11.99	−0.071	+0.004 [−0.215, 0.223]*
(MAXIMA)	IV C.E.R.A. 120, 200 or 360 q4w[d]	172	11.86	−0.025	+0.051 [−0.173, 0.275]*
	IV epoetin alfa or beta according to label tiw to qw	180	11.96	−0.075	
Sulowicz et al.[23]	SC C.E.R.A. 60, 100 or 180 q2w[d]	154	11.70	+0.032	+0.141 [−0.098, 0.380]*
(PROTOS)	SC C.E.R.A. 120, 200 or 360 q4w[d]	153	11.58	−0.131	−0.022 [−0.262, 0.217]*
	SC epoetin alfa or beta according to label tiw to qw	167	11.64	−0.109	
Canaud et al.[24]	SC C.E.R.A. 60, 100 or 180 q2w[d]	123[e]	12.0	+0.063[26]	+0.180 [−0.049, 0.408]*[26]
(STRIATA)	IV darbepoetin alfa according to label qw or q2w	126[e]	11.9	−0.116[26]	
Spinowitz et al.[25]	SC/IV C.E.R.A. 60, 100 or 180 q2w[d,f]	123	11.80	+0.088	+0.118 [−0.116, 0.353]*
(RUBRA)	SC or IV epoetin alfa or beta according to label tiw to qw[f]	133	11.88	−0.030	

a Between baseline and the evaluation period adjusted for covariates.

b Primary endpoint.

c Noninferiority was assumed if the lower limit of the two-sided 97.5% or 95% CI for the between-group difference was greater than −0.75 g/dL.

d The initial dose of C.E.R.A. was based on previous epoetin dose; pts had previously received epoetin <8000 IU, 8000–16 000 or >16 000 IU, respectively.

e Data obtained from the scientific discussion of the European Medicines Agency.[13]

f Administered in pre-filled syringes.

Hb = haemoglobin; **IV** = intravenous; **q2w** = every 2 weeks; **q4w** = every 4 weeks; **qw** = every week; **SC** = subcutaneous; **tiw** = three times per week; * $p < 0.0001$ noninferior vs comparator ESA.

© 2008 Adis Data Information BV. All rights reserved.

Table V. Recommended starting dose of methoxy polyethylene glycol-epoetin beta in patients with anaemia associated with chronic kidney disease previously treated with erythropoiesis-stimulating agents[4]

Previous weekly IV or SC darbepoetin alfa dose (μg/week)	Previous weekly IV or SC epoetin dose (IU/week)	Monthly IV or SC methoxy polyethylene glycol-epoetin beta dose (μg/month)
<40	<8000	120
40–80	8000–16 000	200
>80	>16 000	360

IV = intravenous; **SC** = subcutaneous.

5. Pharmacoeconomics

Data (presented in an abstract) from an observational time and motion study suggest that once-monthly administration of methoxy polyethylene glycol-epoetin beta may reduce the overall time and cost associated with anaemia management in patients with anaemia associated with CKD on dialysis compared with the use of traditional ESAs.[27] In 12 dialysis centres in the UK and Germany, a total of 461 time and motion observations were collected.[27] Costs (2006) were calculated from the time and supplies used for ESA administration (excluding drug acquisition costs) and national estimates of wages for the healthcare workers involved. The estimated average total annual costs for traditional ESA treatment for a hypothetical centre of 100 dialysis patients were €17 031 and £18 739 for the German and UK centre.[27] Assuming 100% conversion from ESAs to once-monthly methoxy polyethylene glycol-epoetin beta in a hypothetical centre of 100 dialysis patients, the estimated time savings were 37–43 days per year and the estimated reduction in annual costs were €9798 (−59%) for the German centre and £6615 (−35%) for the UK centre.[27]

6. Tolerability

A pooled safety analysis of data from four phase II and six phase III trials was reported in the European SPC,[4] the scientific discussion of the EMEA[13] and the US prescribing information.[15] This analysis involved 2737 patients with anaemia associated with CKD; 1789 were treated with methoxy polyethylene glycol-epoetin beta and 948 were treated with a comparator ESA (epoetin alfa, epoetin beta, or darbepoetin alfa). Methoxy polyethylene glycol-epoetin beta was administered once every 2 or 4 weeks in most patients; for >12 months in 1144 patients and for >6 months in 1451 patients.[15] Approximately 85% of patients were receiving dialysis.[15]

According to this pooled analysis, overall adverse event rates were 88.8% in recipients of methoxy polyethylene glycol-epoetin beta and 90.9% in recipients of the comparator ESA; treatment-related adverse events occurred in 6% and 3% of patients, respectively.[13] Hypertension (13%), diarrhoea (11%) and nasopharyngitis (11%) were the most commonly reported adverse events in recipients of methoxy polyethylene glycol-epoetin beta.[15] Most adverse events were mild to moderate in severity, and were consistent with the co-morbidities known in this patient group. Serious adverse events occurred in 37% of methoxy polyethylene glycol-epoetin beta recipients and 40% of recipients of the other ESAs.[13] Serious gastrointestinal haem-

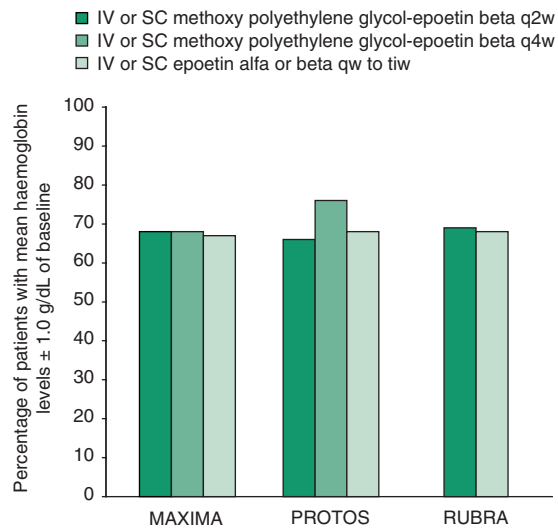

Fig. 1. Percentage of patients (intent-to-treat population) maintaining mean haemoglobin levels within ±1 g/dL of baseline values during an evaluation period in three phase III maintenance trials (MAXIMA,[22] PROTOS[23] and RUBRA[25]). Patients had anaemia associated with chronic kidney disease and were undergoing dialysis. Patients were administered intravenous (IV)[22,25] or subcutaneous (SC)[23,25] methoxy polyethylene glycol-epoetin beta or comparator (IV[22,25] or SC[23,25] epoetin alfa or beta). See table IV for further details of study design, drug dosage and table II for definition of study acronyms. **q2w** = every 2 weeks; **q4w** = every 4 weeks; **qw** = once a week; **tiw** = three times a week.

© 2008 Adis Data Information BV. All rights reserved.

orrhage occurred in 1.2% of methoxy polyethylene glycol-epoetin beta recipients and 0.2% of recipients of the comparators. Serious haemorrhagic adverse events of all types occurred in a similar percentage of patients in either treatment group (5% and 4%).[15] The incidence of death in the randomized phase III population was 5.7% in the methoxy polyethylene glycol-epoetin beta group and 6.1% in the comparator group.[13]

Adverse events reported in the MAXIMA trial in recipients of methoxy polyethylene glycol-epoetin beta or its comparator (epoetin alfa) are shown in figure 2.[22]

Platelet levels were lower with methoxy polyethylene glycol-epoetin beta than comparators, but remained within the normal range. Platelet counts <100 x 10^9 were reported in 7% of methoxy polyethylene glycol-epoetin beta recipients and 4% of recipients of other ESAs.[15]

Neutralizing antibodies to erythropoietin have been reported in patients with pure red cell aplasia and severe anaemia, with or without other cytopenias, in patients receiving other ESAs during postmarketing experience. However, antibodies (assessed using enzyme-linked immunosorbent assay) to methoxy polyethylene glycol-epoetin beta or to epoetin were not detected in 1789 patients treated with this agent during the phase II or III clinical trials.[13,15] No cases of red cell aplasia have been reported in recipients of methoxy polyethylene glycol-epoetin beta.[18]

No clinically relevant changes in vital signs, iron levels or laboratory parameters were reported during the phase III studies.[20-25]

Less pain was associated with subcutaneous administration of methoxy polyethylene glycol-epoetin beta than subcutaneous administration of darbepoetin alfa in a randomized, placebo-controlled, crossover study in 84 healthy volunteers.[28] Pain (assessed on a 100 mm visual analog scale [VAS] immediately after drug administration) was 21.5 and 33.4 mm, respectively ($p < 0.0001$). Pain had almost disappeared in all recipients 1 hour after drug administration (pain VAS 0.26 mm with methoxy polyethylene glycol-epoetin and 0.82 mm with darbepoetin alfa).

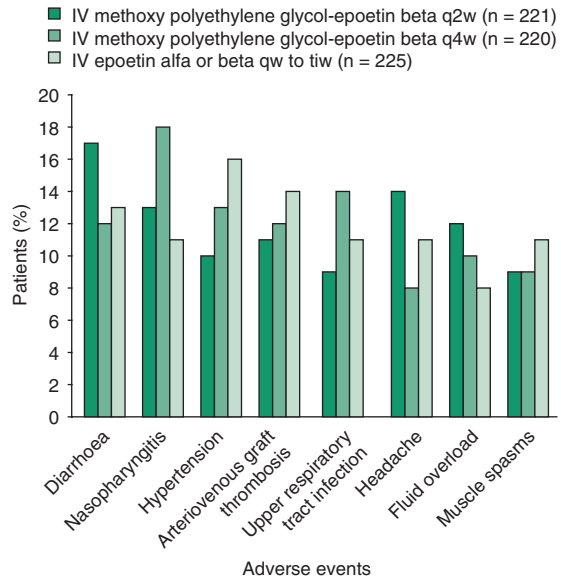

Fig. 2. Incidence of adverse events that occurred in ≥10% of recipients of intravenous (IV) methoxy polyethylene glycol-epoetin beta or comparator (IV epoetin alfa) in the randomized, open-label, parallel-group, multicentre MAXIMA study in patients with anaemia associated with chronic kidney disease.[22] See section 4 for further details of dosage and study design. **q2w** = once every 2 weeks; **q4w** = once every 4 weeks; **qw** = once weekly; **tiw** = three times a week.

7. Dosage and Administration

Methoxy polyethylene glycol-epoetin beta is approved in Europe[4] and in the US[15] for the treatment of anaemia associated with CKD, including those on and not on dialysis. The efficacy and safety of this agent has not been established in other indications.[4] This section will focus on administration details approved for Europe.

Methoxy polyethylene glycol-epoetin beta may be administered subcutaneously (into the abdomen, arm or thigh) or intravenously.[4] Following administration of this agent, haemoglobin levels should be monitored every 2 weeks until they are stabilized and then periodically thereafter.[4]

In ESA-naive patients, the recommended starting dose is 0.6 μg/kg, to be administered once every 2 weeks as a subcutaneous or intravenous injection in order to reach a haemoglobin level >11 g/dL.[4] If haemoglobin levels increase by <1.0 g/dL over a month, then the dose may be increased by approximately 25%. Further increases of approximately

© 2008 Adis Data Information BV. All rights reserved.

25% may be made once monthly until the individual target haemoglobin level is reached.[4]

Patients currently being treated with ESAs can be directly converted to methoxy polyethylene glycol-epoetin beta administered once a month as a single intravenous or subcutaneous injection. The starting dose of this agent is based on the calculated weekly equivalent dose of darbepoetin alfa or epoetin at the time of conversion (see table V). The monthly dose of methoxy polyethylene glycol-epoetin beta may be adjusted by approximately 25% in order to reach a haemoglobin level within the target range.[4]

In patients currently treated with ESAs and in those naive to ESAs, if the haemoglobin level increases by more than 2 g/dL in 1 month or if the haemoglobin level is approaching 12 g/dL, then the methoxy polyethylene glycol-epoetin beta dose should be reduced by approximately 25%. If the haemoglobin levels continue to increase, then methoxy polyethylene glycol-epoetin beta administration should be interrupted until haemoglobin levels begin to decrease (a decrease of approximately 0.35 g/dL per week is expected). Therapy should then be resumed at a dose approximately 25% below the previously administered dose. Dose adjustments should not be made more frequently than once a month.[4]

No adjustment of the starting dosage of methoxy polyethylene glycol-epoetin beta is required in patients aged >65 years. Clinical data regarding the use of this agent in children or adolescents aged <18 years are not available and so the use of this agent in this patient group is not recommended.[4]

Supplementary iron therapy is recommended in all patients with serum ferritin levels <100 μg/L or transferrin saturation <20%. The patient's iron status should be evaluated prior to and during treatment in order to ensure effective erythropoiesis.[4]

Local manufacturer's prescribing information should be consulted for comprehensive dosage and administration guidelines.

8. Place of Methoxy Polyethylene Glycol-Epoetin Beta in Patients with Anaemia Associated with Chronic Kidney Disease

The prevalence of CKD is reflected in the number of patients with end-stage renal disease.[29,30] In the US, the incidence of end-stage renal disease is estimated to be 347 patients per million population (2005 data).[31] Varying incidences of end-stage renal disease have been reported in Europe; for example, the unadjusted incidence was 93 patients per million population in Finland, Norway and England and ranged up to 174 patients per million population in Greece (2005 data).[32] However, the number of patients with end-stage renal disease probably underestimates the total number of patients with CKD, with up to 50-fold more patients estimated to have earlier stages of the disease.[30]

CKD is characterized by a progressive reduction in function of the renal parenchyma.[1,33] CKD has been defined as either kidney damage or a glomerular filtration rate <60 mL/min/1.73 m^2, for ≥3 months.[33] Markers of kidney damage include abnormalities in the composition of the blood or urine, or abnormalities in kidney imaging tests. The clinical course of this disease has also been divided into a continuum of five stages based on glomerular filtration rate.

Anaemia is a common complication of patients with CKD.[34] It is already observed in many patients with early stages of CKD, and in most patients once CKD has progressed to stage 5.[35] The early initiation of anaemia management in patients with CKD, prior to dialysis, may slow the progression of kidney disease,[36] delay the initiation of renal replacement therapy,[36] reduce the risk of cardiac disease and improve survival.[37] The management of anaemia also improves HR-QOL and reduces transfusions and hospitalizations.[38]

According to the European Best Practice Guidelines (EBPG), all patients with CKD, irrespective of the stage of the disease, should be investigated for possible anaemia treatment.[1] A work-up for diagnosis of anaemia should be considered if haemoglobin levels are <11.5 g/dL in adult females, <13.5 g/dL in adult men aged <70 years and <12.0 g/dL in adult men aged >70 years (Europe),[1] or

© 2008 Adis Data Information BV. All rights reserved.

<12.0 g/dL in females and <13.5 g/dL in males (US).[2]

Prior to the mid-1980s, blood transfusion was the only available treatment option in patients with anaemia associated with CKD; however, since this time, the development of epoetin has transformed the management of these patients.[3] Epoetin alfa is available in both the US and Europe, while epoetin beta is available in Europe only. A modified recombinant erythropoietin, darbepoetin alfa, is also available in both Europe and the US. Methoxy polyethylene glycol-epoetin beta is an ESA that is available in Europe and has recently been approved for use in the US.

The US National Kidney Foundation Kidney Diseases Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guideline and Clinical Practice Recommendations,[2,39] the EBPG[1] and National Institute for Health and Clinical Excellence guidelines[40] recommend ESAs for the treatment of anaemia in patients with renal insufficiency.

ESAs are glycated proteins with a peptide core of 165 amino acids; differences in carbohydrate content are responsible for their different half-lives and consequent dosing frequency (see table VI).[42] A major limitation of epoetin, the first ESA to be marketed, is that it is usually administered by injection two or three times weekly. In order to develop a longer-acting erythropoietic agent, additional *N*-linked glycosylation sites were introduced by site-directed mutagenesis into erythropoietin.[44] The resulting 37.1 kDa glycoprotein, darbepoetin alfa, is larger and heavier, with a half-life 3-fold that of epoetin (see table VI). This characteristic has allowed less frequent administration, with most patients receiving injections once weekly or once every 2 weeks.[42,45] In addition, once monthly administration of darbepoetin alfa is indicated during the maintenance phase (European label) for patients not on dialysis who have achieved target haemoglobin levels with administration of this agent once every 2 weeks.[45] The integration of a long linear chain of methyl polyethylene glycol into glycosylated erythropoietin resulted in the generation of methoxy polyethylene glycol-epoetin beta (see section 2). The agent has a longer half-life than other ESAs (see table VI) and allows administration to occur once every 2 weeks during the correction phase or once every 4 weeks during the maintenance phase in CKD patients both on or not on dialysis.

Table VI. Half-lives of erythropoiesis-stimulating agents (ESAs)

ESA	Population	Mean half-life (h)	
		intravenous administration	subcutaneous administration
Epoetin alfa	Healthy volunteers[41]	6.8	19.4
Epoetin beta	Healthy volunteers[41]	8.8	24.2
Darbepoetin alfa	CKD pts not on dialysis[42]		69.6
	CKD pts on dialysis[43]	25.3	48.8
Methoxy polyethylene glycol-epoetin beta[a]	CKD pts not on dialysis[13]b	77	142
	CKD pts on dialysis[13]b	134	139
	Healthy volunteers[12]	133	137

a Small pt numbers and high inter-pt variability may have contributed to the wide numerical range obtained for the half-lives.

b There was no difference in the pharmacokinetic parameters of pts on and not on dialysis in an analysis of 126 pts with CKD.[4]

CKD = chronic kidney disease; **pt(s)** = patient(s).

Iron deficiency may occur with ESA administration because of the increase in erythropoiesis and the increased demand for iron. Sufficient iron should also be administered to maintain serum ferritin levels >100 μg/L and transferrin saturation >20%.[1,39]

Other potential therapies used in the management of anaemia include carnitine, androgens, glutathione, ascorbate (vitamin C) and tocopherol (vitamin E) supplements. However, these agents are not recommended for general or routine use, as data supporting their use are inconclusive.[1,2]

Control of haemoglobin levels within evidence-based targets is important with ESA treatment.[46,47] Haemoglobin levels below the target range represent a loss of therapeutic benefit, increased risk of hospitalization and increased risk of mortality.[48-50] A retrospective study, in 159 720 haemodialysis patients receiving epoetin therapy demonstrated that persistently and transiently low haemoglobin levels and highly variable haemoglobin levels were associated with increased risk of

© 2008 Adis Data Information BV. All rights reserved.

death. Further analysis of the results indicated that the amount of time spent with a low haemoglobin level was a key factor, with Bayesian modelling indicating that patients with ≥3 months with haemoglobin levels <11 g/dL have the highest mortality rates.[46,47]

Controversy exists as to what upper limit of the target haemoglobin levels represents maximum HR-QOL benefits, but minimum ESA-related adverse effects. In the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency)[51] trial that enrolled 1432 patients with stage 3 and 4 CKD, there was an increased risk (34%; p = 0.03) of the composite endpoint (death, myocardial infarction, heart failure and stroke) with a higher haemoglobin target of 13.5 g/dL than in those with a lower target (11.3 g/dL).[51] In the CREATE (Cardiovascular Risk Reduction by Early Anaemia Treatment with Epoetin Beta) trial that enrolled 605 patients with CKD,[52] the incidence of a cardiovascular events was 58 events in patients with a target haemoglobin level of 13.0–15.0 g/dL and 47 events in those with a target of 10.5–11.5 g/dL; the between-group difference was not significant. A recent meta-analysis of nine randomized clinical trials in anaemic patients with CKD treated with erythropoietin demonstrated that there was a 17% increased risk of all-cause mortality (p = 0.03) and a 16% increased risk of arteriovenous access thrombosis (p = 0.001) in patients with a higher target haemoglobin level (12–16 g/dL).[47] However, the methodology, design, execution and analysis of the CHOIR and CREATE trials have been questioned.[53,54] Moreover, the pathogenesis of the adverse effects associated with the higher haemoglobin levels in these trials is not clear, and may involve the effect of achieving the higher haemoglobin level itself or other mechanisms such as the dose of the ESAs, use of iron supplementation, increased blood pressure or ESA hypo-responsiveness.[46]

Arguably, it may not be until the results of larger, adequately powered, well designed trials such as TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy), which is examining the effects of normalizing haemoglobin in patients with type 2 diabetes mellitus, and chronic kidney failure and anaemia, become available that a clear picture of the impact of ESAs and target haemoglobin levels will emerge.[53,54] It has been recommended that such future large-scale controlled trials should be accompanied by relevant laboratory correlative studies (e.g. pretreatment and post-treatment platelet and coagulation function tests) and appropriate study endpoints (including survival, cardiovascular endpoints and HR-QOL).[54] In contrast, other authors have argued that on the basis of the currently available data, further trials to determine haemoglobin target levels are no longer required, should be stopped or, at least, the reasons for their continuation should be made fully available.[55] They suggest that future trials should focus on assessing the impact of ESA dose (rather than haemoglobin level) on mortality and cardiovascular endpoints.

In the light of this currently available data, the US FDA has issued a 'black box' warning underscoring the risks for ESAs.[46] The US label contains a warning that patients with renal failure treated with ESAs experienced greater risks for death and serious cardiovascular events when higher versus lower haemoglobin levels (13.5 vs 11.3 g/dL; 14 vs 10 g/dL) were targeted in two clinical trials.[15] The 'black box' also warns that methoxy polyethylene glycol-epoetin beta is not indicated for the treatment of anaemia in patients with cancer.[15]

The FDA recommends that for anaemic patients with chronic renal failure haemoglobin levels should be maintained within 10–12 g/dL.[56] These recommendations differ somewhat from other current US[2,39] and European[1,40] guidelines for anaemia management in patients with CKD, which recommend the maintenance of haemoglobin levels ≥11 g/dL. The 2007 update of the NKF-KDOQI haemoglobin target recommends that selection of the haemoglobin target and selection of the haemoglobin level at which ESA therapy is initiated in the individual patient should include consideration of potential benefits (including improvement in HR-QOL and avoidance of transfusion) and potential harms (including the risk of life-threatening adverse events).[39] In dialysis and non-dialysis CKD patients treated with ESAs, the selected haemoglobin target should generally be 11–12 g/dL. These updated guidelines also recommend that in dialysis and non-dialysis CKD patients receiving ESA therapy, the haemoglobin target should not be above 13.0 g/dL.[39] EBPG recommends setting individual targets

© 2008 Adis Data Information BV. All rights reserved.

for each patients with the upper limit set according to co-morbid conditions.[1] A haemoglobin level >12 g/dL is not recommended in patients with severe cardiovascular disease (New York Heart Association class III–IV). However, it should be noted that these guidelines were published before the results of the CREATE and CHOIR trials became available.

Even when haemoglobin levels reach the target level, there can be substantial variation with the use of epoetin, with patients cycling in and out of the therapeutic range.[57-59] In one study in 281 dialysis patients treated with epoetin, although mean haemoglobin levels (11.8 g/dL) were within the target range, more than 90% of patients experienced cycling (≥1 cycle of amplitude >1.5 g/dL of >8 weeks duration). Patients in this study experienced about three excursions per year and required about six dose adjustments per year.

An ideal ESA should thus not only be capable of achieving target haemoglobin levels, but also of ensuring that the levels reached remain stable over an extended period of time. Methoxy polyethylene glycol-epoetin beta has a pharmacological profile (see sections 2 and 3) that allows administration over longer intervals (up to 1 month). Potentially, this agent should stimulate erythropoiesis at a more constant rate (rather than the intermittent stimulation provided by traditional ESA), thus ensuring more constant and stable haemoglobin levels.

Phase III correction trials (AMICUS and ARCTOS) demonstrated that methoxy polyethylene glycol-epoetin beta administered intravenously or subcutaneously once every 2 weeks was associated with a smooth and steady rise in haemoglobin levels in patients with CKD (both on and not on dialysis) who had not previously received ESA. Response rates were high (93.3–97.5%), with the change in mean haemoglobin level between baseline and the evaluation period being noninferior to darbepoetin alfa in the ARCTOS study (see section 4). Phase III maintenance trials in patients previously treated with an ESA also demonstrated that methoxy polyethylene glycol-epoetin beta once every 2 or 4 weeks maintained stable haemoglobin levels (within ±1 g/dL of baseline and within a range of 10–13.5 g/dL) over the evaluation period (weeks 29–36) when patients on dialysis were directly converted from other ESAs that were administered one to three times per week (see section 4). Consistent with the similar $t_{1/2}\beta$ values achieved when methoxy polyethylene glycol-epoetin beta is administered via either the intravenous or subcutaneous route of administration (see table I), the route of administration had no impact on the primary efficacy results, with haemoglobin levels remaining stable with both routes of administration of this agent. Moreover, the phase III studies demonstrated the non-inferiority of this agent to its comparators (see section 4). The effect of maintaining haemoglobin levels within the recommended US[39] and European[1] target range on mortality and cardiovascular endpoints has yet to be investigated in long-term trials.

Methoxy polyethylene glycol-epoetin beta was generally well tolerated in the phase II and III trials, with most adverse events being of mild to moderate severity, consistent with the co-morbidities known to occur in this patient group and similar to those reported with other ESAs (section 6). Hypertension, diarrhoea and nasopharyngitis were the most commonly reported adverse events. Serious adverse events occurred in a similar percentage of recipients of methoxy polyethylene glycol-epoetin beta and its comparators (38% vs 42%). Hypertension is commonly associated with use of ESAs and results from multiple mechanisms (including expansion of blood volume, increased blood viscosity and reversal of hypoxic vasodilation).[60]

Pure red cell aplasia and severe anaemia, with or without other cytopenias, have been associated with the development of neutralizing antibodies to erythropoietin in patients treated with other ESA (generally with subcutaneous administration or with formulations of epoetin available outside the US).[60,61] No red cell aplasia has been reported in phase III trials involving methoxy polyethylene glycol-epoetin beta. No clinically relevant changes in vital signs, iron levels or laboratory parameters were reported during the phase III studies.

Given that erythropoietin receptors may be expressed on the surface of a variety of tumours, there is a concern that ESAs may stimulate the growth of malignancies. In November 2007, the FDA approved new labelling strengthening the warnings regarding the use of epoetin alfa and darbepoetin alfa based on the outcomes of six studies showing

© 2008 Adis Data Information BV. All rights reserved.

decreased survival and/or tumour progression in patients with cancer receiving an ESA.[62] A dose-ranging phase II trial in patients with anaemia associated with chemotherapy for advanced non-small cell lung cancer was suspended because there were significantly more deaths in recipients of methoxy polyethylene glycol-epoetin beta than recipients of other ESAs.[15,63]

Pharmacoeconomic studies suggest that treatment of anaemia associated with CKD to recommended targets may result in savings of costs and healthcare resources.[64-66] A retrospective claims analysis of US health plan members demonstrated that in 26 244 patients with anaemia associated with CKD, ESA use was associated with mean total cost savings of $US411 per patient per month. This cost saving reflected reduced inpatient and emergency department visits and costs, and was associated with lower inpatient mortality and a longer time to dialysis. The longer-acting methoxy polyethylene glycol-epoetin beta has the potential to further reduce the cost associated with drug administration. Data obtained from an observational time and motion study conducted in the UK and Germany were used to estimate the time and costs saved by a hypothetical conversion from traditional ESAs to methoxy polyethylene glycol-epoetin beta in a dialysis centre of 100 patients. Annual costs (excluding drug acquisition costs) were estimated to be reduced by as much as 59% as a result of conversion to the longer-acting ESA (see section 5). However, the real cost-benefit of methoxy polyethylene glycol-epoetin beta cannot be determined until the price of this agent is taken into consideration.

In conclusion, in patients with anaemia associated with CKD, subcutaneous or intravenous methoxy polyethylene glycol-epoetin beta achieved a high haemoglobin response rate (ESA-naive patients) when administered once every 2 weeks and maintained stable haemoglobin levels (patients previously treated with ESAs) when administered once monthly.

Disclosure

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

References

1. Locatelli F, Aljama P, Bárány P, et al. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. Nephrol Dial Transplant 2004 May; 19 Suppl. 2: ii1-47
2. National Kidney Foundation - Kidney Disease Outcomes Quality Initiative. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis 2006 May; 47 (5 Suppl. 3): S11-145
3. Macdougall IC, Eckardt K-U. Novel strategies for stimulating erythropoiesis and potential new treatments for anaemia. Lancet 2006 Sep 9; 368 (9539): 947-53
4. F. Hoffmann-La Roche Ltd. Summary of product characteristics: MIRCERA (methoxy polyethylene glycol-epoetin beta) [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/mircera/H-739-PI-en.pdf [Accessed 2008 Mar 14]
5. Macdougall IC, Robson R, Opatrna S, et al. Pharmacokinetics and pharmacodynamics of intravenous and subcutaneous continuous erythropoietin receptor activator (C.E.R.A.) in patients with chronic kidney disease. Clin J Am Soc Nephrol 2006 Nov; 1 (6): 1211-5
6. Jarsch M, Brandt M, Lanzendörfer M, et al. Comparative erythropoietin receptor binding kinetics of C.E.R.A. and epoetin-β determined by surface plasmon resonance and competition binding assay. Pharmacology 2008 Sep 28; 81 (1): 63-9
7. Jarsch M, Kubbies M, Lanzendörfer M, et al. C.E.R.A. acts differently at the erythropoietin (EPO) receptor compared with epoetin beta: UT-7 and CD34+ cell stimulation assays [abstract no. SA-PO209]. 39th Annual Meeting and Scientific Exhibition of the American Society of Nephrology: Renal Week; 2006 Nov 14-19; San Diego (CA)
8. Tare N, Pill J, Haselbeck A. Preclinical pharmacodynamics and pharmacokinetics of CERA (continuous erythropoiesis receptor activator): a new erythropoietic agent for anaemia management in patients with kidney disease [abstract no. M526]. 41st Congress of the European Renal Association and the European Dialysis and Transplant Association; 2004 May 15-18; Lisbon
9. Tillmann HC, Kuhn B, Kränzlin B, et al. Efficacy and immunogenicity of novel erythropoietic agents and conventional rhEPO in rats with renal insufficiency. Kidney Int 2006 Jan; 69 (1): 60-7
10. Reigner B, Jordan P, Pannier A, et al. CERA (continuous erythropoiesis receptor activator), a novel erythropoietic agent: dose-dependent response in phase I studies [abstract no. 2943]. 39th Annual Meeting of the American Society of Clinical Oncology; 2003 May 31-Jun 3; Chicago (IL)
11. Fishbane S, Pannier A, Liogier X, et al. Pharmacokinetic and pharmacodynamic properties of methoxy polyethylene glycol-epoetin beta are unaffected by the site of subcutaneous administration. J Clin Pharmacol 2007 Nov; 47 (11): 1390-7
12. Locatelli F, Reigner B. C.E.R.A.: pharmacodynamics, pharmacokinetics and efficacy in patients with chronic kidney disesase. Expert Opin Investig Drugs 2007; 16 (10): 1649-61
13. European Medicines Association. Scientific discussion: summary of product characteristics: MIRCERA (methoxy polyethylene glycol-epoetin beta) [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/mircera/H-739-en6.pdf [Accessed 2008 Apr 20]
14. Dougherty FC, Reigner B, Jordan P, et al. CERA (continuous erythropoiesis receptor activator): dose-response, pharmacokinetics, and tolerability in phase I multiple ascending dose studies. Support Oncol 2005; 3 (2 Suppl. 1): 10-1

© 2008 Adis Data Information BV. All rights reserved.

15. Hoffmann-La Roche Inc. Full prescribing information (US): Mircera® (methoxy polyethylene glycol-epoetin beta). Nutley (NJ): Hoffmann-La Roche Inc., 2007
16. de Francisco ALM, Sulowicz W, Klinger M, et al. Continuous Erythropoietin Receptor Activator (C.E.R.A.) administered at extended administration intervals corrects anaemia in patients with chronic kidney disease on dialysis: a randomised, multicentre, multiple-dose, phase II study. Int J Clin Pract 2006 Dec; 60 (12): 1687-96
17. Besarab A, Salifu MO, Lunde NM, et al. Efficacy and tolerability of intravenous continuous erythropoietin receptor activator: a 19-week, phase II, multicenter, randomized, open-label, dose-finding study with a 12-month extension phase in patients with chronic renal disease. Clin Ther 2007 Apr; 29 (4): 626-39
18. Locatelli F, Villa G, de Francisco ALM, et al. Effect of a continuous erythropoietin receptor activator (C.E.R.A.) on stable haemoglobin in patients with CKD on dialysis: once monthly administration. Curr Med Res Opin 2007 May; 23 (5): 969-79
19. Provenzano R, Besarab A, Macdougall IC, et al. The continuous erythropoietin receptor activator (C.E.R.A.) corrects anemia at extended administration intervals in patients with chronic kidney disease not on dialysis: results of a phase II study. Clin Nephrol 2007 May; 67 (5): 306-17
20. Klinger M, Arias M, Vargemezis V, 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 hemodialysis or peritoneal dialysis: a randomized trial. Am J Kidney Dis 2007; 50 (6): 989-1000
21. Macdougall IC, Walker R, Provenzano R, et al. C.E.R.A. corrects anemia in patients with chronic kidney disease not on dialysis: results of a randomized clinical trial. Clin J Am Soc Nephrol 2008; 3 (2): 337-47
22. Levin NW, Fishbane S, Cañedo FV, 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 Oct 20; 370 (9596): 1415-21
23. Sulowicz W, Locatelli F, Ryckelynck J-P, et al. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. Clin J Am Soc Nephrol 2007 Jul; 2 (4): 637-46
24. Canaud B, Braun J, Locatelli F, et al. Intravenous (IV) C.E.R.A. (continuous erythropoietin receptor activator) administered once every 2 weeks maintains stable haemoglobin levels in patients with chronic kidney disease on dialysis [abstract no. SP425]. Nephrol Dial Transplant 2006 Jul; 21: iv157
25. Spinowitz B, Coyne DW, Lok CE, et al. C.E.R.A. maintains stable control of hemoglobin in patients with chronic kidney disease on dialysis when administered once every two weeks. Am J Nephrol 2008; 28: 280-9
26. Data on file. Hoffmann-La Roche Ltd., 2008
27. Saueressig U, Sapède C, De Cock E, et al. Staff time and costs for anaemia management with erythropoietic stimulating agents in patients on haemodialysis [abstract no. SaP341]. Nephrol Dial Transplant 2007; 22 Suppl. 6: V1347-8
28. Pannier A, Jordan P, Dougherty FC, et al. Subcutaneous injection pain with C.E.R.A., a continuous erythropoietin receptor activator, compared with darbepoetin alfa. Curr Med Res Opin 2007 Oct 24; 23 (12): 3025-32
29. Hamer RA, El Nahas AM. The burden of chronic kidney disease. BMJ 2006; 332: 563-4
30. El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005; 365 (9456): 331-40
31. Collins AJ, Kasiske B, Herzog C, et al. Excerpts from the United States Renal Data System 2007 Annual Data Report. Am J Kidney Dis 2008; 51: S1-320
32. European Renal Association - European Dialysis and Transplant Association. ERA-EDTA Registry Annual Report 2005 [online]. Available from URL: http://www.era.edta-reg.org [Accessed 2008 Jan 8]
33. National Kidney Foundation - Kidney Disease Outcomes Quality Initiative. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (Suppl. 1): S1-266
34. Astor BC, Muntner P, Levin A, et al. Association of kidney function with anemia: the Third National Health and Nutrition Examination Survey (1988-1994). Arch Intern Med 2002; 162 (12): 1401-8
35. McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 2004; 20 (9): 1501-10
36. Gouva C, Nikolopoulos P, Ioannidis JPA, et al. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Kidney Int 2004; 66 (2): 753-60
37. Lu WX, Jones-Burton C, Zhan M, et al. Survival benefit of recombinant human erythropoietin administration prior to onset of end-stage renal disease: variations across surrogates for quality of care and time. Nephron Clin Pract 2005; 101: c79-86
38. Jones M, Ibels L, Schenkel B, et al. Impact of epoetin alfa on clinical end points in patients with chronic renal failure: a meta-analysis. Kidney Int 2004; 65: 757-67
39. National Kidney Foundation - Kidney Disease Outcomes Quality Initiative. KDOQI clinical practice guideline and clinical practice recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. Am J Kidney Dis 2007; 50 (3): 471-530
40. National Institute for Health and Clinical Excellence. Anaemia management in people with chronic kidney disease [online]. Available from URL: http://www.nice.org.uk/guidance/cg39/niceguidance/pdf/English [Accessed 2008 Mar 14]
41. Halstenson CE, Macres M, Katz SA, et al. Comparative pharmacokinetics and pharmacodynamics of epoetin alfa and epoetin beta. Clin Pharmacol Ther 1991; 50: 702-12
42. Padhi D, Ni L, Cooke B, et al. An extended terminal half-life for darbepoetin alfa: results from a single-dose pharmacokinetic study in patients with chronic kidney disease not receiving dialysis. Clin Pharmacokinet 2006; 45 (5): 503-10
43. Macdougall IC, Gray SJ, Elston O, et al. Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. J Am Soc Nephrol 1999; 10: 2392-5
44. Robinson DM, Easthope SE. Darbepoetin alfa: its use in anemia associated with chronic kidney disease. Biodrugs 2005; 19 (5): 327-43
45. Amgen Europe B.V. Darbepoetin alfa (Aranesp®): summary of product characteristics [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/aranesp/H-332-PI-en.pdf [Accessed 2008 Mar 3]
46. Fishbane S, Besarab A. Mechanism of increased mortality with erythropoietin treatment to higher hemoglobin targets. Clin J Am Soc Nephrol 2007; 2: 1274-82
47. Phrommintikul A, Haas SJ, Elsik M, et al. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. Lancet 2007 Feb 3; 369 (9559): 381-8
48. Ishani A, Solid CA, Weinhandl ED, et al. Association between number of months below K/DOQI haemoglobin target and risk of hospitalization and death. Nephrol Dial Transplant 2008 May; 23 (5): 1682-9

© 2008 Adis Data Information BV. All rights reserved.

49. Regidor DL, Kopple JD, Kovesdy CP, et al. Associations between changes in hemoglobin and administered erythropoiesis-stimulating agent and survival in hemodialysis patients. J Am Soc Nephrol 2006 Apr; 17 (4): 1181-91

50. Gilbertson DE, Ebben JP, Foley RN, et al. Hemoglobin level variability: associations with mortality. Clin J Am Soc Nephrol 2007 Nov; 3: 133-8

51. Singh AK, Szczech L, Tang KL, et al. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006; 355: 2085-98

52. Drüeke TB, Locatelli F, Clyne N, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006; 355: 2071-84

53. Levin A. Understanding recent haemoglobin trials in CKD: methods and lesson learned from CREATE and CHOIR. Nephrol Dial Transplant 2007; 22: 309-12

54. Tefferi A. Pharmaceutical erythropoietin use in patients with cancer: is it time to abandon ship or just drop anchor? Mayo Clin Proc 2007 Nov; 82 (11): 1316-8

55. Strippoli GFM, Tognoni G, Navaneethan SD, et al. Haemoglobin targets: we were wrong, time to move on. Lancet 2007 Feb 3; 369 (9559): 346-50

56. National Kidney Foundation. Preliminary anemia guideline update: new evidence spurs re-examination of 2006 recommendations [online]. Available from URL: http://www.kidneyorg/news/newsroom/newsitem.cfm?id=380 [Accessed 2008 March 26]

57. Fishbane S, Berns JS. Hemoglobin cycling in hemodialysis patients treated with recombinant human erythropoietin. Kidney Int 2005; 68: 1337-43

58. Collins AJ, Brenner RM, Ofman JJ, et al. Epoetin alfa use in patients with ESRD; an analysis of recent US prescribing patterns and hemoglobin outcomes. Am J Kidney Dis 2005; 46 (3): 481-8

59. Berns JS, Elzein H, Lynn RI, et al. Hemoglobin variability in epoetin-treated hemodialysis patients. Kidney Int 2003; 64: 1514-21

60. Wish JB, Coyne DW. Use of erythropoiesis-stimulating agents in patients with anemia of chronic kidney disease: overcoming the pharmacological and pharmacoeconomic limitations of existing therapies. Mayo Clin Proc 2007 Nov; 82 (11): 1371-80

61. Bennett CL, Luminari S, Nissenson AR, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med 2004; 351 (14): 1403-8

62. U.S. Food and Drug Administration. Communication about an ongoing safety review: erythropoiesis-stimulating agents (ESAs) epoetin alfa (marketed as Procite Epogen) darbepoetin alfa (marketed as Aranesp) [online]. Available from URL: http://www.fda.gov/cder/drug/early_comm/ESA.htm [Accessed 2008 Jan 7]

63. Roche. Recruitment temporarily suspended into C.E.R.A. phase II oncology trial [online]. Available from URL: http://roche.com/med-cor-2007-02-23c [Accessed 2008 Jan 7]

64. Collins AJ. Anaemia management prior to dialysis: cardiovascular and cost-benefit observations. Nephrol Dial Transplant 2003; 18 Suppl. 2: ii2-6

65. London R, Solis A, Goldberg GA, et al. Health care resource utilization and the impact of anemia management in patients with chronic kidney disease. Am J Kidney Dis 2002; 40 (3): 539-48

66. Maddux FW, Shetty S, del Aquila MA, et al. Effect of erythropoiesis-stimulating agents on healthcare utilization, costs, and outcomes in chronic kidney disease. Ann Pharmacother 2007; 41 (11): 1761-9

Correspondence: *Monique P. Curran,* Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz

© 2008 Adis Data Information BV. All rights reserved.