CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 125164

LABELING

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: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR AND THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION

See full prescribing information for complete boxed warning

Renal failure: **Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL *[see Warnings and Precautions (5.1)]*.**

Cancer: **Mircera is not indicated for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircera was terminated early because of significantly more deaths among patients receiving Mircera than another ESA. In other studies of ESAs in patients with cancer:**

- **ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid and non-small cell lung malignancies when dose to a target hemoglobin of ≥ 12 g/dL.**
- **The risks of shortened survival and tumor promotion have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL *[see Warnings and Precautions (5.1)]*.**

INDICATIONS AND USAGE

Mircera is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis (1).

Mircera is not indicated for the treatment of anemia due to cancer chemotherapy (1).

DOSAGE AND ADMINISTRATION

Mircera is administered by subcutaneous (SC) or intravenous (IV) injection (2.1).

- 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).
- When Mircera is initiated or the dose adjusted: monitor hemoglobin every two weeks until stabilized, and every two to four weeks thereafter (2.1).
- Reduce the dose of Mircera by approximately 25% if: (2.3)
  - rate of rise in hemoglobin is greater than 1 g/dL in 2 weeks
  - hemoglobin is increasing and approaching 12 g/dL

DOSAGE FORMS AND STRENGTHS

- Single use vials containing 50, 100, 200, 300, 400, 600 or 1000 mcg in 1 mL solution of Mircera (3).
- Single use prefilled syringes containing 50, 75, 100, 150, 200, or 250 mcg in 0.3 mL solution of Mircera and 400, 600 or 800 mcg in 0.6 mL solution of Mircera (3).

CONTRAINDICATIONS

- Uncontrolled hypertension (4).
- History of hypersensitivity to the drug (4).

WARNINGS AND PRECAUTIONS

- Hypertension: Do not treat patients with uncontrolled hypertension. Monitor blood pressure throughout course of therapy. Adjust dose or stop Mircera as necessary (2.3, 5.3).
- Seizures: During the first several months of therapy, closely monitor blood pressure and the presence of premonitory neurologic symptoms. (5.4).
- Pure Red Cell Aplasia (PRCA): If anti-erythropoietin antibody associated anemia is suspected, discontinue Mircera. (5.5, 5.6, 6.2)
- Serious allergic reactions: Discontinue Mircera treatment if serious reaction occurs (5.8).
- Predialysis patients may require lower maintenance doses of Mircera than patients receiving dialysis (5.9).
- Marginally dialyzed patients may require adjustments in dialysis prescription (5.10).

ADVERSE REACTIONS

The most common adverse reactions (≥ 5%) are hypertension, diarrhea, nasopharyngitis, headache, and upper respiratory tract infection (6).

To report SUSPECTED ADVERSE REACTIONS, contact Roche at 1-800-526-6367 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE

Revised: 11/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR AND THROMBOEMBOLIC EVENTS and TUMOR PROGRESSION.

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
- 2.1 Important Dosing Information
- 2.2 Starting Dose
- 2.3 Monitoring and Dose Adjustment
- 2.4 Preparation and Administration of Mircera

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
- 5.1 Increased Mortality, Serious Cardiovascular And Thromboembolic Events
- 5.2 Increased Mortality and/or Tumor Progression
- 5.3 Hypertension
- 5.4 Seizures
- 5.5 Pure Red Cell Aplasia
- 5.6 Lack or Loss of Response to Mircera
- 5.7 Hematologic Effects
- 5.8 Allergic Reactions
- 5.9 Patients with CRF Not Requiring Dialysis
- 5.10 Dialysis Management
- 5.11 Laboratory Monitoring

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity

7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy: Category C
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
- 16.1 How Supplied
- 16.2 Stability and Storage

17 PATIENT COUNSELING INFORMATION
- 17.1 Information for Patients
- 17.2 Medication Guide

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

NOV 1 4 2007

FULL PRESCRIBING INFORMATION

WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR AND THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION

Renal failure: **Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL** ***[see Warnings and Precautions (5.1)].***

Cancer: **Mircera is not indicated for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircera was terminated early because of significantly more deaths among patients receiving Mircera than another ESA. In other studies of ESAs in patients with cancer:**

- **ESAs shortened overall survival and/or time-to-tumor progression in clinical studies in patients with advanced breast, head and neck, lymphoid and non-small cell lung malignancies when dose to a target hemoglobin of ≥ 12 g/dL.**
- **The risks of shortened survival and tumor promotion have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL** ***[see Warnings and Precautions (5.2)].***

1 INDICATIONS AND USAGE

Mircera is indicated for the treatment of anemia associated with chronic renal failure (CRF) in adults, including patients on dialysis and not on dialysis.

Mircera is not indicated for the treatment of anemia due to cancer chemotherapy *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

The dose of Mircera should be reduced as the hemoglobin approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period *[see Warnings and Precautions (5.1)]*. During therapy, hematological parameters should be monitored regularly. Individualize dosing to achieve and maintain hemoglobin levels within the range of 10 to 12 g/dL.

Mircera is administered either intravenously (IV) or subcutaneously (SC). The IV route is recommended for patients receiving hemodialysis because the IV route may be less immunogenic *[see Adverse Reactions (6.2)]*. When administered SC, Mircera should be injected in the abdomen, arm or thigh.

2.2 Starting Dose

<u>Patients Not Currently Treated with an ESA</u>

The recommended starting dose of Mircera for the treatment of anemia in adult CRF 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.

Mircera should be dosed to achieve and maintain hemoglobin between 10 and 12 g/dL. Once the hemoglobin has been maintained within this range, Mircera may be administered once monthly using a dose that is twice that of the every-two-week dose and subsequently titrated as necessary.

Patients Currently Treated with an ESA

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 Monitoring and Dose Adjustment

When Mircera therapy is initiated or adjusted, the hemoglobin should be monitored every two weeks until stabilized, and every two to four weeks thereafter. For patients whose hemoglobin does not attain a level within the range of 10 to 12 g/dL despite the use of appropriate Mircera dose titrations over a 12-week period:

- Do not administer higher Mircera doses and use the lowest dose that will maintain a hemoglobin level sufficient to avoid the need for recurrent RBC transfusions
- Evaluate and treat for other causes of anemia
- Thereafter, continue to monitor the hemoglobin level and if responsiveness improves, make Mircera dose adjustments as described above; discontinue Mircera if responsiveness does not improve and the patient needs recurrent RBC transfusions *[see Warnings and Precautions (5.6, 5.7, 5.11)]*.

Dose adjustments should not be made more often than once a month. A significant change in hemoglobin may not be observed for several weeks after the dose is adjusted. If a dose adjustment is necessary to maintain the recommended hemoglobin level, the dose may be increased or decreased by approximately 25%, as needed.

During Mircera therapy, if the increase in hemoglobin is greater than 1 g/dL in 2 weeks or if the hemoglobin is increasing and approaching 12 g/dL, the dose should be reduced by approximately 25%. If the hemoglobin continues to increase, Mircera should be discontinued until the hemoglobin begins to decrease. Mircera may then be restarted at a dose approximately 25% below the previously administered dose.

For patients not converted from another ESA, if the increase in hemoglobin is less than 1 g/dL over the initial 4 weeks of treatment and iron stores are adequate, the dose of Mircera may be increased by approximately 25% *[see Warnings and Precautions (5.11)]*.

If a dose of Mircera is missed, administer the missed dose as soon as possible and restart Mircera at the prescribed dosing frequency.

2.4 Preparation and Administration of Mircera

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

Always store Mircera vials or 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 coloration prior to administration. Do not use any vials or 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 "Patient Instructions for Use" for complete instructions on the preparation and administration of Mircera. Examine each vial or prefilled syringe for the expiration date. Do not use Mircera after the expiration date.

3 DOSAGE FORMS AND STRENGTHS

Single use vials are available containing 50, 100, 200, 300, 400, 600 or 1000 mcg of Mircera in 1 mL solution.

Single use prefilled syringes are available containing 50, 75, 100, 150, 200, or 250 mcg of Mircera in 0.3 mL solution and 400, 600 or 800 mcg of Mircera in 0.6 mL solution.

4 CONTRAINDICATIONS

Mircera is contraindicated in patients with uncontrolled hypertension *[see Warnings and Precautions (5.3)]*.

Mircera is contradicted in patients with a history of hypersensitivity or allergy to the drug *[see Warnings and Precautions (5.8)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality, Serious Cardiovascular And Thromboembolic Events

Anemia associated with chronic renal failure

Patients experienced greater risks for death and serious cardiovascular events when administered ESAs to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Patients with chronic renal failure and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients. These events included myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis. A rate of hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.

In a randomized prospective trial, 1432 anemic chronic renal failure patients 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. 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).

Increased risk for serious cardiovascular events was also reported from a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure). In this trial, patients were assigned to Epoetin alfa treatment targeted to a maintenance hemoglobin of either 14 ± 1 g/dL or 10 ± 1 g/dL. Higher mortality (35% vs. 29%) was observed in the 634 patients randomized to a target hemoglobin of 14 g/dL than in the 631 patients randomized to a target hemoglobin of 10 g/dL. The reason for the increased mortality observed in this study is unknown; however, 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.

Anemia due to other conditions

The safety and efficacy of Mircera have not been established for use among patients with anemia due to cancer chemotherapy or for reduction in the need for allogeneic RBC transfusion in the peri-surgical setting. In these conditions, clinical trials of ESAs have shown risks for thrombotic events and/or mortality.

In a randomized controlled study (referred to as Cancer Study 1 - the "BEST" study) with another ESA in 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 an ESA was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). The study was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% vs. 0.2%) in the first 4 months of the study were observed 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).

A systematic review of 57 randomized controlled trials (including Cancer Studies 1 and 3 - the "BEST" and "ENHANCE" studies) evaluating 9353 patients with cancer compared ESAs plus RBC transfusion with RBC transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. An increased relative risk (RR) of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08 (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients.

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 Tumor Progression

A dose-ranging trial of Mircera in 153 patients who were undergoing chemotherapy for non-small cell lung cancer was terminated prematurely because significantly more deaths occurred among patients receiving Mircera than another ESA.

Erythropoiesis-stimulating agents, when administered to target a hemoglobin of > 12 g/dL, shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy [Cancer Studies 3 and 4 (DAHANCA 10) in Table 2]. ESAs also shortened survival in patients with metastatic breast cancer (Cancer Study 1) and in patients with lymphoid malignancy (Cancer Study 2) receiving chemotherapy when administered to target a hemoglobin of ≥ 12 g/dL. In addition, ESAs shortened survival in patients with non-small cell lung cancer and in a study enrolling patients with various malignancies who were not receiving chemotherapy or radiotherapy; in these two studies, ESAs were administered to target a hemoglobin of ≥ 12 g/dL (Cancer Studies 5 and 6 in Table 2). Although studies evaluated hemoglobin targets of ≥ 12 g/dL in these tumor types, the risks of shortened survival and tumor progression have not been excluded when ESAs are dosed to target a hemoglobin of < 12 g/dL.

Table 2 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
Radiotherapy Alone				
Cancer Study 3 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 4 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 5 Non-small cell lung cancer (n=70)	12-14 g/dL	Not available	Quality of life	Decreased overall survival
Cancer Study 6 Non-myeloid malignancy (n=989)	12-13 g/dL	10.6 g/dL 9.4, 11.8 g/dL	RBC transfusions	Decreased overall survival

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 5 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 6 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 locoregional progression-free survival and overall survival:

Cancer Study 3 (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 4 (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

Blood pressure should be controlled adequately before initiation of Mircera therapy. Special care should be taken to closely monitor and control blood pressure during Mircera therapy, especially in patients with a history of cardiovascular disease or hypertension. If blood pressure is difficult to control by pharmacologic or dietary measures, the dose of Mircera should be reduced or withheld.

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

5.4 Seizures

Seizures have occurred in patients participating in Mircera clinical studies. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. While the relationship between seizures and the rate of rise of hemoglobin is uncertain, the dose of Mircera should be decreased or withheld if the hemoglobin increases more than 1 g/dL in any 2-week period *[see Dosage and Administration (2.3)]*.

5.5 Pure Red Cell Aplasia

Pure red cell aplasia (PRCA) and severe anemia, with or without other cytopenias, have been associated with the development of neutralizing antibodies to erythropoietin in patients treated with ESAs. PRCA occurred predominantly in patients with CRF receiving an ESA by SC administration. PRCA was not observed in clinical studies of Mircera.

Any patient who develops a sudden loss of response to Mircera, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of the altered hemoglobin response, including evaluation for the development of neutralizing antibodies to erythropoietin *[see Warnings and Precautions (5.6)]*. Serum samples should be obtained at least a month after the last Mircera administration to prevent interference of Mircera with the assay. If anti-erythropoietin antibody-associated anemia is suspected, withhold Mircera and other erythropoietic proteins. Contact Roche at 1-800-526-6367 to perform assays for antibodies.

Mircera should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react *[see Adverse Reactions (6.2)]*.

5.6 Lack or Loss of Response to Mircera

The lack of a hemoglobin response or failure to maintain a hemoglobin response with Mircera doses within the recommended dosing range should prompt a search for causative factors. Deficiencies of iron, folic acid and vitamin B_{12} should be excluded or corrected.

Intercurrent infections, malignancy, inflammation, occult blood loss, hemolysis, severe aluminum toxicity, osteitis fibrosis cystica, underlying hematological disease (e.g., thalassemia, refractory anemia or myelodysplastic disorders) or bone marrow fibrosis, may also compromise the hemoglobin response. In the absence of another etiology, the patient should be evaluated for evidence of PRCA, including tests for the presence of antibodies to erythropoietin *[see Warnings and Precautions (5.5)]*.

5.7 Hematologic Effects

Sufficient time should be allowed to determine a patient's response to a Mircera dose before adjusting the subsequent doses. Because of the time required for erythropoiesis and the red blood cell (RBC) life span, an interval of 2 to 6 weeks may occur between the time of a dose adjustment (initiation, increase, decrease, or discontinuation) and a significant change in hemoglobin. In order to prevent the hemoglobin from exceeding 12 g/dL or rising too rapidly (greater than 1 g/dL in 2 weeks), the guidelines for dose and frequency of dose adjustments should be followed *[see Dosage and Administration (2.3)]*.

Average platelet counts decreased approximately 7% among patients receiving Mircera in clinical studies with most patients maintaining platelet counts within normal levels. The decrease in platelet counts occurred immediately following Mircera initiation and the levels remained stable thereafter. At least one post-baseline platelet count below 100 x 10^9/L was observed in 7.5% of patients treated with Mircera and 4.4% of patients treated with another ESA.

5.8 Allergic Reactions

Serious allergic reactions, consisting of tachycardia, pruritus and rash, have been reported in patients treated with Mircera. If a serious allergic or anaphylactic reaction occurs due to Mircera, treatment should be immediately and permanently discontinued and appropriate therapy should be administered.

5.9 Patients with CRF Not Requiring Dialysis

Patients with CRF not requiring dialysis may require lower maintenance doses of Mircera than patients receiving dialysis. Patients who are not receiving dialysis may be more responsive to the effects of Mircera and require judicious monitoring of blood pressure and hemoglobin. Renal function and fluid electrolyte balance should also be closely monitored.

5.10 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 who are marginally dialyzed may require adjustments in their dialysis prescription.

5.11 Laboratory Monitoring

In order to ensure effective erythropoiesis, iron status should be evaluated for all patients before and during treatment. Provide supplemental iron therapy for patients whose serum ferritin is below 100 mcg/L or whose serum transferrin saturation is below 20%.

During Mircera therapy, monitor hemoglobin every two weeks until the hemoglobin level has stabilized between 10 and 12 g/dL and the maintenance Mircera dose has been established. The hemoglobin should then

be monitored at least monthly. If a patient requires a dose adjustment or is switched to Mircera from another ESA, monitor hemoglobin every two weeks until the hemoglobin level has stabilized *[see Dosage and Administration (2.1)]*.

6 ADVERSE REACTIONS

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

- Increased mortality, serious cardiovascular and thromboembolic events *[see Warnings and Precautions (5.1)]*
- Increased mortality and/or tumor progression *[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 (5.5)]*

The most commonly reported adverse reactions were hypertension *[see Warnings and Precautions (5.3)]*, diarrhea, nasopharyngitis, headache, and upper respiratory tract infection. 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 chronic renal failure therapy and septic shock.

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.

Some of the adverse reactions reported are typically associated with CRF, 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 3 summarizes the most frequent adverse reactions (≥ 5%) in patients treated with Mircera.

Table 3 Adverse Reactions Occurring in ≥ 5% of CRF 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 erythropoietin, in association with PRCA or severe anemia (with or without other cytopenias), have been reported in patients receiving other ESAs during post-marketing experience *[see Warnings and Precautions (5.5)]*. 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.

7 DRUG INTERACTIONS

No formal drug/drug interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Category C

When Mircera 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, Mircera caused exaggerated pharmacodynamic effects in dams. Once-weekly doses of Mircera up to 50 mcg/kg/dose given to pregnant female rats did not adversely affect pregnancy parameters, natural delivery or litter observations. Increased deaths and significant reduction in growth rate of 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.

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.

8.3 Nursing Mothers

It is not known whether Mircera is excreted into human breast milk. In one study in rats, Mircera 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.

10 OVERDOSAGE

The expected manifestations of Mircera overdosage include signs and symptoms associated with an excessive and/or rapid increase in hemoglobin concentration, including any of the cardiovascular events described above *[see Warnings and Precautions (5.1)]* and *[Adverse Reactions (6.1)]*. Patients receiving an overdosage of Mircera should be monitored closely for cardiovascular events and hematologic abnormalities. Polycythemia should be managed acutely with phlebotomy, as clinically indicated. Following resolution of the effects due to Mircera overdosage, reintroduction of Mircera therapy should be accompanied by close monitoring for evidence of rapid increases in hemoglobin concentration (> 1 g/dL per 14 days). In patients with an excessive hematopoietic response, reduce the Mircera dose in accordance with the recommendations described in *Dosage and Administration (2.3)*.

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 IV or SC administration.

Injectable solutions of Mircera in vials and 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 chronic renal failure (CRF) and erythropoietin deficiency is the primary cause of their anemia.

12.2 Pharmacodynamics

Following a single dose of Mircera in CRF 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 (2.3)]*.

12.3 Pharmacokinetics

The pharmacokinetics of Mircera were studied in anemic patients with CRF including patients on dialysis and 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 CRF 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 CRF 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 CRF 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 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

Carcinogenicity

The carcinogenic potential of Mircera has not been evaluated in long-term animal studies. Mircera 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 Mircera was observed only in bone marrow progenitor cells.

Mutagenicity

The mutagenic potential of Mircera has not been evaluated.

Impairment of Fertility

When Mircera 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

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 CRF 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 CRF. 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 4 and Table 5). 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 4 provides the results of the two studies.

Table 4 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 5, 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 5 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 vials and single use prefilled syringes. The vial caps and plungers of prefilled syringes 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 Vial:		**Single Use Prefilled Syringe (PFS) with a Needle Guard. A 27 Gauge, ½ Inch Needle is also provided:**
1 Vial/Pack	**12 Vials/Pack**	**1 PFS/Pack**
50 mcg/1 mL (NDC 0004-0411-09)	50 mcg/1 mL (NDC 0004-0411-06)	50 mcg/0.3 mL (NDC 0004-0401-09)
100 mcg/1 mL (NDC 0004-0413-09)	100 mcg/1 mL (NDC 0004-0413-06)	75 mcg/0.3 mL (NDC 0004-0402-09)
200 mcg/1 mL (NDC 0004-0415-09)	200 mcg/1 mL (NDC 0004-0415-06)	100 mcg/0.3 mL (NDC 0004-0403-09)
300 mcg/1 mL (NDC 0004-0417-09)	300 mcg/1 mL (NDC 0004-0417-06)	150 mcg/0.3 mL (NDC 0004-0404-09)
400 mcg/1 mL (NDC 0004-0418-09)	400 mcg/1 mL (NDC 0004-0418-06)	200 mcg/0.3 mL (NDC 0004-0405-09)
600 mcg/1 mL (NDC 0004-0419-09)	600 mcg/1 mL (NDC 0004-0419-06)	250 mcg/0.3 mL (NDC 0004-0406-09)
1000 mcg/1 mL (NDC 0004-0420-09)	1000 mcg/1 mL (NDC 0004-0420-06)	400 mcg/0.6 mL (NDC 0004-0408-09)
		600 mcg/0.6 mL (NDC 0004-0409-09)
		800 mcg/0.6 mL (NDC 0004-0410-09)

16.2 Stability and Storage

The recommended storage temperature is at 2° to 8°C (36°F to 46°F). Do not freeze or shake. Protect from light.

Storage of vials 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 7 days.

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 (17.2) and Patient Instructions for Use

17.1 Information for Patients

Inform patients of the:

- Need for regular blood pressure monitoring and laboratory tests for hemoglobin in order to lessen the risks for mortality and serious cardiovascular events
- Possible side effects of Mircera, including injection site reactions, allergic reactions and the potential problems due to excessive increases in blood hemoglobin levels *[see Warnings and Precautions (5.1]*
- Signs and symptoms of injection site and allergic reactions
- Importance of compliance with any prescribed dietary restrictions, dialysis regimens or medications, including antihypertensive medications

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 Patient Instructions for Use
- Avoid the reuse of needles, syringes, or unused portions of the Mircera vials or 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

17.2 Medication Guide

MEDICATION GUIDE

MIRCERA® (mir-SER-ah)

(methoxy polyethylene glycol-epoetin beta)

Read this Medication Guide carefully before you start taking Mircera and each time you refill your Mircera prescription. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

Mircera stimulates your bone marrow to make more red blood cells. The increase in red blood cells also increases your hemoglobin level. 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 problems include:

Serious heart problems. These problems include heart attack, stroke, and congestive heart failure.

Blood clots. Mircera treatment increases your chance of a blood clot. If you are scheduled for surgery,

your healthcare provider may prescribe a blood thinner to prevent blood clots. Blood clots can form in your hemodialysis vascular access (such as arteriovenous fistulas) or in blood vessels, especially in the leg (deep venous thrombosis or DVT). Pieces of a blood clot may travel to the lungs. If this happens, blood circulation in the lungs may be blocked (pulmonary embolus).

Tell your healthcare provider or get medical attention right away if you have any of these symptoms while taking Mircera:

- Chest pain
- Trouble breathing or shortness of breath
- Pain in the legs, with or without swelling
- A cool or pale arm or leg
- Sudden confusion or trouble speaking or understanding speech
- Sudden numbness or weakness of the face, an arm or leg, especially on one side of the body
- Sudden trouble seeing in one or both eyes
- Sudden trouble walking, dizziness, loss of balance or coordination, loss of consciousness
- Sudden severe headache with no known cause
- Seizures (convulsions)
- Blood clots in your hemodialysis vascular access (such as arteriovenous fistulas).

It is important for you to have the blood tests ordered by your healthcare provider. Your healthcare provider will try to keep your hemoglobin level between 10 and 12 g/dL.

Mircera is not used to treat anemia caused by cancer chemotherapy. In patients with cancer, drugs that act like Mircera increase the chance of dying sooner or making the cancer grow faster. In a clinical study of cancer patients, more deaths occurred among patients receiving Mircera compared to another drug that also increases blood hemoglobin.

What is Mircera?

Mircera is a man-made form of the human protein erythropoietin. Erythopoietin is normally produced by the kidneys. Mircera and other man-made erythropoietins are ESAs (Erythropiesis-Stimulating Agents). ESAs stimulate bone marrow to make red blood cells. The increase in red blood cells also increases the blood hemoglobin level. Your healthcare provider will prescribe the lowest dose of Mircera needed to help increase your hemoglobin level to between 10 to 12 g/dL and to help avoid the need for red blood cell transfusions.

You may be asked to have certain blood tests, such as hemoglobin, hematocrit, or iron level measurements. Based on your test results, your healthcare provider will adjust the dose of Mircera as needed to reach the right dose for you and to help prevent serious side effects. The right dose for you may change over time.

Mircera is not used to treat anemia that is caused by other health problems, such as cancer.

Mircera has not been studied in children.

Who should not take Mircera?

Do not take Mircera if:

- You have high blood pressure that is not controlled (uncontrolled hypertension)
- You have allergies to Mircera or other ESAs
- You have anemia caused by cancer chemotherapy

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 any history of stroke, blood clots or seizures
- Have blood disorders (such as sickle cell anemia or clotting disorders)
- Are pregnant, think you may be pregnant or plan to become pregnant. The effect of Mircera on pregnant women is unknown. It is also not known if Mircera could harm an unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if Mircera passes into human breast milk.

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

How should I take Mircera?

Mircera is taken as either an intravenous (IV) or subcutaneous (SC) injection. It can take two to six weeks of treatment to see an increase in your hemoglobin level. If the desired increase is not seen, your healthcare provider may change your treatment dose.

- Mircera should be administered by your healthcare provider. In some cases, your healthcare provider may allow you or your caregiver to give the injections at home.
- If you or your caregiver are allowed to give the injections at home, it is important that you carefully follow the instructions that your healthcare provider gives you. Be sure that you read, understand, and follow the "Patient Instructions for Use."
- 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 or your caregiver how much Mircera to use, how to inject it, how often it should be injected and how to safely throw away used needles and syringes.
- Change the skin site for each injection to avoid soreness at any one site. Sometimes a problem may develop at the injection site. If there is a lump, swelling, or bruising at the injection site that does not go away, talk to your healthcare provider.
- **To use Mircera safely at home, it is important that you:**
    - Use the contents of a vial or prefilled syringe one time only
    - Throw away any solution remaining in the vial after use
    - Use a needle and syringe only one time for injection
- If you have a hemodialysis vascular access, regularly check it to make sure it is working. Call your healthcare provider or dialysis center right away if you have any problems or questions.
- If you miss one dose of Mircera, take your dose right away and then continue as you have been told by your healthcare provider. If you miss more than one dose, call your healthcare provider right away for instructions on what to do.

- If you take more than the prescribed amount of Mircera, call your healthcare provider right away for instructions on what to do.
- Continue to follow your healthcare provider's instructions for diet, dialysis, and medicines including medicines for high blood pressure, while taking Mircera.

What are possible side effects of Mircera?

Mircera can cause serious side effects. See **"What is the most important information I should know about Mircera?"**

Other side effects, which may be serious include:

- **High blood pressure.** Your blood pressure may go up when the numbers of red blood cells increase while taking Mircera. This can happen even if you have never had high blood pressure before. Your healthcare provider or caregiver should check your blood pressure often. If you have a history of heart problems or high blood pressure, talk with your healthcare provider about how often to check your blood pressure. Call your healthcare provider if your blood pressure changes from what is normal for you. If your blood pressure does increase, your healthcare provider may prescribe new or more blood pressure medicine.
- **Seizures.** Seizures can occur in people receiving Mircera. If you have any seizures while taking Mircera, get medical help right away and tell your healthcare provider.
- **Serious allergic reaction.** Mircera may cause a serious allergic reaction. Symptoms of a serious allergic reaction may include: a rash all over the body, shortness of breath, wheezing, dizziness, fainting, swelling around the mouth or eyes, fast pulse, or sweating. If a serious allergic reaction occurs, stop using Mircera and call your healthcare provider or get emergency medical help right away.
- **No response or loss of your hemoglobin response to Mircera.** If your hemoglobin does not reach the desired level of 10 to 12 g/dL or your hemoglobin does not stay within this level, 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.

The most common side effects you may have when taking Mircera are:

- Increased blood pressure (hypertension)
- Diarrhea
- Upper respiratory tract infections (cold, cough and sinus infections)
- Headache

Other side effects when taking Mircera may include:

- Decreased blood pressure (hypotension)
- Vomiting
- Constipation
- Urinary tract infections
- Body or muscle aches, including back pain
- Swelling in your arms or legs with or without shortness of breath
- Problems with your hemodialysis vascular access (such as arteriovenous fistulas), including clotting and fistula site problems

- Injection site reactions such as redness, swelling, or itching. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Mircera. Your healthcare provider or pharmacist can give you a more complete list.

How should I store Mircera?

- Keep Mircera in the original package. Protect Mircera from light. Do not use Mircera that has been left in bright light.
- Do not shake Mircera
- Store Mircera 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 or less (25°C or less) for up to 30 days
- Mircera Vials can be stored at room temperature 77°F or less (25°C or less) for up to 7 days
- Do not freeze Mircera. Do not use Mircera that has been frozen or improperly refrigerated. Talk to your healthcare provider or pharmacist with any questions about storing 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 to know more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Mircera that is written for health professionals. For more information, go to www.MIRCERA.com OR call 1-800-526-6367.

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

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

U.S. Govt. Lic. No. 0136

Issued: November 2007

Copyright © 2007 by Hoffmann-La Roche Inc. All rights reserved.

NOV 1 4 2007

MEDICATION GUIDE

MIRCERA® (mir-SER-ah)

(methoxy polyethylene glycol-epoetin beta)

Read this Medication Guide carefully before you start taking Mircera and each time you refill your Mircera prescription. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

Mircera stimulates your bone marrow to make more red blood cells. The increase in red blood cells also increases your hemoglobin level. 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 problems include:

Serious heart problems. These problems include heart attack, stroke, and congestive heart failure.

Blood clots. Mircera treatment increases your chance of a blood clot. If you are scheduled for surgery, your healthcare provider may prescribe a blood thinner to prevent blood clots. Blood clots can form in your hemodialysis vascular access (such as arteriovenous fistulas) or in blood vessels, especially in the leg (deep venous thrombosis or DVT). Pieces of a blood clot may travel to the lungs. If this happens, blood circulation in the lungs may be blocked (pulmonary embolus).

Tell your healthcare provider or get medical attention right away if you have any of these symptoms while taking Mircera:

- Chest pain
- Trouble breathing or shortness of breath
- Pain in the legs, with or without swelling
- A cool or pale arm or leg
- Sudden confusion or trouble speaking or understanding speech
- Sudden numbness or weakness of the face, an arm or leg, especially on one side of the body
- Sudden trouble seeing in one or both eyes
- Sudden trouble walking, dizziness, loss of balance or coordination, loss of consciousness
- Sudden severe headache with no known cause
- Seizures (convulsions)
- Blood clots in your hemodialysis vascular access (such as arteriovenous fistulas).

It is important for you to have the blood tests ordered by your healthcare provider. Your healthcare provider will try to keep your hemoglobin level between 10 and 12 g/dL.

Mircera is not used to treat anemia caused by cancer chemotherapy. In patients with cancer, drugs that act like Mircera increase the chance of dying sooner or making the cancer grow faster. In a clinical study of cancer patients, more deaths occurred among patients receiving Mircera compared to another drug that also increases blood hemoglobin.

What is Mircera?

Mircera is a man-made form of the human protein erythropoietin. Erythopoietin is normally produced by the kidneys. Mircera and other man-made erythropoietins are ESAs (Erythropiesis-Stimulating Agents). ESAs stimulate bone marrow to make red blood cells. The increase in red blood cells also increases the blood

hemoglobin level. Your healthcare provider will prescribe the lowest dose of Mircera needed to help increase your hemoglobin level to between 10 to 12 g/dL and to help avoid the need for red blood cell transfusions.

You may be asked to have certain blood tests, such as hemoglobin, hematocrit, or iron level measurements. Based on your test results, your healthcare provider will adjust the dose of Mircera as needed to reach the right dose for you and to help prevent serious side effects. The right dose for you may change over time.

Mircera is not used to treat anemia that is caused by other health problems, such as cancer.

Mircera has not been studied in children.

Who should not take Mircera?

Do not take Mircera if:

- You have high blood pressure that is not controlled (uncontrolled hypertension)
- You have allergies to Mircera or other ESAs
- You have anemia caused by cancer chemotherapy

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 any history of stroke, blood clots or seizures
- Have blood disorders (such as sickle cell anemia or clotting disorders)
- Are pregnant, think you may be pregnant or plan to become pregnant. The effect of Mircera on pregnant women is unknown. It is also not known if Mircera could harm an unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if Mircera passes into human breast milk.

Tell your healthcare provider about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

How should I take Mircera?

Mircera is taken as either an intravenous (IV) or subcutaneous (SC) injection. It can take two to six weeks of treatment to see an increase in your hemoglobin level. If the desired increase is not seen, your healthcare provider may change your treatment dose.

- Mircera should be administered by your healthcare provider. In some cases, your healthcare provider may allow you or your caregiver to give the injections at home.
- If you or your caregiver are allowed to give the injections at home, it is important that you carefully follow the instructions that your healthcare provider gives you. Be sure that you read, understand, and follow the "Patient Instructions for Use."
- 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 or your caregiver how much Mircera to use, how to inject it, how often it should be injected and how to safely throw away used needles and syringes.

- Change the skin site for each injection to avoid soreness at any one site. Sometimes a problem may develop at the injection site. If there is a lump, swelling, or bruising at the injection site that does not go away, talk to your healthcare provider.

- **To use Mircera safely at home, it is important that you:**
  - Use the contents of a vial or prefilled syringe one time only
  - Throw away any solution remaining in the vial after use
  - Use a needle and syringe only one time for injection

- If you have a hemodialysis vascular access, regularly check it to make sure it is working. Call your healthcare provider or dialysis center right away if you have any problems or questions.
- If you miss one dose of Mircera, take your dose right away and then continue as you have been told by your healthcare provider. If you miss more than one dose, call your healthcare provider right away for instructions on what to do.
- If you take more than the prescribed amount of Mircera, call your healthcare provider right away for instructions on what to do.
- Continue to follow your healthcare provider's instructions for diet, dialysis, and medicines including medicines for high blood pressure, while taking Mircera.

What are possible side effects of Mircera?

Mircera can cause serious side effects. See **"What is the most important information I should know about Mircera?"**

Other side effects, which may be serious include:

- **High blood pressure.** Your blood pressure may go up when the numbers of red blood cells increase while taking Mircera. This can happen even if you have never had high blood pressure before. Your healthcare provider or caregiver should check your blood pressure often. If you have a history of heart problems or high blood pressure, talk with your healthcare provider about how often to check your blood pressure. Call your healthcare provider if your blood pressure changes from what is normal for you. If your blood pressure does increase, your healthcare provider may prescribe new or more blood pressure medicine.
- **Seizures.** Seizures can occur in people receiving Mircera. If you have any seizures while taking Mircera, get medical help right away and tell your healthcare provider.
- **Serious allergic reaction.** Mircera may cause a serious allergic reaction. Symptoms of a serious allergic reaction may include: a rash all over the body, shortness of breath, wheezing, dizziness, fainting, swelling around the mouth or eyes, fast pulse, or sweating. If a serious allergic reaction occurs, stop using Mircera and call your healthcare provider or get emergency medical help right away.
- **No response or loss of your hemoglobin response to Mircera.** If your hemoglobin does not reach the desired level of 10 to 12 g/dL or your hemoglobin does not stay within this level, 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.

The most common side effects you may have when taking Mircera are:

- Increased blood pressure (hypertension)
- Diarrhea

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

Other side effects when taking Mircera may include:

- Decreased blood pressure (hypotension)
- Vomiting
- Constipation
- Urinary tract infections
- Body or muscle aches, including back pain
- Swelling in your arms or legs with or without shortness of breath
- Problems with your hemodialysis vascular access (such as arteriovenous fistulas), including clotting and fistula site problems
- Injection site reactions such as redness, swelling, or itching. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Mircera. Your healthcare provider or pharmacist can give you a more complete list.

How should I store Mircera?

- Keep Mircera in the original package. Protect Mircera from light. Do not use Mircera that has been left in bright light.
- Do not shake Mircera
- Store Mircera 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 or less (25°C or less) for up to 30 days
- Mircera Vials can be stored at room temperature 77°F or less (25°C or less) for up to 7 days
- Do not freeze Mircera. Do not use Mircera that has been frozen or improperly refrigerated. Talk to your healthcare provider or pharmacist with any questions about storing 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 to know more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Mircera that is written for health professionals. For more information, go to www.MIRCERA.com OR call 1-800-526-6367.

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

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

U.S. Govt. Lic. No. 0136

Revised: November 2007

Copyright © 2007 by Hoffmann-La Roche Inc. All rights reserved.

Patient Instructions for Use

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

NOV 1 4 2007

Single Use Prefilled Syringe (for Injection)

Read the Medication Guide that comes with Mircera for the most important information you need to know. It is also very important that you carefully read and understand these instructions for how to give yourself the correct dose of Mircera.

When you receive your supply of Mircera, make sure that:

1. The name Mircera appears on the pack.
2. Mircera is used before the expiration date on the pack. Do not use Mircera after the expiration date.
3. The dosage strength on the Mircera pack matches the strength prescribed [number of micrograms (mcg)].
4. The liquid in Mircera is clear and colorless to slightly yellow. Do not use Mircera if the liquid appears discolored or cloudy, or if it appears to have lumps, flakes or particles in it.
5. The needle cover is on the prefilled syringe of Mircera. Do not use the prefilled syringe of Mircera if the cover on the needle is off.
6. The prefilled syringe and needle used for administration of Mircera is the one prescribed by your healthcare provider. The dose of Mircera will be measured in micrograms (mcg). Mircera can be given either by a prefilled syringe or a vial using a syringe and needle. Mircera prefilled syringes and vials come in several different strengths. If you change from using the vials (syringes and needles) of Mircera to the prefilled syringes, the strength of medicine will be different. Talk with your healthcare provider or pharmacist to be sure you understand the difference. **Use the prefilled syringe only once. Throw away the prefilled syringe in a puncture-proof disposable container after use as instructed by your healthcare provider.**

Your healthcare provider should tell you how to give the correct dose of Mircera:

- How much Mircera to use
- How to inject
- How often it should be injected
- How to throw away used syringes

IMPORTANT: FOLLOW THESE INSTRUCTIONS TO GIVE MIRCERA INJECTIONS AND AVOID POSSIBLE INFECTION.

SETTING UP FOR AN INJECTION

1. Find a clean, flat work surface such as a table.
2. Take a pack of Mircera from the refrigerator. Do not freeze Mircera or use a prefilled syringe that has been frozen. Do not shake Mircera or leave it in bright light. Shaking the prefilled syringe or exposing it to light may damage Mircera and it may not work as well. If the Mircera prefilled syringe has been shaken, the solution may look foamy and should not be used.
3. Take the prefilled syringe of Mircera out of its pack and place it on your flat work surface.
4. Use a prefilled syringe only once.
5. Gather the supplies you will need for an injection (see Figure 1). You will need:

- Mircera prefilled syringe with a clear plastic needle guard attached
- One alcohol swab and one cotton ball or gauze
- Puncture-proof disposable container, which will be given to you by your healthcare provider, for safely throwing away the prefilled syringe after injection

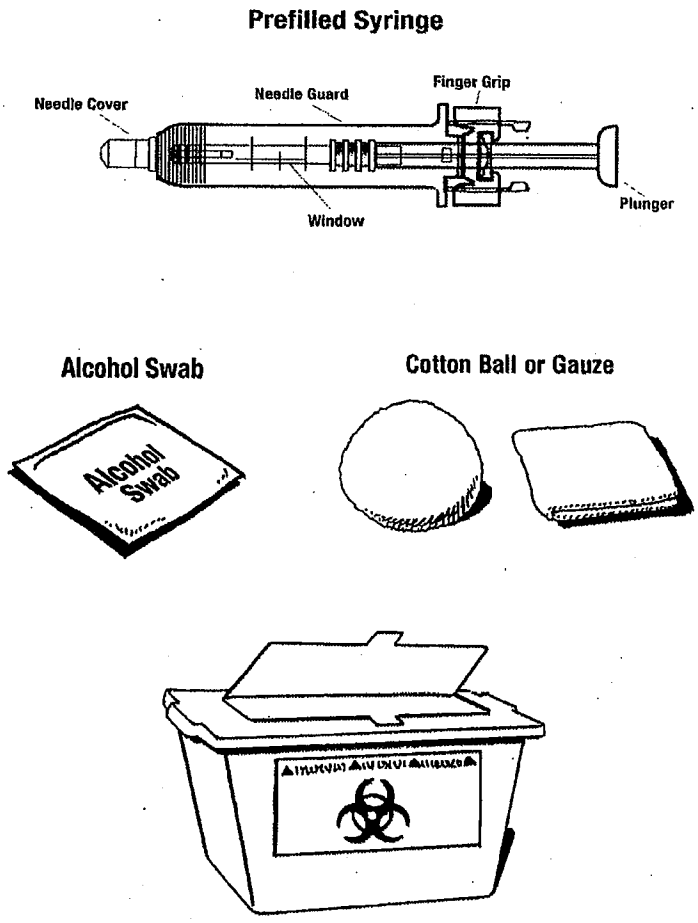

Figure 1.

6. Wash your hands well with soap and warm water before preparing the dose.

PREPARING THE DOSE OF Mircera

1. Open the wrapper and remove the prefilled syringe and needle.

2. Break the seal and remove the plastic cap from the back of the needle (see Figure 2).

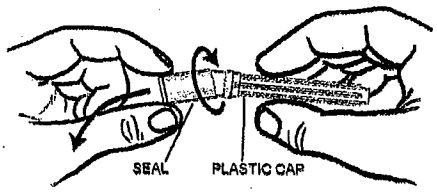

Figure 2.

3. Remove the rubber tip cap from the prefilled syringe. It may require a strong pull (see Figure 3).

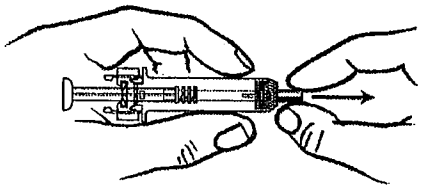

Figure 3.

4. Attach the needle to the prefilled syringe (see Figure 4).

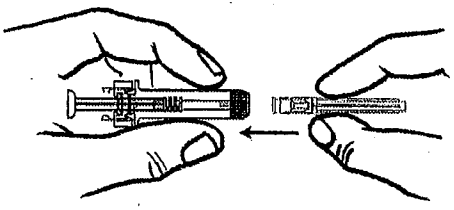

Figure 4.

5. Put the prefilled syringe on its side with the needle cover on. This will keep the needle from touching anything before you use it (see Figure 5).

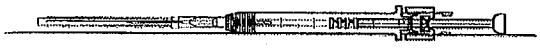

Figure 5.

5 SELECTING AND PREPARING THE INJECTION SITE

1. Choose an injection site (see Figure 6). The three sites where you can inject Mircera include:

- the outer area of the upper arms
- the front of the middle thighs
- the abdomen (except for the two-inch area around the navel)

Choose a new injection site each time you inject Mircera. This helps to avoid soreness at any one site.

Do not inject Mircera into an area on your body that is tender, red, bruised, hard, or that has scars or stretch marks.

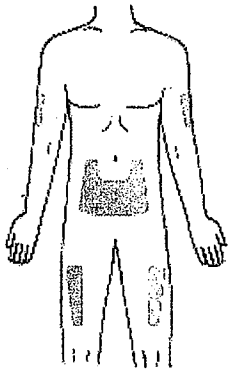

Figure 6.

6

2. Clean the injection site with a new alcohol swab. Do not touch this area again before giving the injection (see Figure 7).

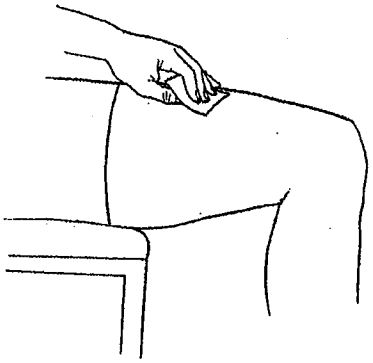

Figure 7.

7 **INJECTING THE DOSE OF Mircera FOR PATIENTS NOT ON HEMODIALYSIS**

1. Remove the plastic cover from the needle (see Figure 8).

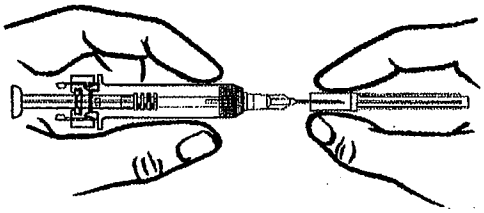

Figure 8.

2. Remove air bubbles from the syringe. Hold the prefilled syringe with the needle pointing up. Tap the prefilled syringe gently to bring the bubbles to the top. Push the plunger up slowly to the correct dose.

3. Hold the prefilled syringe in the hand that you will use to inject Mircera. Use the other hand to pinch a fold of skin at the cleaned injection site (see Figure 9).

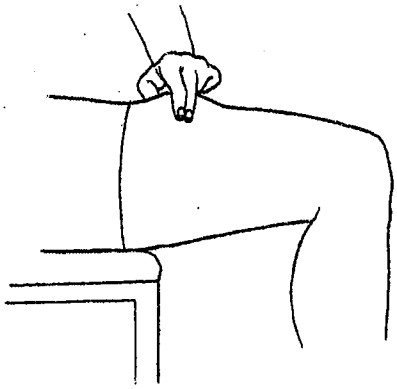

Figure 9.

4. Hold the prefilled syringe like a pencil. Insert the needle in a quick "dart like" motion. Inject either at a slight angle (45 degree angle) or straight up and down (90 degree angle) into the skin (see Figure 10).

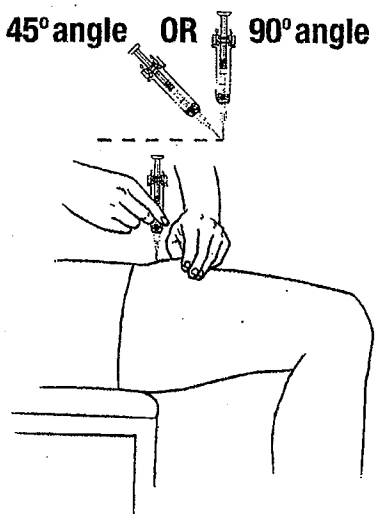

Figure 10.

5. Pull the plunger back slightly after inserting the needle into the skin. If blood comes into the prefilled syringe, do not inject Mircera because the needle has entered a blood vessel. Remove the needle from the skin. Slightly reposition the needle within the cleaned area and repeat. If blood does not come, slowly push the plunger all the way down until all the medicine is injected. The plastic needle guard (a safety mechanism to prevent accidental needle sticks) will not move forward to cover the needle unless the full dose is given. (see Figure 11).

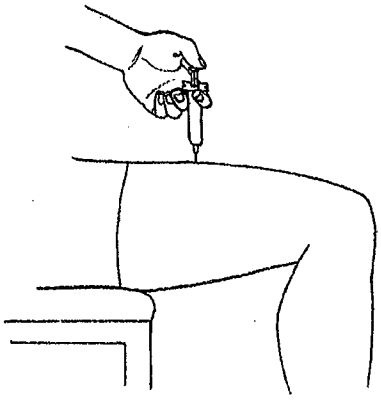

Figure 11.

6. Take the needle out of the skin without releasing the plunger (see Figure 12).

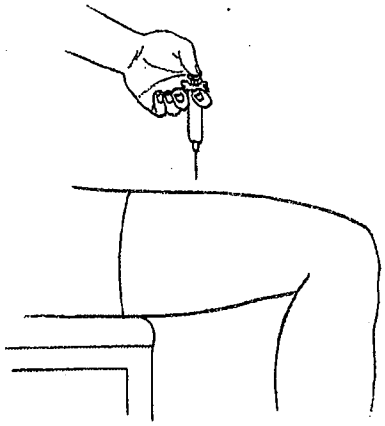

Figure 12.

7. Release the plunger after removing the needle from the skin. This allows the syringe to move back until the entire needle is guarded (see Figure 13).

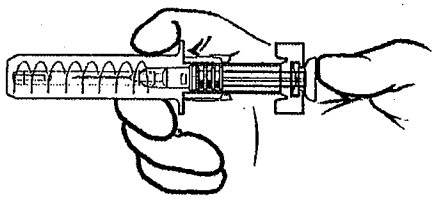

Figure 13.

8

8. Place a cotton ball or gauze over the injection site and press for several seconds (see Figure 14).

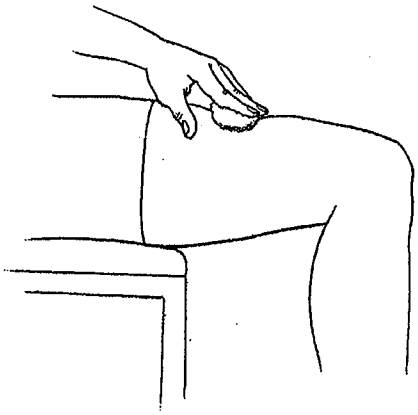

Figure 14.

9. Dispose of the syringe with any remaining liquid in the puncture-proof disposable container. Use the prefilled syringe one time only.

9 **<u>FOR PATIENTS ON HEMODIALYSIS USING VENOUS INJECTION</u>**

1. Clean the venous port of the hemodialysis tubing with a new alcohol swab (see Figure 15).

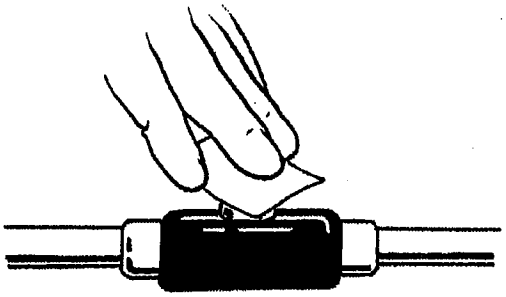

Figure 15.

2. Insert the needle of the syringe into the cleaned venous port and push the plunger all the way down to inject all the medicine (see Figure 16).

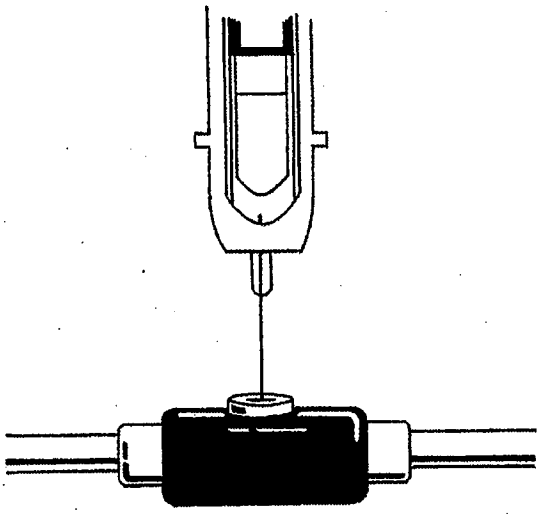

Figure 16.

3. Remove the syringe from the venous port. Dispose of the syringe with any remaining liquid in the puncture-proof disposable container. Use the prefilled syringe one time only.

Disposing of Syringes and Needles

Follow the required state and local laws for disposal of needles and syringes. Ask your healthcare provider or pharmacist about correct disposal of used syringes and needles.

Use the information below as a general guide:

- never re-use a syringe or needle
- place used syringes and needles in the puncture-proof disposable container
- DO NOT use glass or clear plastic containers to throw away syringes and needles
- Throw away the full puncture-proof disposable container as instructed by your healthcare provider or pharmacist

DO NOT throw away the puncture-proof disposable container in your household trash. DO NOT recycle. Keep the container out of the reach of children.

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

U.S. Govt. Lic. No. 0136

Issued: November 2007

xxxxxxxx

Copyright © 2007 by Hoffmann-La Roche Inc. All rights reserved.

Patient Instructions for Use

NOV 1 4 2007

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

Single Use Vial (for Injection)

Read the Medication Guide that comes with Mircera for the most important information you need to know. It is very important that you carefully read and understand these instructions for how to give yourself the correct dose of Mircera.

When you receive your supply of Mircera, make sure that:

1. The name Mircera appears on the pack.
2. Mircera is used before the expiration date on the pack. Do not use Mircera after the expiration date.
3. The dosage strength on the Mircera pack matches the strength prescribed [number of micrograms (mcg)].
4. The liquid in Mircera is clear and colorless to slightly yellow. Do not use Mircera if the liquid appears discolored or cloudy, or if it appears to have lumps, flakes or particles in it.
5. The colored cap is on the vial of Mircera. Do not use the vial of Mircera if the colored cap has been removed.
6. The disposable syringe and needle used for administration of Mircera are the ones prescribed by your healthcare provider. Mircera can be given either by a prefilled syringe or a vial using a syringe and needle. Mircera vials and prefilled syringes come in several different strengths. If you change from using the vials (syringes and needles) of Mircera to the prefilled syringes, the strength of medicine will be different. Talk with your healthcare provider or pharmacist to be sure you understand the difference. **Use the disposable syringe and needle only once. Throw away the syringe and needle in a puncture-proof disposable container after use as instructed by your healthcare provider.**

Your healthcare provider should tell you how to give the correct dose of Mircera:

- How much Mircera to use
- How to inject
- How often it should be injected
- How to throw away used needles and syringes

The dose will be measured in mcg per milliliters (mL). Use only a disposable syringe that is marked in tenths of mL (for example, 0.2 mL). Your healthcare provider may refer to an "mL" as a "cc" (1 mL = 1 cc). Do not use an unmarked syringe. Using an unmarked syringe can lead to a mistake in the dose. If you do not use the correct syringe, you could inject too much or too little Mircera.

IMPORTANT: FOLLOW THESE INSTRUCTIONS TO GIVE MIRCERA INJECTIONS AND AVOID POSSIBLE INFECTION.

SETTING UP FOR AN INJECTION

1. Find a clean, flat work surface such as a table.
2. Take a pack of Mircera from the refrigerator. Do not freeze Mircera or use a vial that has been frozen. Do not shake Mircera or leave it in bright light. Shaking the vial or exposing it to light may damage Mircera and it may not work as well. If the Mircera vial has been shaken, the solution may look foamy and should not be used.
3. Take the vial of Mircera out of its pack and place it on your flat work surface.
4. Use a vial only once. Do not put the needle through the rubber stopper more than once.

5. Gather the supplies you will need for an injection (see Figure 1). You will need:

- Mircera vial and the correct disposable syringe and needle
- Two alcohol swabs and one cotton ball or gauze
- Puncture-proof disposable container, which will be given to you by your healthcare provider, for safely throwing away the needle and syringe after injection

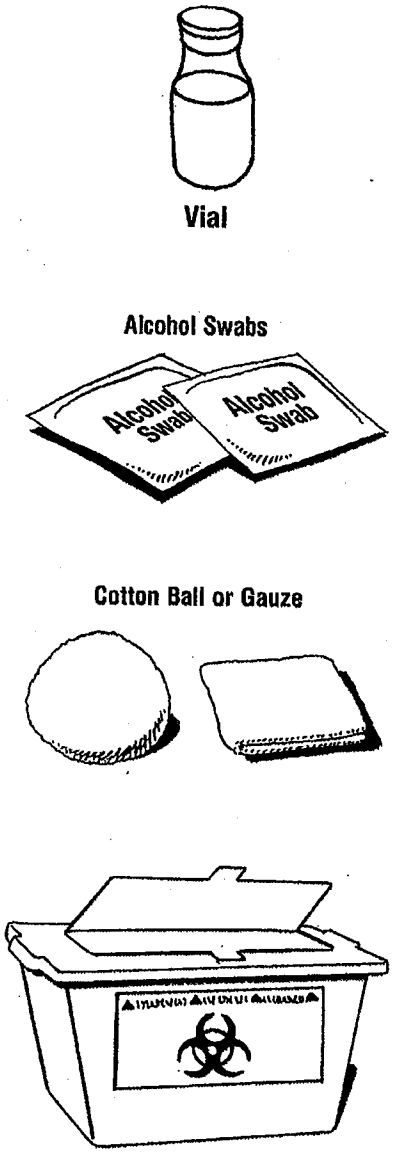

Figure 1.

6. Wash your hands well with soap and warm water before preparing the dose.

9 PREPARING THE DOSE OF Mircera

1. Remove the protective colored cap from the vial (see Figure 2).

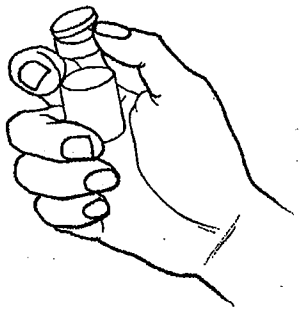

Figure 2.

2. Clean the rubber stopper on the vial with one alcohol swab and put the vial on your flat work surface (see Figure 3).

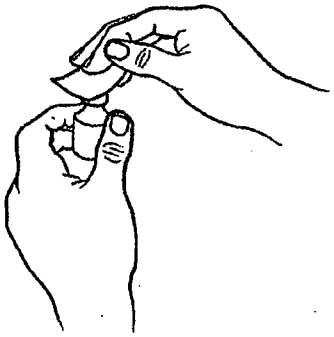

Figure 3.

3. Check the package containing the disposable syringe. If the syringe package is not damaged, open it and take out the syringe. If the package is damaged or has already been opened, do not use that syringe. Throw it away in the puncture-proof disposable container and get a new one.

4. Pull off the needle cover. Then, pull back on the plunger to the dose of Mircera that your healthcare provider has given you (in mL or cc). This will pull air into the syringe (see Figure 4).

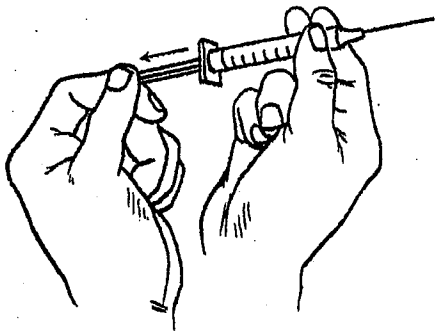

Figure 4.

5. Keep the vial on your flat work surface and insert the needle straight down through the rubber stopper (see Figure 5).

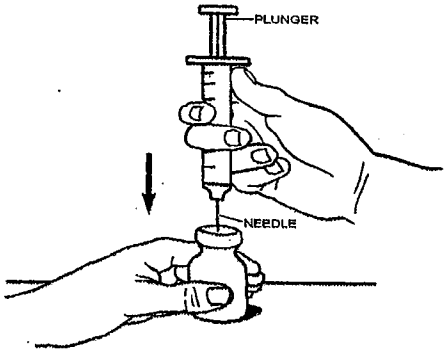

Figure 5.

6. Push down on the plunger of the syringe to inject the air from the syringe into the vial. The air injected into the vial will allow Mircera to be easily withdrawn into the syringe (see Figure 6).

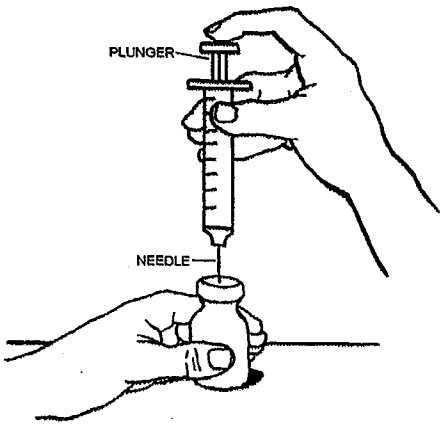

Figure 6.

7. Turn the vial upside down, keeping the needle inside the vial. Make sure that the tip of the needle is in the Mircera liquid. Your other hand will be free to move the plunger. Slowly pull back on the plunger to fill the syringe with Mircera liquid to the number (mL or cc) that matches the dose your healthcare provider has given you (see Figure 7).

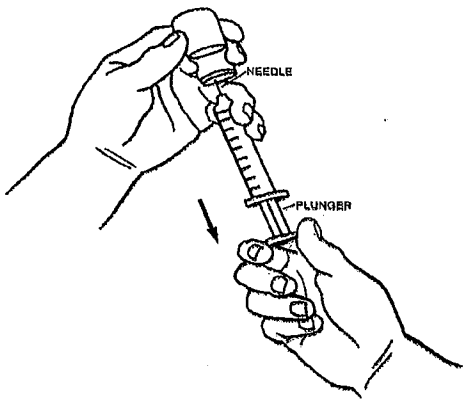

Figure 7.

8. Check for air bubbles in the syringe, keeping the needle inside the vial. Small air bubbles are harmless, but too large an air bubble will not let you draw up the right amount of Mircera. To remove air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe.

9. Slowly push on the plunger to push the solution and the air bubbles out of the syringe and back into the vial (see Figure 8).

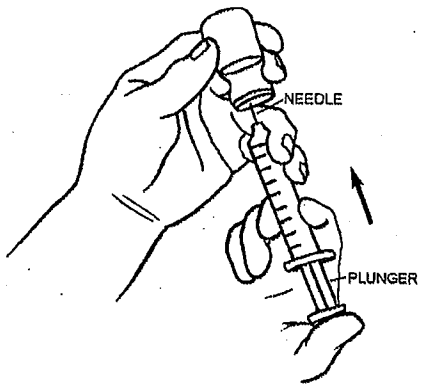

Figure 8.

10. Once again, pull the plunger back to the number on the syringe that matches your dose while making sure the tip of the needle is in the liquid. Check again for air bubbles. If there are still air bubbles, remove them by repeating Steps 8 through 10 (see Figure 9).

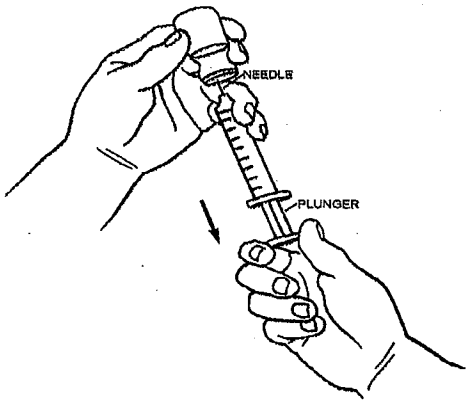

Figure 9.

11. Once you have gotten rid of all air bubbles, check again to make sure you have the right dose. Put the vial on its side with the needle still in it. This will keep the needle from touching anything before you use it (see Figure 10).

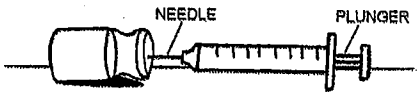

Figure 10.

0 SELECTING AND PREPARING THE INJECTION SITE

1. Choose an injection site (see Figure 11). The three sites where you can inject Mircera include:

- the outer area of the upper arms
- the front of the middle thighs
- the abdomen (except for the two-inch area around the navel)

Choose a new injection site each time you inject Mircera. This helps to avoid soreness at any one site.

Do not inject Mircera into an area on your body that is tender, red, bruised, hard, or that has scars or stretch marks.

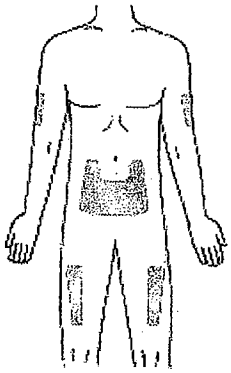

Figure 11.

2. Clean the injection site with a new alcohol swab. Do not touch this area again before giving the injection (see Figure 12).

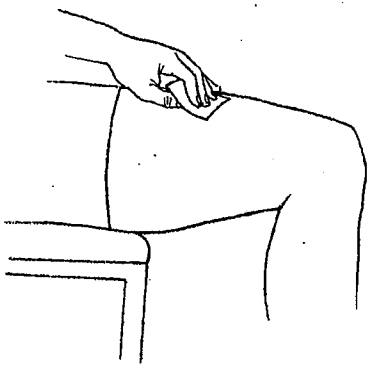

Figure 12.

1 INJECTING THE DOSE OF Mircera FOR PATIENTS NOT ON HEMODIALYSIS

1. Hold the syringe in the hand that you will use to inject Mircera. Use the other hand to pinch a fold of skin at the cleaned injection site (see Figure 13).

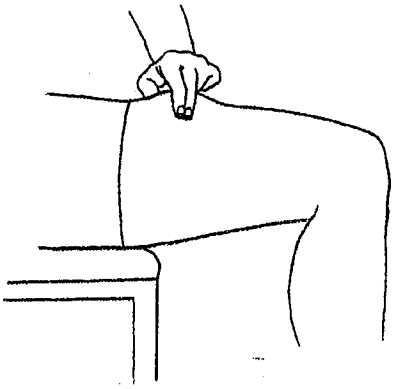

Figure 13.

2. Hold the syringe like a pencil. Insert the needle in a quick "dart like" motion. Inject either at a slight angle (45 degree angle) or straight up and down (90 degree angle) into the skin (see Figure 14).

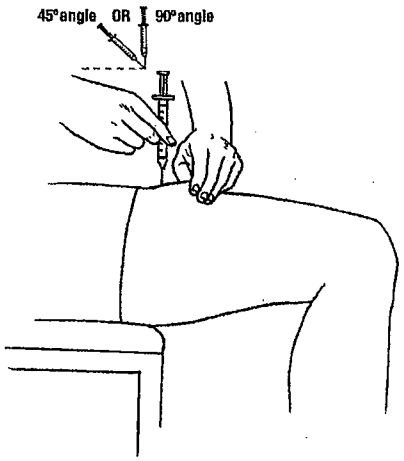

Figure 14.

3. Pull the plunger back slightly after inserting the needle into the skin. If blood comes into the syringe, do not inject Mircera because the needle has entered a blood vessel. Remove the needle from the skin. Slightly reposition the needle within the cleaned area and repeat. If blood does not come, slowly push the plunger all the way down, until all the medicine is injected (see Figure 15).

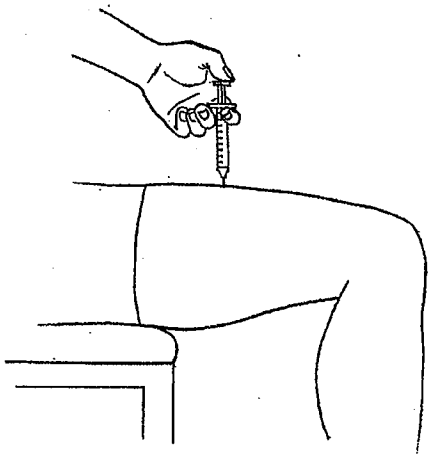

Figure 15.

4. Take the needle out of the skin. Place a cotton ball or gauze over the injection site and press for several seconds (see Figure 16).

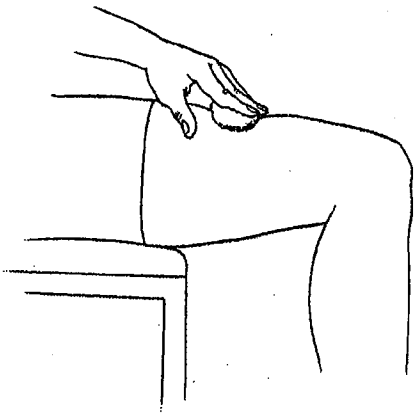

Figure 16.