PDL DRUG REVIEW

Proprietary Name: Mircera®
Common Name: methoxy polyethylene glycol-epoetin beta
PDL Category: Erythropoiesis Stimulating Proteins

Comparable Products	Preferred Drug List Status
Procrit	Preferred with Conditions

Summary

Indications and Usage: For the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis and patients not on dialysis. Limitations of use include that Mircera® is not indicated and not recommended in the treatment of anemia due to cancer chemotherapy OR as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia. Mircera® has not been shown trials to improve symptoms, physical functioning, or health-related quality of life.

This is a pregnancy category C medication. The safety and efficacy of use in children have not been established.

Dosage Forms: Injection: 50mcg, 75mcg, 100mcg, 150mcg, 200mcg, or 250mcg per 0.3ml in single-use prefilled syringes

Recommended Dosage: Iron status should be assessed prior to and during treatment. Iron repletion should be maintained. Supplemental iron therapy should be given when serum ferritin is <100mcg/L or when serum transferrin saturation is <20%. In addition, all causes of anemia should be corrected before starting treatment.

Per the PI: "In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of >11g/dl. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events."

Dosing of Mircera® should be individualized, with the lowest dose necessary to reduce the need for RBC transfusions. It should be given either IV or SC; when given SC, it should be injected in the abdomen, arm, or thigh. For all patients with CKD, monitor hemoglobin when starting or adjusting therapy at least once a week until stable, then monitor at least monthly. Dose adjustments are not required in hepatic impairment.

For patients with CKD on dialysis: Start treatment when hemoglobin is <10g/dl; if hemoglobin approaches or exceeds 11g/dl, reduce or interrupt the dose. The recommended starting dose if not currently treated with an ESA is 0.6mcg/kg as IV or SC once every 2 weeks. Once hemoglobin levels are stabilized, it may be administered once monthly using a dose that is twice that of the every 2 week dose and subsequently titrated as necessary.

For patients with CKD not on dialysis: Consider starting treatment only when hemoglobin level is <10g/dl AND the following considerations apply: the rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion and reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal. If

hemoglobin level exceeds 10g/dl, reduce or interrupt the dose of Mircera®; use the lowest dose needed to reduce the need for RBC transfusions. The recommended starting dose if not currently treated with an ESA is 0.6mcg/kg given as a single IV or SC injection once every 2 weeks. Once hemoglobin is stabile, Mircera® can be given once monthly using a dose that is twice that of the every 2 week dose and subsequently titrated as necessary.

The prescribing information has additional information regarding the Mircera® dose when there is conversion epoetin or darbepoetin.

Drug Interactions: Formal drug interaction studies have not been performed.

Common Adverse Drug Reactions: *There was no placebo data to compare; thus, the incidence of adverse events listed is from patients treated with Mircera®.* The most frequently reported adverse events included hypertension (13%), hypotension (5%), diarrhea (11%), vomiting (6%), constipation (5%), nasopharyngitis (11%), upper respiratory tract infection (9%), urinary tract infection (5%), headache (9%), muscle spasms (8%), back pain (6%), pain in extremity (5%), procedural hypotension (8%), arteriovenous fistula thrombosis (5%), arteriovenous fistula site complication (5%), fluid overload (7%), and cough (6%).

Contraindications: Uncontrolled hypertension; Pure red cell aplasia (PRCA) that begins after treatment with Mircera® or other erythropoietin protein drugs; and History of serious or severe allergic reactions to Mircera®.

Manufacturer: Genentech, Inc

Analysis: Methoxy polyethylene glycol-epoetin beta, the active ingredient of Mircera®, is an erythropoiesis-stimulating agent (ESA). It is an erythropoietin receptor activator that differs from erythropoietin through formation of a chemical bond with a methoxy polyethylene glycol (PEG). Erythropoietin is made in the kidney and released into the blood stream in response to hypoxia; it then interacts with erythroid progenitor cells to increase RBC production. The production of endogenous erythropoietin is impaired with CKD, thus anemia is common in this population primarily due to this erythropoietin deficiency. Nevertheless, Mircera® has a box warning regarding the increased risk of death, MI, stroke, venous thromboembolism (VTE), thrombosis of vascular access, and tumor progression or recurrence.

The box warning indicates that in controlled trials in a population with CKD, patients experienced greater risks for death, serious adverse CV reactions, and stroke when given ESAs to target a hemoglobin level of >11g/dl. As no trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks, it is recommended to use the lowest Mircera® dose sufficient to reduce the need for RBC transfusions. The box warning also indicates that Mircera® is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircera® was terminated early due to more deaths among patients receiving Mircera® vs another ESA. Furthermore, the box warning discusses that ESAs have shown shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.

The safety and efficacy of Mircera® were assessed in 6 open-label studies that included anemic patients with CKD who were randomized to either Mircera® or a comparator ESA. In two of the studies, anemic patients with CKD had not been treated with an ESA at baseline, while 4 of the studies assessed patients who were receiving an ESA for treatment of anemia of CKD at baseline. In all studies, ESAs were given to obtain specific hemoglobin levels; and, after stabilization of hemoglobin levels (12g/dl), the median dose of Mircera® was 150mcg QM.

Study 1 and 2: These studies included patients not currently treated with an ESA. Study 1 included those not receiving dialysis and who were randomized to treatment for 28 weeks, while study 2 included those who were receiving dialysis and who were randomized to treatment for 24 weeks. The table below, adapted from the PI, illustrates the results of the studies. Note that the goal was defined as hemoglobin increase of ≥1g/dL and to a level of ≥11g/dL without RBC transfusion; hemoglobin levels were to be maintained within the range of 11-13g/dL.

Treatment (N)	% Achieving goal	Mean hemoglobin change from baseline (g/dl)	RBC Transfusion
Study 1			
Mircera® (N=162)	98%	2.1	2.5%
Darbepoetin alfa (N=162)	96%	2.0	6.8%
Study 2			
Mircera® (N=135)	93%	2.7	5.2%
Epoetin alfa/beta (N=46)	91%	2.6	4.3%

Study 3, 4, 5, and 6: These studies included patients currently treated with an ESA at baseline and assessed the ability of Mircera® to maintain hemoglobin levels. Patients were randomized to Mircera® or they were maintained on their current ESA dose and schedule. Results are illustrated in the table below, and they suggested that Mircera® Q2W and Q4W maintained hemoglobin levels within the targeted hemoglobin range (10-13.5g/dl).

Treatment (N)	Mean hemoglobin at baseline	Evaluation period hemoglobin (mean)	Between-group difference (g/dL)
Study 3			
Mircera® IV Q2W (N=223)	12	11.9	0
Mircera® IV Q4W (N=224)	11.9	11.9	0.1
Epoetin alfa/beta IV (N=226)	12	11.9	N/A
Study 4			
Mircera® SC Q2W (N=190)	11.7	11.7	0.1
Mircera® SC Q4W (N=191)	11.6	11.5	-0.0
Epoetin beta SC (N=191)	11.6	11.5	N/A
Study 5			
Mircera® IV Q2W (N=157)	12.0	12.1	0.2
Darbepoetin alfa IV (N=156)	11.9	11.8	N/A
Study 6			
Mircera® IV/SC Q2W (N=68)	11.8	11.9	0.1
Epoetin alfa IV/SC (N=168)	11.9	11.8	0.1

Place in Therapy: Mircera® is indicated for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis and patients not on dialysis. It is considered a continuous erythropoietin receptor activator (CERA) with a considerably longer half-life than erythropoietin or darbepoetin.[2] Registration trials found Mircera® given every 2 or 4 weeks to be as effective as erythropoietin given one to three times daily, as well as darbepoetin.

There is no clear consistent evidence that Mircera® is safer or more effective than the currently preferred more cost effective agents within this same class when used according to FDA approved indications and dosing. It is recommended that Mircera® remain non-preferred and require prior authorization and be available to the few who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Mircera [package insert]. South San Francisco, CA: Genentech USA, Inc, a member of the Roche Group; 2014.

[2] UpToDate for desktop. Erythropoietin: Subcutaneous administration. Accessed July 2015.