

# Continuous Erythropoietin Receptor Activator (Mircera<sup>®</sup>) for Renal Anemia

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## Summary

- ✓ **Continuous erythropoietin receptor activator (CERA) is a third-generation erythropoiesis stimulating agent (ESA). CERA is used to correct anemia and maintain hemoglobin levels in patients with renal (kidney) failure. CERA is administered either once every two weeks (to correct anemia) or once per month (to maintain hemoglobin levels). This offers a potential advantage over other ESAs that require more frequent administration.**
- ✓ **Two phase 3 trials involving erythropoietin-naïve patients found no difference between correcting renal anemia with CERA once every two weeks compared to results with other ESAs that were administered up to three times weekly. Four phase 3 trials reported that maintenance of stable hemoglobin levels in dialysis patients with once-monthly CERA was comparable to other agents that were administered up to three times weekly. Further clinical trials are needed to examine other important outcomes, such as mortality and major adverse effects.**
- ✓ **The most common adverse effects with CERA were hypertension, diarrhea, headache, and upper respiratory tract infection. There was a higher risk of procedural hypotension (low blood pressure during administration), gastrointestinal hemorrhage, and tachycardia with CERA compared to other ESAs.**
- ✓ **Administration of CERA at extended intervals may simplify anemia management, reduce the burden on patients, and decrease health care staff time spent administering the treatment.**

## Background

The kidneys filter wastes from the body, maintain cellular homeostasis, and produce hormones to regulate blood pressure, bone density, and red blood cell production. Patients with chronic kidney disease (CKD) experience a long-term, progressive decline in kidney function. Anemia, defined as a hemoglobin (Hb) concentration less than 11 g/dL, results when the kidneys produce insufficient erythropoietin to stimulate red blood cell production.<sup>1,2</sup> When fewer red blood cells carry oxygen from the lungs to other organs in the body, renal anemia bears clinical consequences, including fatigue, impaired cardiac function, increased hospitalization, and mortality.<sup>3</sup> Renal anemia is managed by administering synthetic hormones known as erythropoiesis stimulating agents (ESAs) at least once weekly. A therapy that requires less frequent administration may simplify anemia management in this growing patient population.<sup>4</sup>

## The Technology

Continuous erythropoietin receptor activator (CERA) or methoxypolyethylene glycol-epoetin- $\beta$ , known by the brand name Mircera<sup>®</sup> (F. Hoffmann-La Roche Ltd, Basel, Switzerland), is the first of a new class of longer-acting ESAs designed to correct and maintain Hb levels in CKD patients. Unlike shorter-acting ESAs, CERA's lower affinity for erythropoietic receptors prompts repeated binding, further stimulating red blood cell production by bone marrow. CERA's long half-life allows for administration once every two weeks to correct anemia and once-monthly to maintain target Hb levels.<sup>5</sup>

## Regulatory Status

Mircera<sup>®</sup> does not currently have Health Canada approval for marketing. The US Food and Drug Administration (FDA) approved Mircera for the treatment of renal anemia in November 2007.<sup>6</sup> The label was finalized after the FDA Cardiovascular and Renal Drugs Advisory Committee made overall recommendations on the safety of ESAs in Fall 2007.<sup>7</sup>

The European Commission granted approval for CERA in July 2007. The approved indications are for administration once every two weeks to correct anemia and once-monthly to maintain Hb levels in CKD patients, including both patients on dialysis and those not on dialysis.<sup>6,8</sup>

## Patient Group

Chronic kidney disease is characterized by a reduction in blood filtration, defined as a glomerular filtration rate of less than 60 mL/min/1.73m<sup>2</sup> for three months or longer.<sup>9</sup> Kidney disease is staged I to V, based on disease progression. In 2004, 31,000 Canadians had end-stage kidney disease (stage V), and 19,000 of these individuals were on dialysis.<sup>10</sup> This number is expected to double over the next 10 years.<sup>10,11</sup> In the US, it is estimated that 5.4% of the population (aged 20 years and over) has stage III CKD and 0.4% have stages IV/V CKD.<sup>3,12</sup> Iron deficiency is common in patients with CKD, particularly those in more advanced stages.<sup>3</sup> Only patients with anemia not resolved with iron replacement would benefit from ESAs.

## Current Practice

Current practice guidelines recommend early anemia management in CKD patients not yet on dialysis, targeting Hb levels ranging from 11 g/dL to 12 g/dL.<sup>2</sup> ESAs developed to treat anemia include epoetin-alpha ( $\alpha$ ), epoetin-beta ( $\beta$ ), epoetin-omega ( $\omega$ ), epoetin-delta ( $\delta$ ), and darbepoetin- $\alpha$ . Epoetin- $\alpha$  (Eprex™, Janssen-Ortho Inc.) and darbepoetin- $\alpha$  (Aranesp®, Amgen Inc.) are approved for renal anemia management in Canada.<sup>13</sup> Intravenous administration of epoetin- $\alpha$  and darbepoetin- $\alpha$  results in half-lives of seven hours and 25 hours, respectively.<sup>14</sup> Subcutaneous administration of epoetin- $\alpha$  and darbepoetin- $\alpha$  results in half-lives of 19 hours and 49 hours, respectively.<sup>14</sup> Epoetin- $\alpha$  requires dosing once to three times per week, while darbepoetin- $\alpha$  may be administered once-weekly or once every two weeks. Though rare, anti-erythropoietin antibody-mediated pure red-cell aplasia, or a sudden decrease in red blood cell production, is associated with ESA use and may lead to blood transfusion dependency. Current therapy with ESAs requires iron supplementation, frequent monitoring, and dose adjustments by health care providers.<sup>14</sup>

## The Evidence

Existing trials comparing CERA to other ESAs do not assess a number of important outcomes such as mortality or major side effects. Four phase 3 trials have been published in full,<sup>15-18</sup> and two are reported only in abstracts or non-peer-reviewed literature.<sup>5,6</sup> Phase 3 trials, involving 2,400 patients from 29 countries, include two correction and four maintenance studies, and an extension study, comparing intravenous or subcutaneous CERA to commercially available ESAs (Table 1).<sup>5,6,15-18</sup> All studies were multi-centre, open-label, randomized controlled trials. Assessed weekly, Hb levels were maintained at 10 g/dL to 13.5 g/dL, and patients received supplemental iron. Following stabilization of Hb levels (12 g/dL), the median monthly CERA dose in the clinical trials was 150  $\mu$ g (range 97  $\mu$ g to 270  $\mu$ g).<sup>6</sup>

Two studies of 181 dialysis and 324 pre-dialysis epoetin-naïve patients evaluated anemia correction.<sup>5,18</sup> In correction studies, the median dose of CERA given once every two weeks was 0.6  $\mu$ g/kg.<sup>6</sup> The primary endpoint was the Hb response rate, defined as an increase of greater than 1 g/dL above baseline and achieving a target Hb greater than 11 g/dL during the correction period without red blood cell transfusion. The AMICUS study compared anemia correction in dialysis patients using CERA (0.4  $\mu$ g/kg) administered intravenously once every two weeks to patients in a control group who received epoetin- $\alpha$  or epoetin- $\beta$  intravenously three times per week for 24 weeks.<sup>5,18</sup> The ARCTOS study compared CERA (0.6  $\mu$ g/kg) administered subcutaneously once every two weeks, to weekly subcutaneous darbepoetin- $\alpha$  in pre-dialysis patients for 28 weeks.<sup>5</sup> The populations were male (46% to 65%), mean age 54 to 65 years, and 25% to 47% had diabetes. In the AMICUS study, the mean Hb increased from 9.4 g/dL at baseline to 12.1 g/dL after 24 weeks in the CERA group (mean change 2.7 g/dL  $\pm$  1.5 g/dL) and from 9.4 g/dL at baseline to 12.0 g/dL in the epoetin- $\alpha/\beta$  group (mean change 2.6 g/dL  $\pm$  1.3 g/dL).<sup>5,6,18</sup> In the ARCTOS study, the mean Hb increased from 10.2 g/dL at baseline to 12.3 g/dL after 28 weeks in the CERA group (mean change 2.1 g/dL) and from 10.2 g/dL at baseline to 12.2 g/dL in the darbepoetin- $\alpha$  group (mean change 2.0 g/dL).<sup>5,6</sup> Renal anemia was corrected in more than 90% of ESA-naïve patients on and not on dialysis receiving CERA once every two weeks.<sup>5</sup>

**Table 1: CERA Anemia Correction and Hb Maintenance Trials**

Phase III Studies	Anemia Correction		Hb Maintenance			
	AMICUS <sup>5,18</sup>	ARCTOS <sup>5</sup>	MAXIMA <sup>5,16</sup>	PROTOS <sup>5,15</sup>	STRIATA <sup>5</sup>	RUBRA <sup>5,17</sup>
Inclusion Criteria	Baseline Hb: 8-11 g/dL Serum ferritin ≥100µg/L		Stable baseline Hb: 10.5-13 g/dL Serum ferritin ≥100µg/L			
Intervention	CERA IV 1x/2wk	CERA SC 1x/2wk	CERA IV 1x/2wk CERA IV 1x/4wk	CERA SC 1x/2wk CERA SC 1x/4wk	CERA IV 1x/2wk	CERA IV/SC pre-filled syringes 1x/2wk
Comparator	EPO IV 3x/wk	DAR SC 1x/wk	EPO IV 1-3x/wk	EPO SC 1-3x/wk	DAR IV 1x/wk or 1x/2wk	EPO IV/SC 1-3x/wk
Population	N=181 dialysis EPO-naïve	N=324 pre-dialysis EPO-naïve	N=673 dialysis	N=572 dialysis	N=313 dialysis	N=336 dialysis
Evaluated/ Randomized	124/135 CERA 41/46 EPO	145/162 CERA 153/162 DAR	190/223 CERA 1x/2wk 183/224 CERA 1x/4wk 199/226 EPO	161/190 CERA 1x/2wk 166/191 CERA 1x/4wk 175/191 EPO	130/157 CERA 136/156 DAR	168/168 CERA 150/168 EPO
Patient Characteristics Male (%) Mean Age (Years) Diabetes (%)	Male: 65% Mean age: 54 Diabetes: 25%	Male: 46% Mean age: 65 Diabetes: 47%	Male: 58% Mean age: 59 Diabetes: 40%	Male: 59% Mean age: 61 Diabetes: 25%	Male: 58% Mean age: 62 Diabetes: 24%	Male: 65% Mean age: 60 Diabetes: 36%
Outcome	Hb response rate (95% CI) Mean change in Hb from baseline (g/dL)		Between group (CERA versus ESA) difference of the mean change in Hb from baseline to follow-up (97% CI)			
Follow-up	24 weeks	28 weeks	29-36 weeks	29-36 weeks	29-36 weeks	29-36 weeks
Mean Baseline Hb <sup>6</sup>	CERA: 9.4 g/dL EPO: 9.4 g/dL	CERA: 10.2 g/dL DAR: 10.2 g/dL	CERA 1x/2wk: 12.0 g/dL CERA 1x/4wk: 11.9 g/dL EPO: 12.0 g/dL	CERA 1x/2wk: 11.7 g/dL CERA 1x/4wk: 11.6 g/dL EPO: 11.6 g/dL	CERA: 12.0 g/dL DAR: 11.9 g/dL	CERA: 11.8 g/dL EPO: 11.9 g/dL
Mean Follow-up Hb <sup>6</sup>	CERA: 12.1 g/dL EPO: 12.0g/dL <sup>19</sup>	CERA: 12.3 g/dL DAR: 12.2 g/dL <sup>19</sup>	CERA 1x/2wk: 11.9 CERA 1x/4wk: 11.9 g/dL EPO: 11.9 g/dL	CERA 1x/2wk: 11.7 g/dL CERA 1x/4wk: 11.5 g/dL EPO: 11.5 g/dL	CERA: 12.1 g/dL DAR: 11.8 g/dL	CERA: 11.9 g/dL EPO: 11.8 g/dL
Results Hb Response Rate; Mean HB Change from Baseline or Mean Change in Hb Between Groups <sup>6</sup>	Response rate (%): CERA: 93 (88, 97) EPO: 91 (79, 98)  Mean Hb change: CERA: 2.7 g/dL EPO: 2.6 g/dL	Response rate (%): CERA: 98 (94, 99) DAR: 96 (92, 99)  Mean Hb change: CERA: 2.1 g/dL DAR: 2.0 g/dL	Mean Hb change between groups: CERA IV 1x/2wk versus EPO: 0.0 (-0.2, 0.2) g/dL CERA IV 1x/4wk versus EPO: 0.1 (-0.2, 0.3) g/dL	Mean Hb change between groups: CERA SC 1x/2wk versus EPO: 0.1 (-0.1, 0.4) g/dL CERA SC 1x/4wk versus EPO: -0.0 (-0.3, 0.2) g/dL	Mean Hb change between groups: CERA IV 1x/2wk versus DAR: 0.2 (-0.0, 0.4) g/dL	Mean Hb change between groups: CERA IV/SC 1x/2wk versus EPO: 0.1 (-0.1, 0.4) g/dL
Limitations Possible Bias	Studies were not blinded due to concurrent therapy (transfusions, iron supplements, dosing). <sup>5</sup> Median dose adjustments were slightly higher in ESA recipients. These could lead to possible selection and performance biases.					

CERA=continuous erythropoietin receptor activator; CI=confidence interval; DAR=darbepoietin- $\alpha$ ; EPO=erythropoietin- $\alpha/\beta$ ; ESA=erythropoiesis stimulating agents; Hb=hemoglobin; Hb response rate=Hb increase of  $\geq 1$ g/dL to a target level of  $\geq 11$  g/dL without transfusion; IV=intravenous; RR=relative risk; SC=subcutaneous; wk=week; x=times

Four studies assessed Hb maintenance in a total of 1,894 dialysis patients previously maintained on ESA therapy.<sup>5,6,15-17</sup> The primary endpoint was the change in Hb concentration from baseline to the end of the evaluation period. The populations were primarily male (58 to 65%), mean age 59 to 62 years, and 24% to 40% of patients had diabetes.<sup>5</sup> During the evaluation period (weeks 29 to 36), between 66% and 76% of patients maintained an average Hb concentration within  $\pm 1$  g/dL of their baseline Hb. CERA once- or twice-monthly maintained Hb levels in dialysis patients previously maintained on ESAs administered up to three times weekly.<sup>5,15-17</sup>

## Adverse Effects

Safety data from 28 studies involving 2,737 CKD patients were evaluated. The most commonly reported adverse events in 1,789 CERA users were hypertension (13%), diarrhea (11%), headache (9%), and upper respiratory tract infection (9%).<sup>5</sup> Adverse events that occurred in at least 2% of patients and at a higher frequency in CERA recipients compared to patients receiving epoetin or darbepoetin included procedural hypotension (8.2% versus 5.6%), gastrointestinal hemorrhage (2.0% versus 0.7%), and tachycardia (2.1% versus 1.0%).<sup>5</sup>

ESAs increase the risk of death, tumor progression, cardiovascular and thromboembolic events when administered to a Hb > 12 g/dL.<sup>6,20</sup> A rate Hb rise of > 1 g/dL over two weeks contributes to these risks.<sup>5</sup> Fifteen of 126 adverse events occurred with Hb > 13 g/dL.<sup>5</sup> Pure red cell aplasia has not been observed in CERA users in clinical trials thus far.<sup>5</sup>

## Administration and Cost

CERA is available in vials and pre-filled syringes at strengths ranging from 50  $\mu$ g/mL to 1,000  $\mu$ g/mL.<sup>6</sup> With training, patients can inject themselves subcutaneously or intravenously through a hemodialysis line. Dosing is adjusted based on Hb level, monitored every two weeks until levels are stable and periodically thereafter. ESA-naïve patients receive a starting dose of 0.6  $\mu$ g/kg body weight once every two weeks, while those switching from a short-acting ESA are dosed from 120  $\mu$ g to 360  $\mu$ g every two weeks.<sup>8</sup>

The manufacturer's price for CERA is currently unavailable as it has not yet been approved in Canada. In Ontario, the provincial drug formulary currently lists reimbursement of other ESAs at C \$142.50 per 10,000 IU/mL of epoetin- $\alpha$  (Eprex<sup>®</sup>) and C \$402.00 per 150  $\mu$ g/0.3 mL of darbepoetin- $\alpha$  (Aranesp<sup>®</sup>).<sup>21</sup> The annual cost of erythropoietin therapy in patients with chronic kidney disease in Canada has been estimated at between C \$5,000 and C \$10,000 per patient.<sup>22</sup>

## Concurrent Developments

Products in clinical development for stimulating erythropoiesis include biosimilar epoetins, erythropoietin-mimetic peptides (EMPs), and hypoxia-inducible factor (HIF) stabilizers. Hematide<sup>™</sup> (Affymax, Inc.), an EMP that is administered monthly, binds and activates the erythropoietin receptor, but is structurally unrelated to erythropoietin, which reduces the chance for antibody and pure red cell aplasia development. Hematide<sup>™</sup> can be produced without the need for cell culture, which may provide greater stability at a lower cost. FG-2216 (FibroGen), a first generation hypoxia-inducible factor (HIF) stabilizer, is a transcription factor that regulates erythropoietic gene expression, iron absorption, and energy metabolism. HIF stabilizers are administered orally to activate endogenous erythropoietin production, and can do so through extra-renal mechanisms in individuals without kidneys.<sup>23</sup>

## Rate of Technology Diffusion

In the US, the FDA review of the safety of ESAs delayed final approval and labeling of Mircera<sup>®</sup> until November 2007. Amgen, the manufacturer of Epogen<sup>®</sup> (epoetin- $\alpha$ ) and Aranesp<sup>®</sup>, has a patent infringement suit against Roche and is appealing a decision by the International Trade Commission allowing importation of Mircera<sup>®</sup>. If marketed, the product will likely compete with darbepoetin- $\alpha$  (Aranesp<sup>®</sup>) that is administered every two weeks in pre-dialysis patients and weekly in dialysis patients.<sup>7</sup>

## Implementation Issues

Administration of CERA at once-monthly intervals may simplify anemia management and reduce the burden for patients and health care professionals. A recent conference abstract reported results of a time-in-motion study conducted in 12 dialysis centers in Germany and the United Kingdom. The investigators

concluded that, for a centre of 100 patients, if all patients with anemia were managed with CERA, a total of 37 (in the UK) and 43 (in Germany) working days per year of health care professionals' time (including nurses, technicians and physicians) could be saved.<sup>24</sup> However, the true cost-benefit of CERA cannot be determined until the price is available.

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