HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Mircera safely and effectively. See full prescribing information for Mircera.

Mircera® (methoxy polyethylene glycol-epoetin beta)

Solution for Injection: Intravenous [IV] or Subcutaneous [SC] use
Initial U.S. Approval: 2007

WARNINGS: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENCE

See full prescribing information for complete boxed warning

Chronic Kidney Disease:

- **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 greater than 11 g/dL (5.1).**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks (5.1).**
- **Use the lowest Mircera dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).**

Cancer:

- **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 because of more deaths among patients receiving Mircera than another ESA (5.2).**
- **ESAs 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 (5.2).**

----------RECENT MAJOR CHANGES----------

Boxed Warning	10/2014
Indications and Usage (1.2)	10/2014
Dosage and Administration (2.1, 2.2)	10/2014
Contraindications (4)	10/2014
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.6, 5.7, 5.8, 5.9)	10/2014

---------- INDICATIONS AND USAGE----------

Mircera is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia associated with chronic kidney disease (CKD in adult patients on dialysis and patients not on dialysis (1.1).

Limitations of Use

Mircera is not indicated and is not recommended for use:

- In the treatment of anemia due to cancer chemotherapy (1.2).
- As a substitute for RBC transfusions in patients who require immediate correction of anemia (1.2)

Mircera has not been shown to improve quality of life, fatigue, or patient well-being.

----------DOSAGE AND ADMINISTRATION----------

Mircera is administered by subcutaneous (SC) or intravenous (IV) injection (2.2).

- Initial Treatment: 0.6 mcg/kg body weight administered once every two weeks (2.2).
- Conversion from Another ESA: dosed once monthly or once every two weeks based on total weekly epoetin alfa or darbepoetin alfa dose at time of conversion (2.2).

---------- DOSAGE FORMS AND STRENGTHS----------

- Injection: 50, 75, 100, 150, 200, or 250 mcg in 0.3 mL solution of Mircera in single-use prefilled syringes (3).

---------- CONTRAINDICATIONS ----------

- Uncontrolled hypertension (4).
- Pure red cell aplasia (PRCA) that begins after treatment with Mircera or other erythropoietin protein drugs (4)
- History of serious allergic reactions to Mircera, including anaphylaxis (4).

---------- WARNINGS AND PRECAUTIONS ----------

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism: Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefits (5.1 and 14). Use caution in patients with coexistent cardiovascular disease and stroke (5.1).
- Hypertension: Control hypertension prior to initiating and during treatment with Mircera (5.3).
- Seizures: Seizures have occurred in CKD patients participating in Mircera clinical studies. Increase monitoring of these patients for changes in seizure frequency or premonitory symptoms (5.4).
- PRCA: If severe anemia and low reticulocyte count develop during Mircera treatment, withhold Mircera and evaluate for PRCA (5.6).

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥ 10%) are hypertension, diarrhea, nasopharyngitis. (6).

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised: 08/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNINGS: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS, AND TUMOR PROGRESSION OR RECURRENCE

Chronic Kidney Disease *[see Warnings and Precautions (5.1)]*

- **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 greater than 11 g/dL.**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest Mircera dose sufficient to reduce the need for red blood cell (RBC) transfusions.**

Cancer *[see Warnings and Precautions (5.2)]*

- **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 because of more deaths among patients receiving Mircera than another ESA.**
- **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.**

1 INDICATIONS AND USAGE

1.1 Anemia Due to Chronic Kidney Disease

Mircera is indicated for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis and patients not on dialysis.

1.2 Limitations of Use

Mircera is not indicated and is not recommended:

- In the treatment of anemia due to cancer chemotherapy *[see Warnings and Precautions (5.2)]*
- As a substitute for RBC transfusions in patients who require immediate correction of anemia *[see Clinical Pharmacology (12.2)]*

Mircera has not been shown to improve symptoms, physical functioning or health-related quality of life.

2 DOSAGE AND ADMINISTRATION

2.1 Evaluation of Iron Stores and Nutritional Factors

Evaluate the iron status in all patients before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating Mircera *[see Warnings and Precautions (5.9)]*.

2.2 Patients with Chronic Kidney Disease

Individualize dosing and use the lowest dose of Mircera sufficient to reduce the need for RBC transfusions *[see Warnings and Precautions (5.1)]*. 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 greater than 11 g/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 *[see Boxed Warning and Clinical Studies (14)]*.

For **all** patients with CKD:

When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly. When adjusting therapy consider hemoglobin rate of rise, rate of decline, ESA responsiveness and hemoglobin variability. A single hemoglobin excursion may not require a dosing change.

- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of Mircera by 25% or more as needed to reduce rapid responses.
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.
- For patients who do not respond adequately over a 12-week escalation period, increasing the Mircera dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions. Evaluate other causes of anemia. Discontinue Mircera if responsiveness does not improve.

Mircera is administered either intravenously (IV) or subcutaneously (SC). When administered SC, Mircera should be injected in the abdomen, arm or thigh.

For Patients with CKD **on dialysis**:

- Initiate Mircera treatment when the hemoglobin level is less than 10 g/dL.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of Mircera.
- The recommended starting dose of Mircera for the treatment of anemia in adult CKD patients who are not currently treated with an ESA is 0.6 mcg/kg body weight administered as a single IV or SC injection once every two weeks. The IV route is recommended for patients receiving hemodialysis because the IV route may be less immunogenic *[see Adverse Reactions (6.2)]*.
- Once the hemoglobin has been stabilized, Mircera may be administered once monthly using a dose that is twice that of the every-two-week dose and subsequently titrated as necessary.

For Patients with CKD **not on dialysis**:

- Consider initiating Mircera treatment only when the hemoglobin level is less than 10 g/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 the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of Mircera, and use the lowest dose of Mircera sufficient to reduce the need for RBC transfusions.
- The recommended starting dose of Mircera for the treatment of anemia in adult CKD patients who are not currently treated with an ESA is 0.6 mcg/kg body weight administered as a single IV or SC injection once every two weeks.
- Once the hemoglobin has been stabilized, Mircera may be administered once monthly using a dose that is twice that of the every-two-week dose and subsequently titrated as necessary.

Refer patients who self-administer Mircera to the Instructions for Use *[see Patient Counseling Information (17)]*.

Conversion from Epoetin alfa or Darbepoetin alfa to Mircera in Patients with CKD

Mircera can be administered once every two weeks or once monthly to patients whose hemoglobin has been stabilized by treatment with an ESA (see Table 1). The dose of Mircera, given as a single IV or SC injection, should be based on the total weekly ESA dose at the time of conversion.

Table 1 Mircera Starting Doses for Patients Currently Receiving an ESA

Previous Weekly Epoetin alfa Dose (units/week)	**Previous Weekly Darbepoetin alfa Dose (mcg/week)**	**Mircera Dose**	
		Once Monthly (mcg/month)	Once Every Two Weeks (mcg/every two weeks)
< 8000	< 40	120	60
8000 - 16000	40 - 80	200	100
> 16000	> 80	360	180

2.3 Preparation and Administration of Mircera

Mircera is packaged as single-use prefilled syringes. Mircera contains no preservatives. Discard any unused portion. Do not pool unused portions from the prefilled syringes. Do not use the prefilled syringe more than one time.

Always store Mircera prefilled syringes in their original cartons. Vigorous shaking or prolonged exposure to light should be avoided.

Do not mix Mircera with any parenteral solution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any prefilled syringes exhibiting particulate matter or a coloration other than colorless to slightly yellowish.

For administration using the prefilled syringe, the plunger must be fully depressed during injection in order for the needle guard to activate. Following administration, remove the needle from the injection site and then release the plunger to allow the needle guard to move up until the entire needle is covered.

See “Instructions for Use” for complete instructions on the preparation and administration of Mircera. Examine each prefilled syringe for the expiration date. Do not use Mircera after the expiration date.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50, 75, 100, 150, 200, or 250 mcg of Mircera in 0.3 mL solution in single-use prefilled syringes

4 CONTRAINDICATIONS

Mircera is contraindicated in patients with:

- Uncontrolled hypertension *[see Warnings and Precautions (5.3)]*
- Pure red cell aplasia (PRCA) that begins after treatment with Mircera or other erythropoietin protein drugs *[see Warnings and Precautions (5.6)]*

- History of serious or severe allergic reactions to Mircera (e.g. anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria).

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

- In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.

- Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit *[see Clinical Studies (14)]*. Use caution in patients with coexistent cardiovascular disease and stroke *[see Dosage and Administration (2.2)]*. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.

- In controlled clinical trials of patients with cancer, ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.

- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

The design and overall results of the 3 large trials comparing higher and lower hemoglobin targets are shown in Table 2 (Normal Hematocrit Study (NHS), Correction of Hemoglobin Outcomes in Renal Insufficiency (CHOIR) and Trial to Reduce Cardiovascular Events with Aranesp® Therapy (TREAT)).

Table 2: Randomized Controlled Trials Showing Adverse Cardiovascular Outcomes in Patients With CKD

	NHS (N = 1265)	**CHOIR (N = 1432)**	**TREAT (N = 4038)**
Time Period of Trial	1993 to 1996	2003 to 2006	2004 to 2009
Population	CKD patients on hemodialysis with coexisting CHF or CAD, hematocrit 30 ± 3% on epoetin alfa	CKD patients not on dialysis with hemoglobin < 11 g/dL not previously administered epoetin alfa	CKD patients not on dialysis with type II diabetes, hemoglobin ≤ 11 g/dL
Hemoglobin Target; Higher vs. Lower (g/dL)	14.0 vs. 10.0	13.5 vs. 11.3	13.0 vs. ≥ 9.0
Median (Q1, Q3) Achieved Hemoglobin level (g/dL)	12.6 (11.6, 13.3) vs. 10.3 (10.0, 10.7)	13.0 (12.2, 13.4) vs. 11.4 (11.1, 11.6)	12.5 (12.0, 12.8) vs. 10.6 (9.9, 11.3)
Primary Endpoint	All-cause mortality or nonfatal MI	All-cause mortality, MI, hospitalization for CHF, or stroke	All-cause mortality, MI, myocardial ischemia, heart failure, and stroke
Hazard Ratio or Relative Risk (95% CI)	1.28 (1.06 - 1.56)	1.34 (1.03 - 1.74)	1.05 (0.94 - 1.17)
Adverse Outcome for Higher Target Group	All-cause mortality	All-cause mortality	Stroke
Hazard Ratio or Relative Risk (95% CI)	1.27 (1.04 - 1.54)	1.48 (0.97 - 2.27)	1.92 (1.38 - 2.68)

Patients with Chronic Kidney Disease

NHS: A prospective, randomized, open-label study of 1265 patients with chronic kidney disease on dialysis with documented evidence of congestive heart failure or ischemic heart disease was designed to test the hypothesis that a higher target hematocrit (Hct) would result in improved outcomes compared with a lower target Hct. In this study, patients were randomized to epoetin alfa treatment targeted to a maintenance hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL. The trial was terminated early with adverse safety findings of higher mortality in the high hematocrit target group. Higher mortality (35% vs. 29%) was observed for the patients randomized to a target hemoglobin of 14 g/dL than for the patients randomized to a target hemoglobin of 10 g/dL. For all-cause mortality, the HR=1.27; 95% CI (1.04, 1.54); p=0.018. The incidence of nonfatal myocardial infarction, vascular access thrombosis, and other thrombotic events was also higher in the group randomized to a target hemoglobin of 14 g/dL.

CHOIR: In a randomized prospective trial, 1432 patients with anemia due to CKD who were not undergoing dialysis were assigned to epoetin alfa treatment targeting a maintenance hemoglobin concentration of 13.5 g/dL or 11.3 g/dL. The trial was terminated early with adverse safety findings. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group (HR 1.3, 95% CI: 1.0, 1.7 p=0.03).

TREAT: A randomized, double-blind, placebo-controlled, prospective trial of 4038 patients with: CKD not on dialysis (eGFR of 20 – 60 mL/min), anemia (hemoglobin levels ≤ 11 g/dL), and type 2 diabetes mellitus, patients were randomized to receive either darbepoetin alfa treatment or a matching placebo. Placebo group patients also received darbepoetin alfa when their hemoglobin levels were below 9 g/dL. The trial objectives were to demonstrate the benefit of darbepoetin alfa treatment of the anemia to a target hemoglobin level of 13 g/dL, when compared to a "placebo" group, by reducing the occurrence of either of two primary endpoints: (1) a composite cardiovascular endpoint of all-cause mortality or a specified cardiovascular event (myocardial ischemia, CHF, MI, and CVA) or (2) a composite renal endpoint of all-cause mortality or progression to end stage renal disease. The overall risks for each of the two primary endpoints (the cardiovascular composite and the renal composite) were not reduced with darbepoetin alfa treatment (see Table 2), but the risk of stroke was increased nearly two-fold in the darbepoetin alfa -treated group versus the placebo group: annualized stroke rate 2.1% vs. 1.1%, respectively, HR 1.92; 95% CI: 1.38, 2.68; p < 0.001. The relative risk of stroke was particularly high in patients with a prior stroke: annualized stroke rate 5.2% in the darbepoetin alfa-treated group and 1.9% in the placebo group, HR 3.07; 95% CI: 1.44, 6.54. Also, among darbepoetin alfa-treated subjects with a past history of cancer, there were more deaths due to all causes and more deaths adjudicated as due to cancer, in comparison with the control group.

Patients with Cancer

An increased incidence of thromboembolic reactions, some serious and life-threatening, occurred in patients with cancer treated with ESAs.

In a randomized, placebo-controlled study (Study 1 in Table 3 *[see Warnings and Precautions (5.2)]*) of 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when epoetin alfa was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). This study was terminated prematurely when interim results demonstrated a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic reactions (1.1% vs. 0.2%) in the first 4 months of the study among patients treated with epoetin alfa. Based on Kaplan-Meier estimates, at the time of study

termination, the 12-month survival was lower in the epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

Patients Having Surgery

Mircera is not approved for reduction of RBC transfusions in patients scheduled for surgical procedures.

An increased incidence of deep vein thrombosis (DVT) in patients receiving epoetin alfa undergoing surgical orthopedic procedures has been observed. In a randomized controlled study (referred to as the "SPINE" study), 681 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, received epoetin alfa and standard of care (SOC) treatment, or SOC treatment alone. Preliminary analysis showed a higher incidence of DVT, determined by either Color Flow Duplex Imaging or by clinical symptoms, in the epoetin alfa group [16 patients (4.7%)] compared to the SOC group [7 patients (2.1%)]. In addition, 12 patients in the epoetin alfa group and 7 patients in the SOC group had other thrombotic vascular events.

Increased mortality was observed in a randomized placebo-controlled study of epoetin alfa in adult patients who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to epoetin alfa versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events.

5.2 Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients with Cancer

Mircera is not indicated and is not recommended for use in the treatment of anemia due to cancer chemotherapy. A dose-ranging trial of Mircera in 153 patients who were undergoing chemotherapy for non-small cell lung cancer was terminated prematurely because more deaths occurred among patients receiving Mircera than another ESA.

ESAs resulted in decreased locoregional control/progression-free survival and/or overall survival (see Table 3). These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy (Studies 5 and 6), in patients receiving chemotherapy for metastatic breast cancer (Study 1) or lymphoid malignancy (Study 2), and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Studies 7 and 8).

Table 3 Randomized, Controlled Trials with Decreased Survival and/or Decreased Locoregional Control

Study/Tumor (n)	Hemoglobin Target	Achieved Hemoglobin (Median Q1,Q3*)	Primary Endpoint	Adverse Outcome for ESA-containing Arm
Chemotherapy				
Cancer Study 1 Metastatic breast cancer (n=939)	12-14 g/dL	12.9 g/dL 12.2, 13.3 g/dL	12-month overall survival	Decreased 12-month survival
Cancer Study 2 Lymphoid malignancy (n=344)	13-15 g/dL (M) 13-14 g/dL (F)	11.0 g/dL 9.8, 12.1 g/dL	Proportion of patients achieving a hemoglobin response	Decreased overall survival
Cancer Study 3 Early breast cancer (n=733)	12.5-13 g/dL	13.1 g/dL 12.5, 13.7 g/dL	Relapse-free and overall survival	Decreased 3-year relapse-free and overall survival
Cancer Study 4 Cervical cancer (n=114)	12-14 g/dL	12.7 g/dL 12.1, 13.3 g/dL	Progression-free and overall survival and locoregional	Decreased 3-year progression-free and overall survival and locoregional

			control	control
Radiotherapy Alone				
Cancer Study 5 Head and neck cancer (n=351)	>15 g/dL (M) >14 g/dL (F)	Not available	Locoregional progression-free survival (LRPFS)	Decreased 5-year locoregional progression-free survival Decreased overall survival
Cancer Study 6 Head and neck cancer (n=522)	14-15.5 g/dL	Not available	Locoregional disease control (LRC)	Decreased locoregional disease control
No Chemotherapy or Radiotherapy				
Cancer Study 7 Non-small cell lung cancer (n=70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
Cancer Study 8 Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

*Q1= 25th percentile; Q3= 75th percentile

Decreased overall survival:

Cancer Study 1 (the "BEST" study) was previously described *[see Warnings and Precautions (5.1)]*. Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator assessed time to tumor progression was not different between the two groups. Survival at 12 months was significantly lower in the epoetin alfa arm (70% vs. 76%, HR 1.37, 95% CI: 1.07, 1.75; p=0.012).

Cancer Study 2 was a Phase 3, double-blind, randomized (darbepoetin alfa vs. placebo) study conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to darbepoetin alfa as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Cancer Study 7 was a Phase 3, multicenter, randomized (epoetin alfa vs. placebo), double-blind study, in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in survival in favor of the patients on the placebo arm of the trial was observed (median survival 63 vs. 129 days; HR 1.84; p=0.04).

Cancer Study 8 was a Phase 3, double-blind, randomized (darbepoetin alfa vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. The median survival was shorter in the darbepoetin alfa treatment group (8 months) compared with the placebo group (10.8 months); HR 1.30, 95% CI: 1.07, 1.57.

Decreased progression-free survival and overall survival:

Cancer Study 3 (the "PREPARE" study) was a randomized controlled study in which darbepoetin alfa was administered to prevent anemia conducted in 733 women receiving neo-adjuvant breast cancer treatment. A final analysis was performed after a median follow-up of approximately 3 years at which time the survival rate was lower (86% vs. 90%, HR 1.42, 95% CI: 0.93, 2.18) and relapse-free survival rate was lower (72% vs. 78%, HR 1.33, 95% CI: 0.99, 1.79) in the darbepoetin alfa-treated arm compared to the control arm.

Cancer Study 4 (protocol GOG 191) was a randomized controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic events in epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the epoetin alfa-treated group compared to control (59% vs. 62%, HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the epoetin alfa-treated group compared to control (61% vs. 71%, HR 1.28, 95% CI: 0.68, 2.42).

Cancer Study 5 (the "ENHANCE" study) was a randomized controlled study in 351 head and neck cancer patients where epoetin beta or placebo was administered to achieve target hemoglobins of 14 and 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving epoetin beta (HR 1.62, 95% CI: 1.22, 2.14, p=0.0008) with a median of 406 days epoetin beta vs. 745 days placebo. Overall survival was significantly shorter in patients receiving epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p=0.02).

Decreased locoregional control:

Cancer Study 6 (DAHANCA 10) was conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy randomized to darbepoetin alfa with radiotherapy or radiotherapy alone. An interim analysis on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving darbepoetin alfa (RR 1.44, 95% CI: 1.06, 1.96; p=0.02). Overall survival was shorter in patients receiving darbepoetin alfa (RR 1.28, 95% CI: 0.98, 1.68; p=0.08).

5.3 Hypertension

Mircera is contraindicated in patients with uncontrolled hypertension.

In Mircera clinical studies, approximately 27% of patients with CKD, including patients on dialysis and patients not on dialysis, required intensification of antihypertensive therapy. Hypertensive encephalopathy and/or seizures have been observed in patients with CKD treated with Mircera *[see Warnings and Precautions (5.4)]*.

Appropriately control hypertension prior to initiation of and during treatment with Mircera. Reduce or withhold Mircera if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions *[see Patient Counseling Information (17)]*.

5.4 Seizures

Seizures have occurred in patients participating in Mircera clinical studies. During the first several months following initiation of Mircera, monitor patients closely for premonitory neurologic symptoms. Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms, or change in seizure frequency.

5.5 Lack or Loss of Hemoglobin Response to Mircera

For lack or loss of hemoglobin response to Mircera, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding).

If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA *[see Warnings and Precautions (5.6)]*. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient response to Mircera therapy *[see Dosage and Administration (2.2)]*.

5.6 Pure Red Cell Aplasia

Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in the postmarketing setting in patients treated with

Mircera. This has been reported predominantly in patients with CKD receiving ESAs by SC administration. PRCA was not observed in clinical studies of Mircera.

PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which Mircera is not approved).

If severe anemia and low reticulocyte count develop during treatment with Mircera, withhold Mircera and evaluate patients for neutralizing antibodies to erythropoietin *[see Warnings and Precautions (5.5)]*. Serum samples should be obtained at least a month after the last Mircera administration to prevent interference of Mircera with the assay. Contact Roche at 1-888-835-2555 to perform assays for binding and neutralizing antibodies. Permanently discontinue Mircera in patients who develop PRCA following treatment with Mircera or other erythropoietin protein drugs. Do not switch patients to other ESAs as antibodies may cross-react *[see Adverse Reactions (6.2)]*.

5.7 Serious Allergic Reactions

Serious allergic reactions, including anaphylactic reactions, angioedema, bronchospasm, tachycardia, pruritus skin rash, urticaria, and Stevens-Johnson syndrome/toxic epidermal necrolysis have been reported in patients treated with Mircera. If a serious allergic or anaphylactic reaction occurs due to Mircera, immediately and permanently discontinue Mircera and administer appropriate therapy.

5.8 Dialysis Management

Therapy with Mircera results in an increase in red blood cells and a decrease in plasma volume, which could reduce dialysis efficiency; patients may require adjustments in their dialysis prescription after initiation of Mircera. Patients receiving Mircera may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

5.9 Laboratory Monitoring

Evaluate transferrin saturation and serum ferritin prior to and during Mircera treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20% *[see Dosage and Administration (2.1)]*.

The majority of patients with CKD will require supplemental iron during the course of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin is stable and sufficient to minimize the need for RBC transfusion. Thereafter, hemoglobin should be monitored at least monthly provided hemoglobin levels remain stable *[see Dosage and Administration (2.2]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism *[see Warnings and Precautions (5.1)]*
- Increased mortality and/or tumor progression in patients with cancer *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Seizures *[see Warnings and Precautions (5.4)]*
- Pure red cell aplasia *[see Warnings and Precautions (5.6)]*
- Serious allergic reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

The data described below reflect exposure to Mircera in 2737 patients, including 1451 exposed for 6 months and 1144 exposed for greater than one year. Mircera was studied primarily in active-controlled studies (n=1789 received Mircera, and n=948 received another ESA) and in long-term follow up studies. The population was 18 to 92 years of age, 58% male, and the percentage of Caucasian, Black (including African Americans), Asian

and Hispanic patients were 73%, 20%, 5%, and 9%, respectively. Approximately 85% of the patients were receiving dialysis. Most patients received Mircera using dosing regimens of once every two or four weeks, administered SC or IV.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of Mircera cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

The most commonly reported adverse reactions in ≥10% of patients were hypertension *[see Warnings and Precautions (5.3)]*, diarrhea, and nasopharyngitis. The most common adverse reactions that led to treatment discontinuation in the Mircera clinical studies were: hypertension, coronary artery disease, anemia, concomitant termination of other CKD therapy and septic shock. Some of the adverse reactions reported are typically associated with CKD, or recognized complications of dialysis, and may not necessarily be attributable to Mircera therapy. Adverse reaction rates did not importantly differ between patients receiving Mircera or another ESA.

Table 4 summarizes the most frequent adverse reactions (≥ 5%) in patients treated with Mircera.

Table 4 Adverse Reactions Occurring in ≥ 5% of CKD Patients

Adverse Reaction	Patients Treated with Mircera (n=1789)
VASCULAR	
Hypertension	13%
Hypotension	5%
GASTROINTESTINAL	
Diarrhea	11%
Vomiting	6%
Constipation	5%
INFECTIONS AND INFESTATIONS	
Nasopharyngitis	11%
Upper Respiratory Tract Infection	9%
Urinary Tract Infection	5%
NERVOUS SYSTEM	
Headache	9%
MUSCULOSKELETAL AND CONNECTIVE TISSUE	
Muscle Spasms	8%
Back Pain	6%
Pain in Extremity	5%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Procedural Hypotension	8%
Arteriovenous Fistula Thrombosis	5%
Arteriovenous Fistula Site Complication	5%
METABOLISM AND NUTRITION	
Fluid Overload	7%
RESPIRATORY, THORACIC AND MEDIASTINAL	
Cough	6%

In the controlled trials, the rates of serious adverse reactions did not importantly differ between patients receiving Mircera and another ESA (38% vs. 42%) except for the occurrence of serious gastrointestinal

hemorrhage (1.2% vs. 0.2%). Serious hemorrhagic adverse reactions of all types occurred among 5% and 4% of patients receiving Mircera or another ESA, respectively.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibodies to Mircera that cross-react with endogenous erythropoietin and other ESAs can result in PRCA or severe anemia (with or without other cytopenias) *[see Warnings and Precautions (5.6)]*. Compared to SC administration, the IV route of administration may lessen the risk for development of antibodies to Mircera.

In 1789 patients treated with Mircera in clinical studies, antibody testing using an enzyme-linked immunosorbent assay (ELISA) was conducted at baseline and during treatment. Antibody development was not detected in any of the patients.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Mircera with the incidence of antibodies to other ESAs may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Mircera. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity

Stevens-Johnson syndrome/toxic epidermal necrolysis has been reported *[see Warnings and Precautions (5.7)]*.

Pure Red Cell Aplasia (PRCA)

Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in patients treated with Mircera *[see Warnings and Precautions (5.6)]*.

7 DRUG INTERACTIONS

No formal drug/drug interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Category C

Risk Summary

There are no adequate and well-controlled studies in pregnant women. Mircera should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

When methoxy polyethylene glycol-epoetin beta was administered subcutaneously to rats and rabbits during gestation, bone malformation was observed in both species at 50 mcg/kg once every three days. This effect was observed as missing caudal vertebrae resulting in a thread-like tail in one rat fetus, absent first digit metacarpal and phalanx on each forelimb resulting in absent polex in one rabbit fetus, and fused fourth and fifth cervical vertebrae centra in another rabbit fetus. Dose-related reduction in fetal weights was observed in both rats and rabbits. At doses 5 mcg/kg once every three days and higher, methoxy polyethylene glycol-epoetin beta caused exaggerated pharmacodynamic effects in dams. Once-weekly doses of methoxy polyethylene glycol-epoetin beta up to 50 mcg/kg/dose given to pregnant rats did not adversely affect pregnancy parameters, natural delivery or litter observations. Increased deaths and significant reduction in the growth rate of the F1 generation

were observed during lactation and early post weaning period. However, no remarkable effect on reflex, physical and cognitive development or reproductive performance was observed in F1 generation of any dose groups.

8.3 Nursing Mothers

It is not known whether Mircera is excreted into human breast milk. In one study in rats, methoxy polyethylene glycol-epoetin beta was excreted into maternal milk. Because many drugs are excreted in human milk, caution should be exercised when Mircera is administered to a nursing woman.

8.4 Pediatric Use

The safety and efficacy of Mircera in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of Mircera did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

In a study comparing 12 patients with severe (Child-Pugh Classification Grade C) hepatic impairment to 12 healthy volunteers, the single-dose pharmacokinetic disposition of Mircera was not altered in patients with hepatic impairment. No adjustment of the starting dose is necessary in patients with hepatic impairment.

10 OVERDOSAGE

Mircera overdosage can elevate hemoglobin levels above the desired level, which should be managed with discontinuation or reduction of Mircera dosage and/or with phlebotomy, as clinically indicated *[see Pharmacodynamics (12.2)]*. Cases of severe hypertension have been observed following overdose with ESAs *[see Warnings and Precautions (5.3)]*.

11 DESCRIPTION

Mircera, methoxy polyethylene glycol-epoetin beta, is an ESA which differs from erythropoietin through formation of a chemical bond between either the N-terminal amino group or the ε-amino group of any lysine present in erythropoietin, predominantly Lys^{52} and Lys^{45}, and methoxy polyethylene glycol (PEG) butanoic acid (approximately 30,000 daltons). This results in a total molecular weight of approximately 60,000 daltons. Mircera is formulated as a sterile, preservative-free protein solution for intravenous or subcutaneous administration.

Injectable solutions of Mircera in prefilled syringes are formulated in an aqueous solution containing sodium phosphate, sodium sulphate, mannitol, methionine and poloxamer 188. The solution is clear, colorless to slightly yellowish and the pH is 6.2 ± 0.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mircera is an erythropoietin receptor activator with greater activity *in vivo* as well as increased half-life, in contrast to erythropoietin. A primary growth factor for erythroid development, erythropoietin is produced in the kidney and released into the bloodstream in response to hypoxia. In responding to hypoxia, erythropoietin interacts with erythroid progenitor cells to increase red cell production. Production of endogenous erythropoietin is impaired in patients with CKD and erythropoietin deficiency is the primary cause of their anemia.

12.2 Pharmacodynamics

Following a single-dose of Mircera in CKD patients, the onset of hemoglobin increase (defined as an increase > 0.4 g/dL from baseline) was observed 7 to 15 days following initial dose administration *[see Dosage and Administration (2.2)]*.

12.3 Pharmacokinetics

The pharmacokinetics of Mircera were studied in anemic patients with CKD including patients on dialysis and those not on dialysis. Mircera pharmacokinetics, based on population analyses, were not altered by age, gender, race, or the use of dialysis.

Following an IV administration of Mircera 0.4 mcg/kg body weight to CKD patients receiving peritoneal dialysis, the observed terminal half-life was 134 ± 65 hours (mean ± SD), and the total systemic clearance was 0.49 ± 0.18 mL/hr/kg. Following a SC administration of Mircera 0.8 mcg/kg to CKD patients receiving peritoneal dialysis, the terminal half-life was 139 ± 67 hours. The maximum serum concentrations of Mircera were observed 72 hours (median value) following the SC administration. The absolute bioavailability of Mircera after the SC administration was 62%.

In CKD patients receiving multiple Mircera doses, pharmacokinetics were studied after the first dose and on week 9 and week 19 or 21. Multiple dosing was found to have no effect on clearance, volume of distribution or bioavailability of Mircera. Based on population analyses of the clinical studies, Mircera did not accumulate following administration every four weeks. However, when Mircera was administered every 2 weeks, blood concentrations at steady state increased by 12%.

A comparison of serum concentrations of Mircera measured before and after hemodialysis in 41 patients showed that hemodialysis did not alter serum concentrations.

The single-dose pharmacokinetics of Mircera in patients with severe (Child-Pugh Classification Grade C) hepatic impairment and healthy volunteers were similar.

The site of SC injection (abdomen, arm or thigh) had no clinically important effects on the pharmacokinetics or pharmacodynamics of Mircera in healthy volunteers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with Mircera. Methoxy polyethylene glycol-epoetin beta did not induce a proliferative response in either the erythropoietin receptor positive cell lines HepG2 and K562 or the erythropoietin receptor negative cell line RT112 in vitro. In addition, using a panel of human tissues, the in vitro binding of methoxy polyethylene glycol-epoetin beta was observed only in bone marrow progenitor cells.

When methoxy polyethylene glycol-epoetin beta was administered subcutaneously to male and female rats prior to and during mating, reproductive performance, fertility, and sperm assessment parameters were not affected.

14 CLINICAL STUDIES

Patients with chronic kidney disease on dialysis: ESA effects on rates of transfusion

In early clinical studies conducted in CKD patients on dialysis, ESAs have been shown to reduce the use of RBC transfusions. These studies enrolled patients with mean baseline hemoglobin levels of approximately 7.5 g/dL and ESAs were generally titrated to achieve a hemoglobin level of approximately 12 g/dL. Fewer transfusions were given during the ESA treatment period when compared to a pre-treatment interval.

In NHS, the yearly transfusion rate was 51.5% in the lower hemoglobin group (10 g/dL) and 32.4% in the higher hemoglobin group (14 g/dL).

Patients with chronic kidney disease not on dialysis: ESA effects on rates of transfusion

In TREAT, a randomized, double-blind trial of 4038 patients with CKD and type 2 diabetes not on dialysis, a post-hoc analysis showed that the proportion of patients receiving RBC transfusions was lower in patients administered an ESA to target a hemoglobin of 13 g/dL compared to the control arm in which the ESA was administered intermittently if hemoglobin concentration decreased to less than 9 g/dL (15% versus 25%, respectively). In CHOIR, a randomized open-label study of 1432 patients with CKD not on dialysis, use of an ESA to target a higher (13.5 g/dL) versus lower (11.3 g/dL) hemoglobin goal did not reduce the use of RBC transfusions. In each trial, no benefits occurred for the cardiovascular or end-stage renal disease outcomes. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile *[see Warnings and Precautions (5.1)]*.

ESA effects on quality of life

Mircera use has not been demonstrated in controlled clinical trials to improve quality of life, fatigue, or patient well-being.

ESA effects on rates of death and other serious cardiac adverse events

Three randomized outcome trials (NHS, CHOIR and TREAT) have been conducted in patients with CKD using Epogen/PROCRIT/Aranesp to target higher vs. lower hemoglobin levels. Though these trials were designed to establish a cardiovascular or renal benefit of targeting higher hemoglobin levels, in all 3 studies, patients randomized to the higher hemoglobin target experienced worse cardiovascular outcomes and showed no reduction in progression to ESRD. In each trial, the potential benefit of ESA therapy was offset by worse cardiovascular safety outcomes resulting in an unfavorable benefit-risk profile *[see Warnings and Precautions (5.1)]*.

Other ESA trials

The efficacy and safety of Mircera were assessed in six open-label, multi-center clinical studies that randomized patients to either Mircera or a comparator ESA. Two studies evaluated anemic patients with CKD who were not treated with an ESA at baseline and four studies evaluated patients who were receiving an ESA for treatment of the anemia of CKD. In all studies, patients were assessed as clinically stable at baseline and without evidence of infection or inflammation as determined by history and laboratory data, including C-reactive protein (CRP $\leq$ 15 mg/L for study 1 and CRP $\leq$ 30 mg/L for studies 2 to 6). A CRP value above the threshold led to the exclusion of no more than 3% of the screened patients.

In the clinical studies, ESAs were administered to achieve specific hemoglobin levels (see Table 5 and Table 6). Following stabilization of hemoglobin levels (12 g/dL), the median monthly Mircera dose was 150 mcg (range of 97 mcg to 270 mcg).

Patients Not Currently Treated with an ESA

In Study 1 patients who were not receiving dialysis were randomized to Mircera or darbepoetin alfa, administered for 28 weeks. The starting dose of Mircera was 0.6 mcg/kg administered SC once every two weeks and the starting dose of darbepoetin alfa was 0.45 mcg/kg administered SC once a week. In Study 2, patients who were receiving dialysis were randomized to Mircera or another ESA (epoetin alfa or epoetin beta), administered for 24 weeks. The starting dose of Mircera was 0.4 mcg/kg administered IV once every two weeks and the starting dose of the comparator was administered IV three times a week, consistent with the product's recommended dose. In these studies, the observed median dose of Mircera once every two weeks over the course of the correction/evaluation period was 0.6 mcg/kg. Table 5 provides the results of the two studies.

Table 5 Clinical Studies in Patients Not Currently Treated with an ESA

Group (n)	Percent Achieving Goal* (95% CI)	Mean Hemoglobin Change from Baseline (g/dL)	RBC Transfusion, %
Study 1			
Mircera (n=162)	98 (94, 99)	2.1	2.5
Darbepoetin alfa (n=162)	96 (92, 99)	2.0	6.8
Study 2			
Mircera (n=135)	93 (88, 97)	2.7	5.2
Epoetin alfa/beta (n=46)	91 (79, 98)	2.6	4.3

*Goal: hemoglobin increase of at least 1 g/dL and to a level of at least 11 g/dL without RBC transfusion; hemoglobin levels were to be maintained within the range of 11 to 13 g/dL.

Patients Currently Treated with an ESA

Four studies assessed the ability of Mircera to maintain hemoglobin concentrations among patients currently treated with other ESAs. Patients were randomized to receive Mircera administrations either once every two weeks or once every four weeks, or to continue their current ESA dose and schedule. The initial Mircera dose was determined based on the patient's previous weekly ESA dose. As shown in Table 6, treatment with Mircera once every two weeks and once every four weeks maintained hemoglobin concentrations within the targeted hemoglobin range (10 to 13.5 g/dL).

Table 6 Clinical Studies in Patients Currently Treated with an ESA

Group (n)	Mean Baseline Hemoglobin	Evaluation Period Hemoglobin (Mean)	Between-group Difference *, g/dL (95% or 97.5% CI)
Study 3			
Mircera IV every 2 weeks (n=223)	12.0	11.9	0.0 (−0.2, 0.2)
Mircera IV every 4 weeks (n=224)	11.9	11.9	0.1 (−0.2, 0.3)
Epoetin alfa/beta IV (n=226)	12.0	11.9	n/a
Study 4			
Mircera SC every 2 weeks (n=190)	11.7	11.7	0.1 (−0.1, 0.4)
Mircera SC every 4 weeks (n=191)	11.6	11.5	−0.0 (−0.3, 0.2)
Epoetin beta SC (n=191)	11.6	11.5	n/a
Study 5			
Mircera IV every 2 weeks (n=157)	12.0	12.1	0.2 (−0.0, 0.4)
Darbepoetin alfa IV (n=156)	11.9	11.8	n/a

Study 6			
Mircera IV/SC every 2 weeks (n= 68)	11.8	11.9	0.1 (−0.1, 0.4)
Epoetin alfa IV/SC (n=168)	11.9	11.8	0.1 (−0.1, 0.4)

*Mircera versus comparator mean hemoglobin difference in the evaluation period; 97.5% CI are shown for studies that compared two Mircera groups to another ESA (Studies 3 and 4) and 95% CI are shown for the other studies.
n/a = not applicable

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Mircera is available in single-use prefilled syringes. The syringe plungers are designated with unique colors for each dosage strength. The prefilled syringes are supplied with a 27 gauge, ½ inch needle. To reduce the risk of accidental needlesticks after application, each prefilled syringe is equipped with a needle guard that covers the needle during disposal.

Mircera is available in the following pack sizes:

Single Use Prefilled Syringe (PFS) with a Needle Guard.
A 27 Gauge, ½ Inch Needle is also provided:

1 PFS/Pack

50 mcg/0.3 mL
(NDC 0004-0401-09)

75 mcg/0.3 mL
(NDC 0004-0402-09)

100 mcg/0.3 mL
(NDC 0004-0403-09)

150 mcg/0.3 mL
(NDC 0004-0404-09)

200 mcg/0.3 mL
(NDC 0004-0405-09)

250 mcg/0.3 mL
(NDC 0004-0406-09)

16.2 Stability and Storage

The recommended storage temperature is at 2°C to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light. Keep Mircera in the original package until use.

Storage of prefilled syringes over the recommended temperature (2°C to 8°C), when necessary, is permissible only for temperatures up to 25°C (77°F) and for no more than 30 days.

17 PATIENT COUNSELING INFORMATION

See Medication Guide and Instructions for Use

Prior to treatment, inform patients of the risks and benefits of Mircera.

Inform patients:

- To read the Medication Guide and to review and discuss any questions or concerns with their healthcare provider before starting Mircera and at regular intervals while receiving Mircera
- Of the increased risks of mortality, serious cardiovascular reactions, thromboembolic reactions, stroke, and tumor progression *[see Warnings and Precautions (5.1, 5.2)]*
- To undergo regular blood pressure monitoring, adhere to prescribed anti-hypertensive regimen and follow recommended dietary restrictions
- To seek medical care immediately if they experience any symptoms of an allergic reaction with use of Mircera *[see Warnings and Precautions (5.7)]*
- To contact their healthcare provider for new-onset neurologic symptoms or change in seizure frequency
- Of the need to have regular laboratory tests for hemoglobin

Administer Mircera under the direct supervision of a healthcare provider or, in situations where a patient has been trained to administer Mircera at home, provide instruction on the proper use of Mircera, including instructions to:

- Carefully review the Medication Guide and the Instructions for Use
- Avoid the reuse of needles, syringes, or unused portions of the Mircera single-use prefilled syringes and to properly dispose of these items
  Always keep a puncture-proof disposal container available for the disposal of used syringes and needles

MEDICATION GUIDE
MIRCERA® (mir-SER-ah)
(methoxy polyethylene glycol-epoetin beta)

Read this Medication Guide:

- before you start Mircera.
- if you are told by your healthcare provider that there is new information about Mircera.
- if you are told by your healthcare provider that you may inject Mircera at home, read this Medication Guide each time you receive a new supply of medicine.

This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Talk with your healthcare provider regularly about the use of Mircera and ask if there is new information about Mircera.

What is the most important information I should know about Mircera?

Mircera may cause serious side effects that can lead to death, including:

For people with cancer: Mircera is not for use to treat anemia that is caused by cancer chemotherapy. If you have certain cancers, your tumor may grow faster and you may die sooner if you take Mircera.

- **Serious heart problems, such as heart attack or heart failure, and stroke**. You may die sooner if you are treated with Mircera to increase red blood cells (RBCs) to near the same level found in healthy people.
- **Blood clots**. Blood clots may happen at any time while taking Mircera. If you are receiving Mircera for any reason and you are going to have surgery, talk to your healthcare provider about whether or not you need to take a blood thinner to lessen the chance of blood clots during or following surgery. Clots can form in blood vessels (veins), especially in your leg (deep venous thrombosis or DVT). Pieces of a blood clot may travel to the lungs and block the blood circulation in the lungs (pulmonary embolus).
- Call your healthcare provider or get medical help right away if you have any of these symptoms:
  - Chest pain
  - Trouble breathing or shortness of breath
  - Pain in your legs, with or without swelling
  - A cool or pale arm or leg
  - Sudden confusion, trouble speaking, or trouble understanding others' speech
  - Sudden numbness or weakness in your face, arm or leg, especially on one side of your body
  - Sudden trouble seeing
  - Sudden trouble walking, dizziness, loss of balance or coordination
  - Loss of consciousness (fainting)
  - Hemodialysis vascular access stops working

See **"What are the possible side effects of Mircera?" below for more information.**

If you decide to take Mircera, your healthcare provider should prescribe the smallest dose of Mircera that is necessary to reduce your chance of needing red blood cell transfusions.

What is Mircera?

Mircera is a prescription medicine used to treat anemia. People with anemia have a lower-than-normal number of RBCs. Mircera works like the human protein called erythropoietin to help your body make more RBCs. Mircera is used to reduce or avoid the need for RBC transfusion.

Mircera may be used to treat anemia if it is caused by chronic kidney disease (you may or may not be on dialysis).

If your hemoglobin level stays too high or if your hemoglobin goes up too quickly, this may lead to serious health problems which may result in death. These serious health problems may happen if you take Mircera, even if you do not have an increase in your hemoglobin level. Mircera is not for use for the treatment of anemia:

- that is caused by cancer chemotherapy
- in place of emergency treatment for anemia (red blood cell transfusions)

Mircera has not been proven to improve the quality of life, fatigue, or well-being.

It is not known if Mircera is safe and effective in children.

Who should not take Mircera?

Do not take Mircera if you:

- Have high blood pressure that is not controlled (uncontrolled hypertension)
- Have been told by your healthcare provider that you have or have ever had a type of anemia called Pure Red Cell Aplasia (PRCA) that starts after treatment with Mircera or other erythropoietin protein medicines
- Have had serious allergic reactions to Mircera

What should I tell my healthcare provider before taking Mircera?

Mircera may not be right for you. **Tell your healthcare provider about all of your medical conditions**, including if you:

- Have heart disease
- Have or develop cancer
- Have high blood pressure
- Have had a seizure (convulsion) or stroke
- Have any other medical conditions
- Are pregnant or plan to become pregnant. It is not known if Mircera may harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if Mircera passes into your breast milk.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of your medicines with you and show it to your healthcare provider when you get a new medicine.

How should I take Mircera?

- If you or your caregiver has been trained to give Mircera shots (injections) at home:
  - Be sure that you read, understand, and follow the “Instructions for Use” that come with Mircera.
  - Take Mircera exactly as your healthcare provider tells you to. Do not change the dose of Mircera unless told to by your healthcare provider.

- Your healthcare provider will show you how much Mircera to use, how to inject it, how often it should be injected, and how to safely throw away the used prefilled syringes and needles.
- If you take more than your prescribed dose of Mircera, call your healthcare provider right away for instructions on what to do.

- During treatment with Mircera, continue to follow your healthcare provider's instructions for diet, dialysis, and medicines, including medicines for high blood pressure.
- Have your blood pressure checked as instructed by your healthcare provider.

What are possible side effects of Mircera?

Mircera may cause serious side effects.

- See **"What is the most important information I should know about Mircera?"**
- **High blood pressure.** High blood pressure is a common side effect of Mircera in patients with chronic kidney disease. Your blood pressure may go up or be difficult to control with blood pressure medicine while taking Mircera. This can happen even if you have never had high blood pressure before. Your healthcare provider should check your blood pressure often. If your blood pressure does go up, your healthcare provider may prescribe new or more blood pressure medicine.
- **Seizures.** If you have any seizures while taking Mircera, get medical help right away and tell your healthcare provider.
- **No response or loss of your hemoglobin response to Mircera.** If your hemoglobin does not increase, or if the increase cannot be maintained, your healthcare provider will look for the cause of the problem. Your dose of Mircera or other medicines may need to be changed.
- **Antibodies to Mircera.** Your body may make antibodies to Mircera. These antibodies can block or reduce your body's ability to make red blood cells, and cause you to have severe anemia. Call your healthcare provider if you have unusual tiredness, lack of energy, dizziness or fainting. You may need to stop taking Mircera.
- **Serious allergic reaction.** Serious allergic reactions can cause a rash over your whole body, shortness of breath, wheezing, dizziness and fainting because of a drop in blood pressure, swelling around your mouth or eyes, fast pulse, or sweating. If you have a serious allergic reaction, stop using Mircera and call your healthcare provider or get emergency medical help right away.

Common side effects of Mircera include:

- Diarrhea
- Upper respiratory tract infections (cold, cough and sinus infections)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of Mircera. Your healthcare provider can give you a more complete list. Tell your healthcare provider about any side effects that bother you or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Mircera?

- Store Mircera prefilled syringes in the refrigerator at 36°F to 46°F (2°C to 8°C).

- If a refrigerator is not available, Mircera prefilled syringes can be stored at room temperature 77°F (25°C) for no more than 30 days.
- **Do not freeze Mircera**. Do not use Mircera that has been frozen or improperly refrigerated.
- Keep Mircera in the original package.
- Protect Mircera from light.
- Do not shake Mircera.

Keep Mircera and all medicines out of the reach of children.

General information about Mircera

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Mircera for a condition for which it was not prescribed. Do not give Mircera to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Mircera. If you would like more information about Mircera, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Mircera that is written for health professionals.

What are the ingredients in Mircera?

Active ingredient: methoxy polyethylene glycol-epoetin beta
Inactive ingredients: sodium phosphate, sodium sulphate, mannitol, methionine and poloxamer 188

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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