MIRCERA®
methoxy polyethylene glycol-epoetin beta

MIRCERA® (methoxy polyethylene glycol-epoetin beta) Injection, For Intravenous or Subcutaneous Use

PRODUCT MONOGRAPH

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS and TUMOR PROGRESSION OR RECURRENCE[1]

Chronic Kidney Disease:

- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest Mircera dose sufficient to reduce the need for red blood cell (RBC) transfusions.**

Cancer:

- **Mircera is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircera was terminated early because of more deaths among patients receiving Mircera than another ESA.**
- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.**

Please see additional Important Safety Information, full Prescribing Information, including Boxed WARNING, and Medication Guide.

TABLE OF CONTENTS

Section 1: EXECUTIVE SUMMARY

Anemia and Chronic Kidney Disease (CKD)

Anemia is defined as a state in which the quality and/or quantity of circulating red blood cells (RBC)s are below normal. It is usually detected by low blood hemoglobin concentration, which can be directly measured and has an international standard.[2]

Anemia is a common complication in CKD and its prevalence increases with CKD progression. One major cause of anemia in CKD is erythropoietin production deficiency due to kidney damage. Other factors may contribute to the anemia in CKD, including decreased red blood cell survival, iron and folate deficiencies, and the accumulation of toxic inhibitors of erythropoiesis.[3]

The Kidney Disease Improving Global Outcomes (KDIGO) and National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline and Clinical Practice Recommendations for Anemia in CKD recommend monitoring patients with CKD for anemia and initiating treatment with ESAs only after addressing all correctable causes of anemia, including iron deficiency and inflammation.[4-6]

Treatment of Anemia in CKD

MIRCERA (methoxy polyethylene glycol-epoetin beta) injection, a US Food and Drug Administration (FDA)-approved ESA, is indicated for the treatment of anemia associated with CKD.[1]

- MIRCERA is approved for both the correction and maintenance of hemoglobin levels in adult patients and for the maintenance of hemoglobin levels in pediatric patients.[1]
- MIRCERA is approved for adult patients with CKD not on dialysis, receiving peritoneal dialysis, or on hemodialysis, and for pediatric patients (ages 5-17 years) on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.[1]

The efficacy and safety of MIRCERA has been studied in 6 phase III open-label, multicenter clinical studies in adult patients.[7-12] Two studies evaluated anemic patients with CKD who were not treated with an ESA at baseline, and 4 studies evaluated patients who were previously receiving an ESA for treatment of the anemia of CKD.[7-12] The results of the studies in treatment-naive patients indicated that MIRCERA effectively corrected anemia in 93% to 98% of patients.[1] The remaining studies demonstrated that MIRCERA consistently maintained hemoglobin levels in the hemoglobin target range.

More recently, the safety and efficacy of MIRCERA was studied in pediatric patients (ages 5-17 years) with CKD who were on hemodialysis and who had stable hemoglobin levels while previously receiving another ESA. An open-label, multiple-dose, multicenter trial was conducted to determine the dose of intravenous MIRCERA when converting from treatment with another ESA (epoetin alfa/beta or darbepoetin alfa).[1,13]

MIRCERA has a unique dosing regimen and can be dosed every 2 weeks in adult patients and monthly in adult and pediatric patients.[1]

MIRCERA is currently available as a single-dose prefilled syringe in 6 strengths.[1]

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Section 2: PRODUCT INFORMATION

2.1 Indications and Limitations of Use[1]

Anemia Due to CKD

MIRCERA (methoxy polyethylene glycol-epoetin beta) is indicated for the treatment of anemia associated with CKD in:

- Adult patients on dialysis and adult patients not on dialysis
- Pediatric patients (ages 5-17 years) on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA

Limitations of Use

MIRCERA is not indicated and is not recommended for use:

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

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

2.2 Safety of MIRCERA[1]

2.2.1 Adverse Reactions

Serious adverse reactions in patients treated with MIRCERA include the following:

- Increased mortality, myocardial infarction (MI), stroke, and thromboembolism
- Increased mortality and/or tumor progression in patients with cancer
- Hypertension
- Seizures
- Pure red cell aplasia (PRCA)
- Serious allergic reactions
- Severe cutaneous reactions

Clinical Trials Experience

In clinical trials, 2737 adult patients were exposed to MIRCERA, 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, n=948 received another ESA) and in long-term follow-up studies.

In the controlled trials, the rates of serious adverse reactions did not significantly differ between patients receiving MIRCERA and another ESA (38% vs 42%), except for the occurrence of serious gastrointestinal hemorrhage (1.2% vs 0.2%). Adverse reaction rates did not importantly differ between patients receiving MIRCERA or another ESA.

The most commonly reported adverse reactions in ≥10% of patients were hypertension, diarrhea, and nasopharyngitis. The most common adverse reactions that led to treatment discontinuation in the MIRCERA clinical studies were hypertension, coronary artery disease, anemia, concomitant termination of other CKD therapy, and septic shock.

Table1 identifies adverse reactions that occurred in ≥5% of adult patients with CKD treated with MIRCERA.

Table 1: Adverse Reactions Occurring in ≥5% of Adult Patients with CKD[1]

Body System	Adverse Reactions	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%

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection 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 in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Neutralizing antibodies to MIRCERA that cross-react with endogenous erythropoietin (EPO) and other ESAs can result in PRCA or severe anemia (with or without other cytopenias). Compared to subcutaneous administration, the intravenous 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.

Postmarketing Experience

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

Hypersensitivity

Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) has been reported.

Pure Red Cell Aplasia (PRCA)

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

2.2.2 Contraindications

MIRCERA is contraindicated in patients with:

- Uncontrolled hypertension
- PRCA that begins after treatment with MIRCERA or other EPO protein drugs
- History of serious or severe allergic reactions to MIRCERA (e.g., anaphylactic reactions, angioedema, bronchospasm, pruritus, skin rash, urticaria)

2.2.3 Warnings and Precautions

Increased Mortality, Myocardial Infarction (MI), Stroke, and Thromboembolism

- In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 to 14 g/dL) to lower targets (9 to 11.3 g/dL), ESAs increased the risk of death, MI, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.
- Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke.
- Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for adverse cardiovascular reactions and mortality than other patients.
- A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may also contribute to these risks.
- In controlled clinical trials of patients with cancer, ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions (ARs) included MI and stroke.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery and the risk of deep venous thrombosis in patients undergoing orthopedic procedures.
- **MIRCERA is not approved for reduction of RBC transfusions in patients scheduled for surgical procedures.**

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

- MIRCERA is not indicated and is not recommended for use in the treatment of anemia due to cancer chemotherapy.
- A dose-ranging trial of MIRCERA in 153 patients who were undergoing chemotherapy for non-small cell lung cancer was terminated prematurely because more deaths occurred among patients receiving MIRCERA than another ESA.
- ESAs resulted in decreased locoregional control/progression-free survival and/or overall survival. These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy, in patients receiving chemotherapy for metastatic breast cancer or lymphoid malignancy, and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy.

Hypertension

- MIRCERA is contraindicated in patients with uncontrolled hypertension.
- In MIRCERA clinical studies, approximately 27% of patients with CKD, including patients on dialysis and patients not on dialysis, required intensification of antihypertensive therapy. Hypertensive encephalopathy and/or seizures have been observed in patients with CKD treated with MIRCERA.
- Appropriately control hypertension prior to initiation of and during treatment with MIRCERA. Reduce or withhold MIRCERA if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Seizures

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

Lack or Loss of Hemoglobin Response to MIRCERA

- For lack or loss of hemoglobin response to MIRCERA, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding).
- If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient response to MIRCERA therapy.

Pure Red Cell Aplasia (PRCA)

- Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to EPO, have been reported in the postmarketing setting in patients treated with MIRCERA. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA was not observed in clinical studies of MIRCERA.
- PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which MIRCERA is not approved).
- If severe anemia and low reticulocyte count develop during treatment with MIRCERA, withhold MIRCERA and evaluate patients for neutralizing antibodies to EPO. Serum samples should be obtained at least a month after the last MIRCERA administration to prevent interference of MIRCERA with the assay. Contact Vifor at 1-800-576-8295 to perform assays for binding and neutralizing antibodies. Permanently discontinue MIRCERA in patients who develop PRCA following treatment with MIRCERA or other EPO protein drugs. Do not switch patients to other ESAs as antibodies may cross-react.

Serious Allergic Reactions

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

Severe Cutaneous Reactions

- Blistering and skin exfoliation reactions including Erythema multiforme and Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with ESAs (including MIRCERA) in the postmarketing setting. Discontinue MIRCERA therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.

Dialysis Management

- Patients may require adjustments in their dialysis prescription after initiation of MIRCERA. Patients receiving MIRCERA may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

2.3 Treatment with MIRCERA[1]

2.3.1 Important Dosing Information

Evaluation of Iron Stores and Nutritional Factors

- Evaluate the iron status in all patients before and during treatment.
- Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course of ESA therapy.

Monitoring of Response to Therapy

- Correct or exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating MIRCERA.
- Following initiation of therapy and after each dose adjustment, monitor hemoglobin weekly until the hemoglobin level is stable and sufficient to minimize the need for RBC transfusion.

2.3.2 MIRCERA Treatment for All Patients with CKD

- Individualize dosing and use the lowest dose of MIRCERA sufficient to reduce the need for RBC transfusions.
- Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events.

Monitoring and Dose Adjustment

- When initiating or adjusting therapy, monitor hemoglobin levels at least weekly until stable, then monitor at least monthly.
- When adjusting therapy, consider hemoglobin rate of rise, rate of decline, ESA responsiveness, and hemoglobin variability.
- A single hemoglobin excursion may not require a dosing change.
- Do not increase the dose more frequently than once every 4 weeks. Decreases in dose can occur more frequently. Avoid frequent dose adjustments.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in any 2-week period), reduce the dose of MIRCERA by 25% or more as needed to reduce rapid responses.
- For patients who do not respond adequately, if the hemoglobin has not increased by more than 1 g/dL after 4 weeks of therapy, increase the dose by 25%.
- For patients who do not respond adequately over a 12-week escalation period, increasing the MIRCERA dose further is unlikely to improve response and may increase risks. Use the lowest dose that will maintain a hemoglobin level sufficient to reduce the need for RBC transfusions.
- Evaluate other causes of anemia. Discontinue MIRCERA if responsiveness does not improve.

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Preparation and Administration

- MIRCERA is administered either intravenously or subcutaneously in adult patients and only intravenously in pediatric patients.
- When administered subcutaneously, MIRCERA should be injected into the abdomen, arm, or thigh.
- MIRCERA is packaged as single-dose prefilled syringes. MIRCERA contains no preservatives. Discard any unused portion. Do not pool unused portions from the prefilled syringes. Do not use the prefilled syringe more than once.
- Always store MIRCERA prefilled syringes in their original cartons. Vigorous shaking or prolonged exposure to light should be avoided.
- Do not mix MIRCERA with any parenteral solution.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any prefilled syringes exhibiting particulate matter or a coloration other than colorless to slightly yellowish.
- For administration using the prefilled syringe, the plunger must be fully depressed during injection in order for the needle guard to activate. Following administration, remove the needle from the injection site and then release the plunger to allow the needle guard to move up until the entire needle is covered.
- See Instructions for Use for complete instructions on the preparation and administration of MIRCERA. Examine each prefilled syringe for the expiration date. Do not use MIRCERA after the expiration date.

Inject in abdomen, arm or thigh

2.3.3 MIRCERA Treatment in Adult Patients with CKD

MIRCERA is indicated for the treatment of anemia associated with CKD in adult patients on dialysis and adult patients not on dialysis.

MIRCERA Treatment in Adult Patients with CKD on Dialysis

- Initiate MIRCERA treatment when the hemoglobin level is less than10 g/dL in adult patients with CKD who are not currently treated with an ESA.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of MIRCERA.
- The recommended starting dose of MIRCERA for the treatment of anemia in adult patients with CKD who are not currently treated with an ESA is 0.6 mcg/kg body weight administered as a single intravenous or subcutaneous injection once every 2 weeks.
- The intravenous route is recommended for patients on hemodialysis because the intravenous route may be less immunogenic.
- Once the hemoglobin has been stabilized, MIRCERA may be administered once monthly using a dose that is twice that of the every-2-weeks dose and subsequently titrated as necessary.

MIRCERA Treatment in Adult Patients with CKD Not on Dialysis

- Consider initiating MIRCERA treatment only when the hemoglobin level is less than 10 g/dL and the following considerations apply:
  - The rate of hemoglobin decline indicates the likelihood of requiring a RBC transfusion, and
  - Reducing the risk of alloimmunization and/or other RBC transfusion-related risks is a goal
- If the hemoglobin level exceeds 10 g/dL, reduce or interrupt the dose of MIRCERA, and use the lowest dose of MIRCERA sufficient to reduce the need for RBC transfusions.
- The recommended starting dose of MIRCERA for the treatment of anemia in adult patients with CKD who are not currently treated with an ESA is 0.6 mcg/kg body weight administered as a single intravenous or subcutaneous injection once every 2 weeks.
- Once the hemoglobin has been stabilized, MIRCERA may be administered once monthly using a dose that is twice that of the every-2-weeks dose and subsequently titrated as necessary.

Conversion from Epoetin alfa or Darbepoetin alfa to MIRCERA

- MIRCERA can be administered once every 2 weeks or once monthly to patients whose hemoglobin has been stabilized by treatment with an ESA (see **Table 2**).
- The dose of MIRCERA, given as a single intravenous or subcutaneous injection, should be based on the total weekly ESA dose at the time of conversion.

Table 2: MIRCERA Starting Doses for Adult Patients Currently Receiving an ESA[1]

Previous Weekly Epoetin alfa Dose (units/week)	Previous Weekly Darbepoetin alfa Dose (mcg/week)	MIRCERA Dose	
		Once Monthly (mcg/month)	Once Every 2 Weeks (mcg/every 2 weeks)
less than 8000	less than 40	120	60
8000 to 16000	40 to 80	200	100
more than 16000	more than 80	360	180

MIRCERA®
methoxy polyethylene glycol-epoetin beta

2.4 Efficacy of MIRCERA in Phase III Clinical Trials*[1,7-12]

The efficacy and safety of MIRCERA in adult patients were assessed in 6 open-label, multicenter clinical studies that randomized patients to either MIRCERA or a comparator ESA.

Two studies evaluated anemic patients with CKD who were not treated with an ESA at baseline, and four studies evaluated patients who were receiving an ESA for treatment of the anemia of CKD. In all studies, patients were assessed as clinically stable at baseline and without evidence of infection or inflammation as determined by history and laboratory data, including C-reactive protein (CRP) (CRP ≤ 15 mg/L for the ARCTOS study and CRP ≤ 30 mg/L for the remaining studies). A CRP value above the threshold led to the exclusion of no more than 3% of the screened patients.

2.4.1 Patients Not Currently Treated with an ESA

In the ARCTOS (Administration of C.E.R.A. in CKD patients to treat anemia with a Twice-mOnthly Schedule) study, patients not on dialysis were randomized to MIRCERA or darbepoetin alfa for 28 weeks. The starting dose of MIRCERA was 0.6 mcg/kg administered subcutaneously once every 2 weeks and the starting dose of darbepoetin alfa was 0.45 mcg/kg administered subcutaneously once a week.[7]

In the AMICUS (C.E.R.A. adMinistered Intravenously for anemia Correction and sUStained maintenance in dialysis) study, patients on hemodialysis or peritoneal dialysis were randomized to MIRCERA or another ESA (epoetin alfa or epoetin beta) for 24 weeks. The starting dose of MIRCERA was 0.4 mcg/kg administered intravenously once every 2 weeks and the starting dose of the comparator was administered intravenously 3 times a week, consistent with the product's recommended dose.[8]

In these studies, the observed median dose of MIRCERA once every 2 weeks over the course of the correction/evaluation period was 0.6 mcg/kg.

The primary endpoints of these studies were:

ARCTOS: Hemoglobin level response rate during correction and evaluation period and difference in mean change in hemoglobin concentration between baseline and evaluation period.

AMICUS: Hemoglobin level response rate during correction period.

In both studies, response rate was defined as an increase in hemoglobin level of at least 1 g/dL versus baseline and to a hemoglobin level of at least 11 g/dL without blood transfusion during the correction and evaluation period in the intent-to-treat (ITT) population. Hemoglobin levels were to be maintained within the range of 11 to 13 g/dL.

Table 3 provides the results of these two studies.

*Note: At the time of the studies, higher hemoglobin targets were recommended compared to current clinical guidelines and MIRCERA Prescribing Information.

Table 3: Phase III Clinical Studies in Patients Not Currently Treated with an ESA[1,7,8]

Group (n)	Percent Achieving Goal* (95% CI)	Mean Hemoglobin Change From Baseline (g/dL)	RBC Transfusion (%)
ND-CKD	**ARCTOS**		
MIRCERA (subcutaneously every 2 weeks) (n=162)	98 (94-99)	2.1	2.5
Darbepoetin alfa (subcutaneously once weekly) (n=162)	96 (92-99)	2.0	6.8
Patients on Dialysis	**AMICUS**		
MIRCERA (intravenously every 2 weeks) (n=135)	93 (88-97)	2.7	5.2
Epoetin alfa/beta (intravenously 3 times per week) (n=46)	91 (79-98)	2.6	4.3

*__Primary endpoint:__ Hemoglobin level response rate (hemoglobin increase of at least 1 g/dL and to a level of at least 11 g/dL without RBC transfusion) in ITT population. Hemoglobin levels were to be maintained within the range of 11 to 13 g/dL.

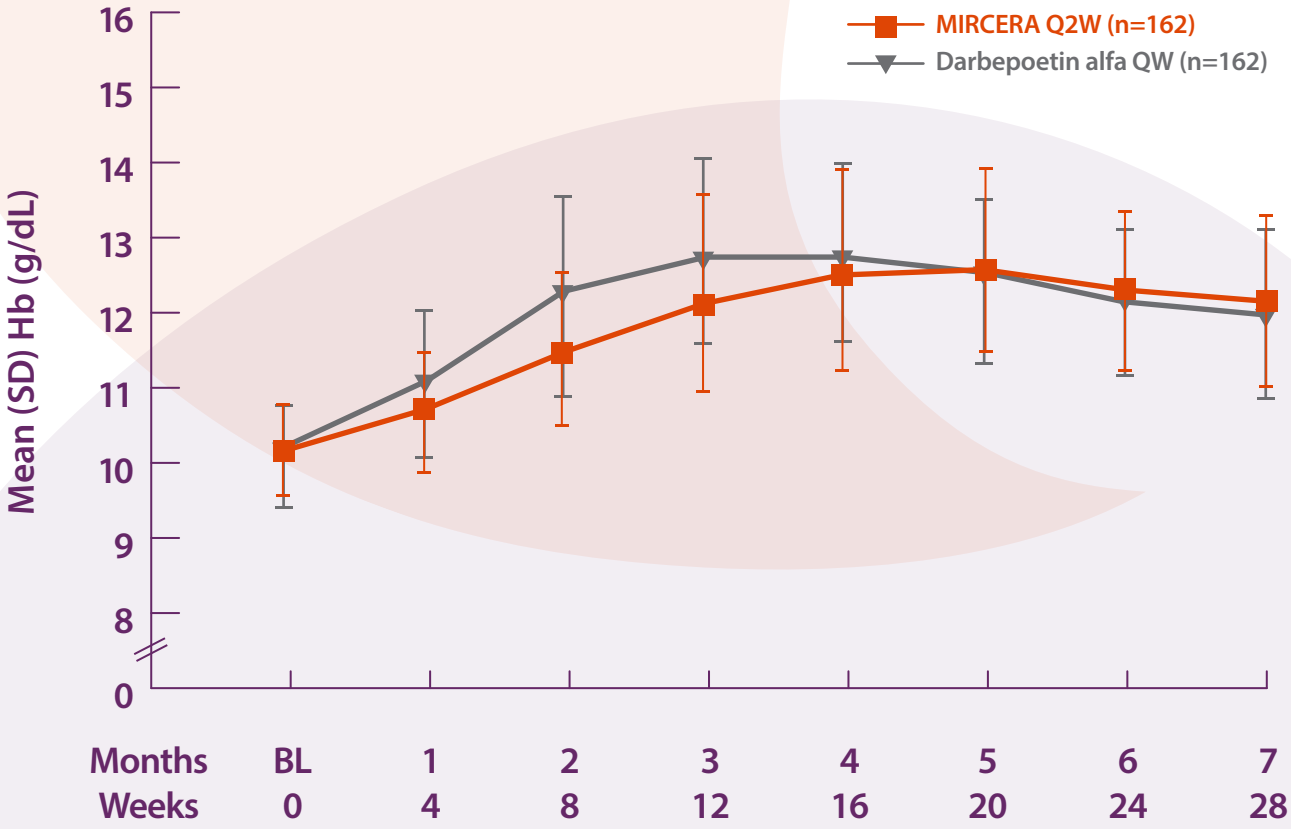
ND-CKD=non-dialysis chronic kidney disease, RBC=red blood cell, CI=confidence interval

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Mean monthly hemoglobin concentrations in Phase III Clinical Studies (ARCTOS and AMICUS) in patients not currently treated with an ESA are depicted in Figure 1 and Figure 2.

Figure 1: Mean Monthly Hemoglobin Concentrations[7]
(in the ITT population)

ARCTOS: Efficacy of Subcutaneous MIRCERA Administered Every 2 Weeks Compared with Darbepoetin alfa Administered Once Every Week in Patients with CKD Who Are Not on Dialysis

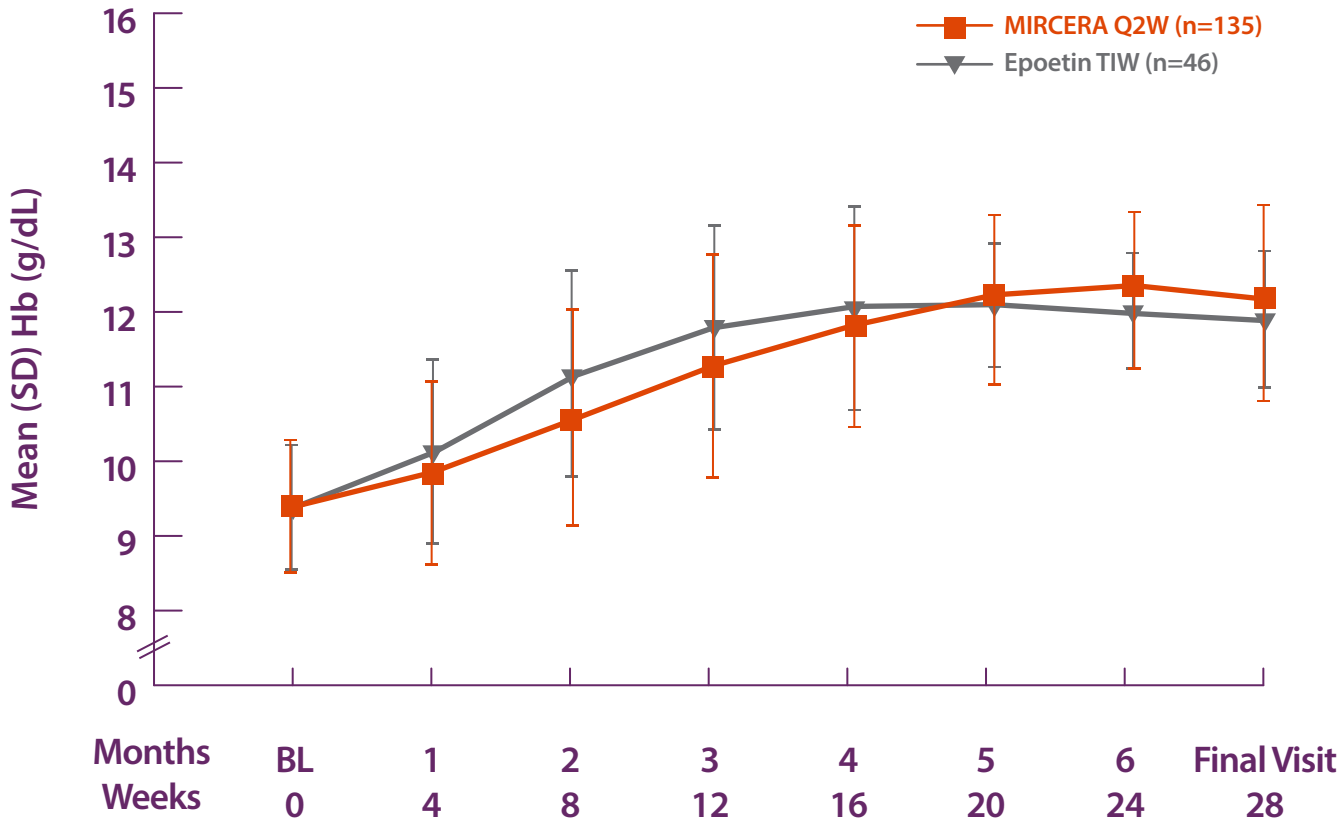


Secondary endpoint: Mean hemoglobin concentration during the correction and evaluation period in ITT population.

QW=once every week, Q2W=once every 2 weeks, SD=standard deviation, Hb=hemoglobin, BL=baseline, ITT population=intent-to-treat population

Figure 2: Mean Monthly Hemoglobin Concentrations[8]
(in the ITT population)

AMICUS: Efficacy of Intravenous MIRCERA Administered Every 2 Weeks Compared with Epoetin Administered 3 Times Weekly in Patients with CKD on Hemodialysis or Peritoneal Dialysis



Secondary endpoint: Mean hemoglobin concentration during the correction period in ITT population.

Q2W=once every 2 weeks, TIW=3 times weekly, SD=standard deviation, Hb=hemoglobin, BL=baseline, ITT population=intent-to-treat population

MIRCERA®
methoxy polyethylene glycol-epoetin beta

2.4.2 Patients Currently Treated with an ESA

Four studies assessed the ability of MIRCERA to maintain hemoglobin levels among patients currently treated with other ESAs. Patients were randomized to receive MIRCERA either once every 2 weeks or once every 4 weeks, or to continue their current ESA dose and schedule.

At the time of the studies, higher hemoglobin targets were recommended compared to current clinical guidelines and the MIRCERA Prescribing Information.

The initial MIRCERA dose was determined based on the patient's previous weekly ESA dose. As shown in Table 4 and Table 5, treatment with MIRCERA once every 2 weeks and once every 4 weeks maintained hemoglobin levels within the targeted hemoglobin range (10-13.5 g/dL).[1]

In the MAXIMA (Maintenance of hAemoglobin eXcels with IV adMinistration of C.E.R.A.) study, the observed median doses of MIRCERA were 57 mcg once every 2 weeks and 175 mcg once every 4 weeks during the assessment period and the rest of the study.[9]

In the PROTOS (Patients Receiving C.E.R.A. Once a month for the mainTenance Of Stable haemoglobin) study, the MIRCERA median doses over the evaluation period and the rest of the study were 56 mcg once every 2 weeks and 150 mcg once every 4 weeks. In this study, MIRCERA was administered subcutaneously.[10]

In the STRIATA (Stabilizing haemoglobin TaRgets in dialysis following IV C.E.R.A. Treatment of Anaemia) study, the median dose of MIRCERA was 0.35 mcg/kg/week during the evaluation period and the rest of the study.[11]

In the RUBRA (TaRgeting sUstained haemogloBin in dialysis with IV and SC C.E.R.A. Administration) study, the MIRCERA median dose was 60 mcg once every 2 weeks during the evaluation period.[12]

The primary endpoint in these trials was a mean change in hemoglobin level between baseline and evaluation period.

Table 4: Phase III Clinical Studies in Patients Currently Treated with an ESA[1,9,10]

Group (n)	Mean Baseline Hemoglobin (g/dL)	Evaluation Period (weeks 29-36) Mean Hemoglobin (g/dL)	Between-Group Difference* g/dL (97.5% CI)
Patients on Dialysis	**MAXIMA**		
MIRCERA (intravenously every 2 weeks) (n=223)	12.0	11.9	0.0 (-0.2 to 0.2)
MIRCERA (intravenously every 4 weeks) (n=224)	11.9	11.9	0.1 (-0.2 to 0.3)
Epoetin alfa/beta (intravenously 1-3 times weekly) (n=226)	12.0	11.9	n/a
Patients on Dialysis	**PROTOS**		
MIRCERA (subcutaneously every 2 weeks) (n=190)	11.7	11.7	0.1 (-0.1 to 0.4)
MIRCERA (subcutaneously every 4 weeks) (n=191)	11.6	11.5	-0.0 (-0.3 to 0.2)
Epoetin beta (subcutaneously 1-3 times weekly) (n=191)	11.6	11.5	n/a

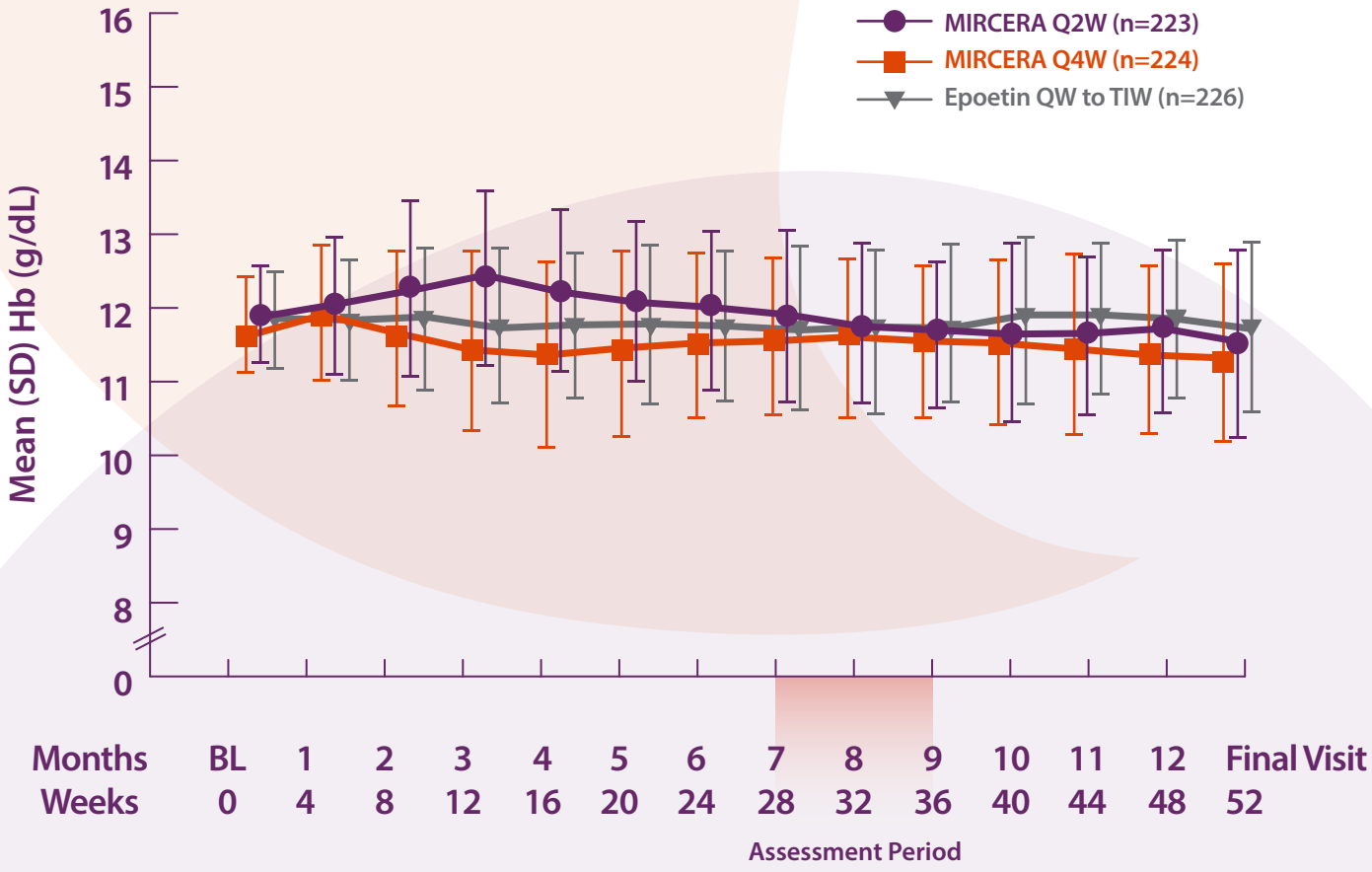
Primary endpoint: Mean change in hemoglobin level between baseline and evaluation period.
This analysis is from the per-protocol (primary analysis) population; numbers indicate total patients randomized.
*MIRCERA versus comparator mean hemoglobin difference in the evaluation period.
CI=confidence interval, n/a=not applicable

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Mean monthly hemoglobin concentrations in Phase III Clinical Studies (MAXIMA, PROTOS, STRIATA and RUBRA) in patients currently treated with an ESA are depicted in Figures 3-6.

Figure 3: Mean Monthly Hemoglobin Concentrations[9]
(in the ITT population)

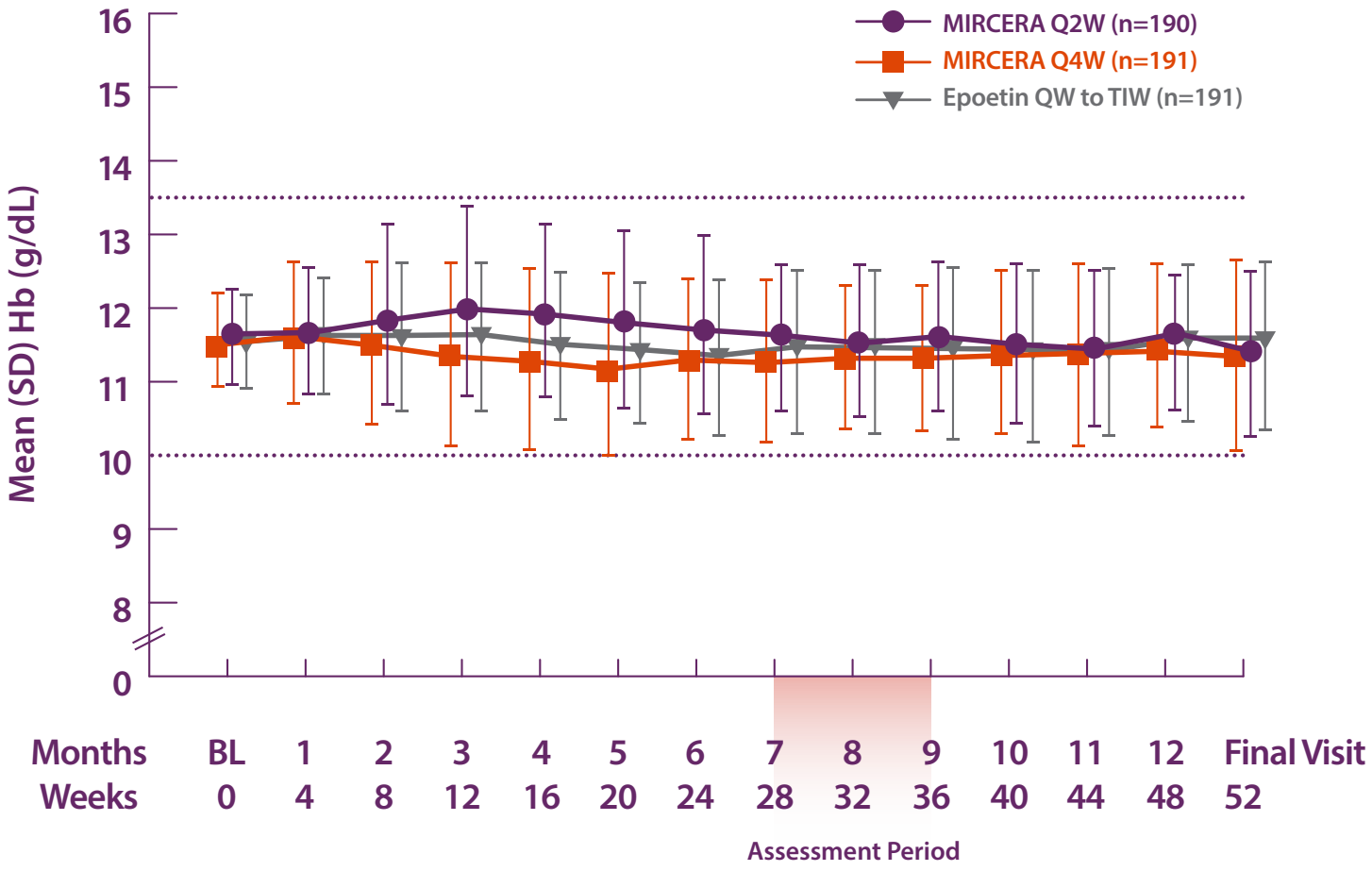
MAXIMA: Efficacy of Intravenous MIRCERA Administered Every 2 or 4 Weeks Compared with Epoetin Administered 1-3 Times per Week in Patients with CKD on Dialysis



QW=once every week, Q2W=once every 2 weeks, Q4W=once every 4 weeks, TIW=3 times weekly, SD=standard deviation, Hb=hemoglobin, BL=baseline, ITT population=intent-to-treat population

Figure 4: Mean Monthly Hemoglobin Concentrations[10]
(in the ITT population)

PROTOS: Efficacy of Subcutaneous MIRCERA Administered Every 2 or 4 Weeks Compared with Epoetin Administered 1-3 Times Weekly in Patients with CKD on Dialysis



QW=once every week, Q2W=once every 2 weeks, Q4W=once every 4 weeks, TIW=3 times weekly, SD=standard deviation, Hb=hemoglobin, BL=baseline, ITT population=intent-to-treat population

MIRCERA®
methoxy polyethylene glycol-epoetin beta

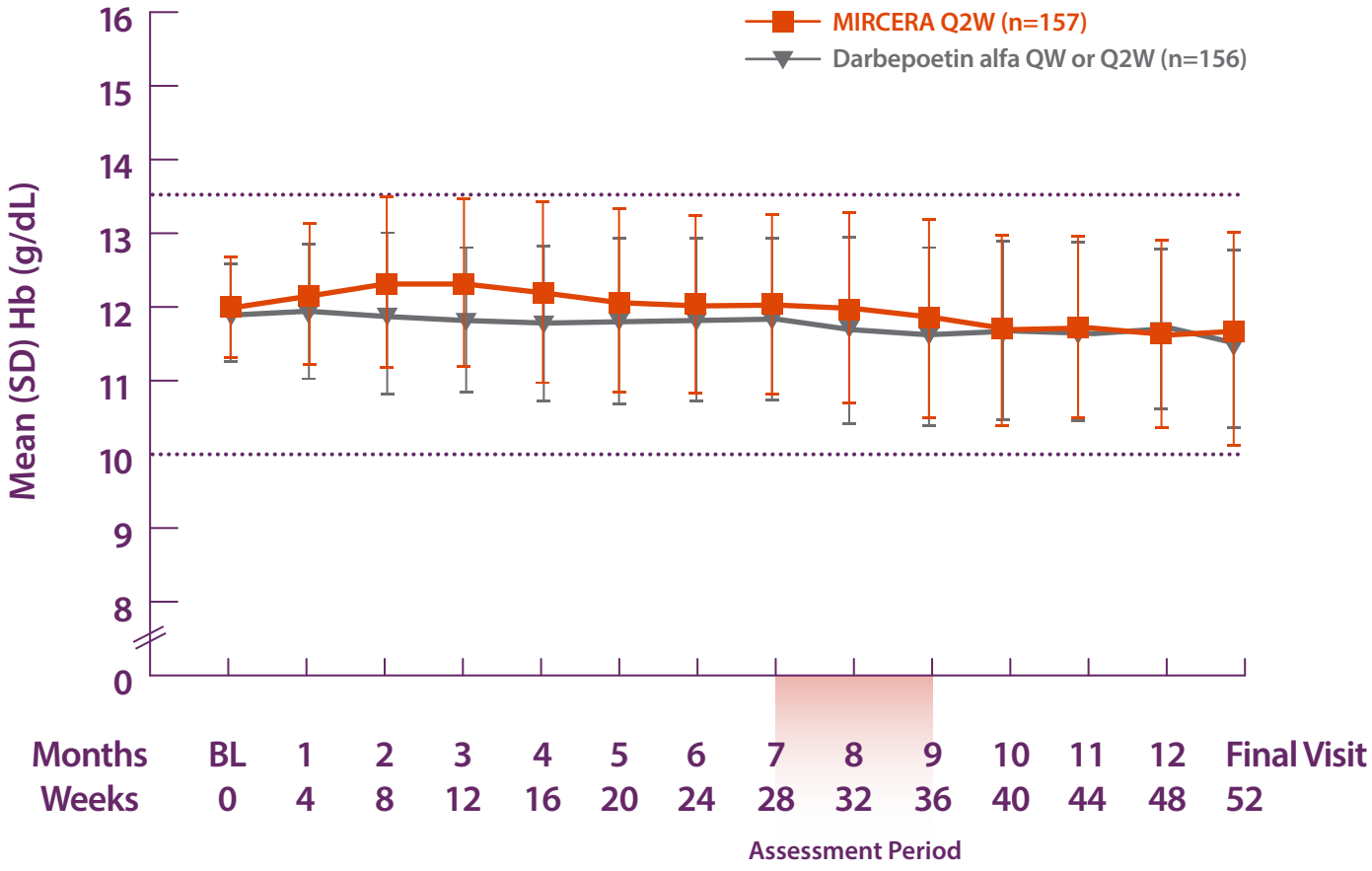
Table 5: Phase III Clinical Studies in Patients Currently Treated with an ESA[1,11,12]

Group (n)	Mean Baseline Hemoglobin (g/dL)	Evaluation Period (weeks 29-36) Mean Hemoglobin (g/dL)	Between-Group Difference* g/dL (95% CI)
Patients on Dialysis	**STRIATA**		
MIRCERA (intravenously every 2 weeks) (n=157)	12.0	12.1	0.2 (-0.0 to 0.4)
Darbepoetin alfa (intravenously once weekly or once every 2 weeks) (n=156)	11.9	11.8	n/a
Patients on Dialysis	**RUBRA**		
MIRCERA (intravenously/ subcutaneously every 2 weeks) (n=168)	11.8	11.9	0.1 (-0.1 to 0.4)
Epoetin alfa (intravenously/ subcutaneously 1-3 times weekly) (n=168)	11.9	11.9	n/a

Primary endpoint: Mean change in hemoglobin between baseline and the evaluation period.
This analysis is from the per-protocol (primary analysis) population; numbers indicate total patients randomized.
*MIRCERA versus comparator mean hemoglobin difference in the evaluation period.
CI=confidence interval, n/a=not applicable

Figure 5: Mean Monthly Hemoglobin Concentrations[11]
(in the ITT population)

STRIATA: Efficacy of Intravenous MIRCERA Administered Every 2 Weeks Compared with Darbepoetin alfa Administered Once Weekly or Once Every 2 Weeks in Patients with CKD on Dialysis

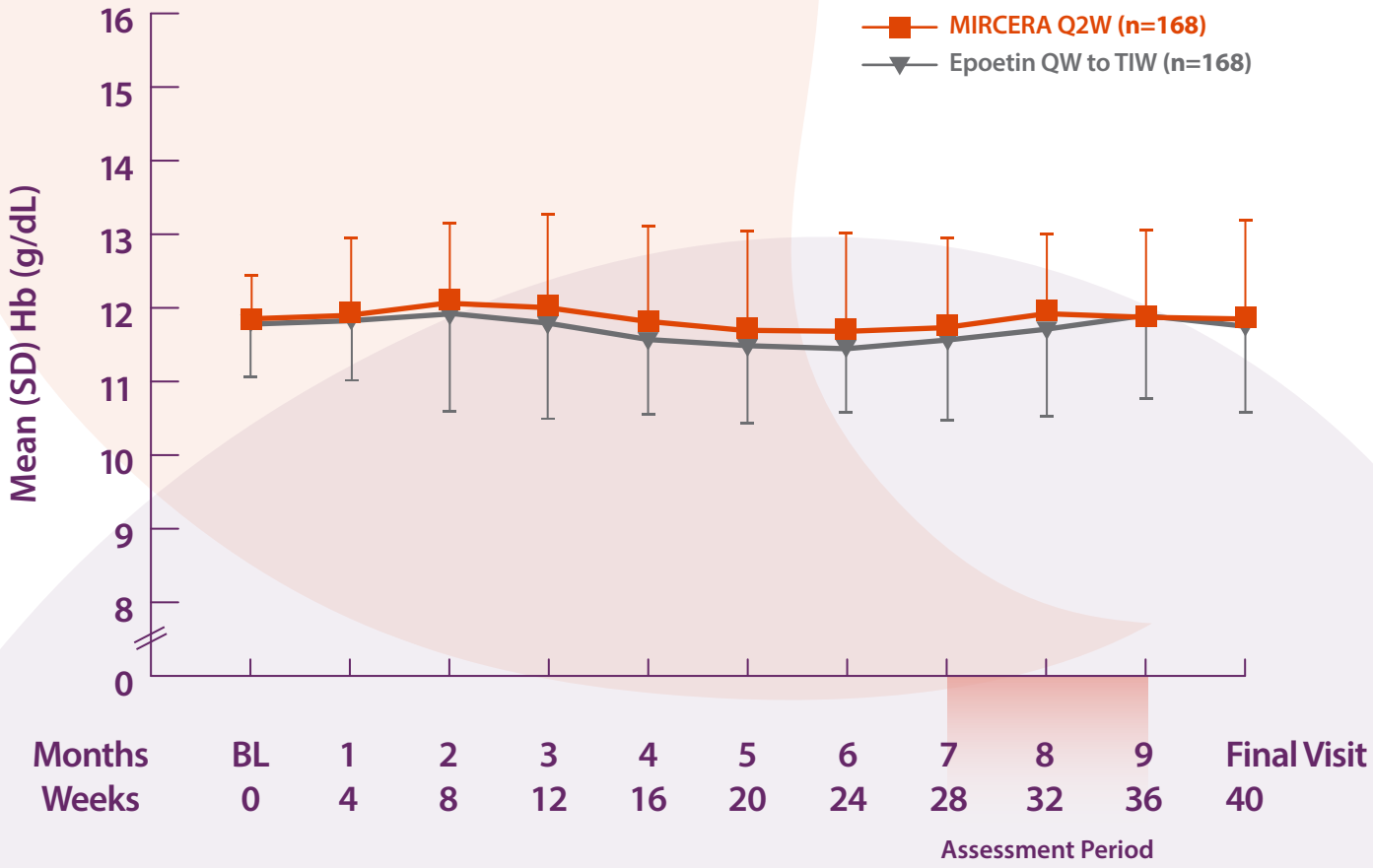


QW=once every week, Q2W=once every 2 weeks, SD=standard deviation, Hb=hemoglobin, BL=baseline, ITT population=intent-to-treat population

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Figure 6: Mean Monthly Hemoglobin Concentrations[12]
(in the ITT population)

RUBRA: Efficacy of Intravenous or Subcutaneous MIRCERA Administered Every 2 Weeks Compared with Epoetin Administered 1-3 Times per Week in Patients with CKD on Dialysis



QW=once every week, Q2W=once every 2 weeks, TIW=three times weekly, SD=standard deviation, Hb=hemoglobin, BL=baseline
ITT population=intent-to-treat population

2.5 MIRCERA Efficacy, Safety, and Treatment in Pediatric Patients on Hemodialysis[1]

MIRCERA is indicated for the treatment of anemia associated with CKD in pediatric patients (ages 5-17 years) on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.

2.5.1 Clinical Study with Pediatric Patients: Efficacy and Safety of MIRCERA

The efficacy and safety of MIRCERA for the treatment of anemia due to CKD have been established in pediatric patients (ages 5-17 years) on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA. The use of MIRCERA in this pediatric age group is supported by evidence from adequate and well-controlled studies of MIRCERA in adults and a dose-finding study in 64 pediatric patients (ages 5-17 years) with CKD on hemodialysis.

- In an open-label, multiple-dose, multicenter study, 64 pediatric patients (ages 5-17 years) with CKD who were on hemodialysis and who had stable hemoglobin levels while previously receiving another ESA (epoetin alfa/beta or darbepoetin alfa) were then converted to MIRCERA administered intravenously once every 4 weeks for 20 weeks (core study period). After the first administration of MIRCERA, dosage adjustments were permitted to maintain target hemoglobin levels.
- Patients who completed the core study period with hemoglobin within ±1 g/dL of their baseline hemoglobin and within the target range of 10 to 12 g/dL were eligible to enter an optional 52-week safety extension period (total duration of treatment, up to 73 weeks).
- In the extension period, 25 (of 37) patients were treated for at least an additional 5 months. During the whole study (core study and safety extension), 33 patients were exposed to MIRCERA for at least 6 months and 19 were exposed for greater than15 months.
- The adverse reaction profile observed in pediatric patients was consistent with the safety profile found in adults.
- The efficacy and safety of MIRCERA have not been established in patients less than 5 years of age.
- All reported adverse reactions regardless of causality (more than 5% incidence) in the pediatric population included headache (22%), nasopharyngitis (22%), hypertension (19%), vomiting (11%), bronchitis (9%), abdominal pain (8%), arteriovenous fistula thrombosis (6%), cough (6%), device-related infection (6%), hyperkalemia (6%), pharyngitis (6%), pyrexia (6%), thrombocytopenia (6%), and thrombosis in device (6%).

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Efficacy was established based on the change in hemoglobin concentration (g/dL) between the baseline and evaluation periods. Of the two conversion factors studied, the recommended conversion factor for MIRCERA was confirmed based on patients maintaining hemoglobin within target levels.

- Among the 48 patients who received MIRCERA dosed using the recommended conversion factor, 9 patients withdrew due to renal transplant, 2 patients withdrew due to administrative reasons, 1 died, and 1 patient refused treatment. One of the 13 patients who withdrew from the study entered the evaluation period (weeks 17-21).
- For the 36 patients who entered the evaluation period and received the dose of MIRCERA calculated using the recommended conversion factor, the mean change in hemoglobin concentration from baseline between the baseline and the evaluation period was -0.15 g/dL with 95% CI (-0.49 to 0.2).
- Supportive efficacy results in the group treated with MIRCERA using the recommended conversion factor demonstrated that 75% of patients maintained hemoglobin values within ±1 g/dL of baseline and 81% maintained hemoglobin values within 10 to 12 g/dL during the evaluation period. Dose decreases and increases were reported in 38% of patients.

The efficacy and safety of MIRCERA have not been established in pediatric patients of any age in the following conditions:

- For subcutaneous administration
- For treatment of anemia in patients with CKD on peritoneal dialysis
- For treatment of anemia in patients with CKD not yet on dialysis
- For patients whose hemoglobin level has not been previously stabilized by treatment with an ESA

2.5.2 MIRCERA Dosing and Administration in Pediatric Patients

ONLY administer MIRCERA intravenously in pediatric patients.

Conversion from Epoetin alfa or Darbepoetin alfa to MIRCERA in Pediatric Patients with CKD on Hemodialysis

- Administer MIRCERA intravenously once every 4 weeks to pediatric patients (ages 5-17 years) whose hemoglobin level has been stabilized by treatment with an ESA.
- Administer MIRCERA as an intravenous injection at the dose (in micrograms) based on the total weekly ESA dose at the time of conversion (see Table 6).

Table 6: MIRCERA Starting Doses for Pediatric Patients Currently Receiving an ESA[1]

Epoetin alfa	Darbepoetin alfa
4 x previous weekly epoetin alfa dose (Units)/125	**4 x previous weekly darbepoetin alfa dose (mcg)/0.55**
e.g., 4 x 1500 Units of epoetin alfa per week/125 = 48 mcg of MIRCERA once every 4 weeks	e.g., 4 x 20 mcg of darbepoetin alfa per week/0.55 = 145.5 mcg of MIRCERA once every 4 weeks

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Section 3: DESCRIPTION AND CLINICAL PHARMACOLOGY

3.1 Description[1]

MIRCERA (methoxy polyethylene glycol-epoetin beta) is an ESA that differs from erythropoietin (EPO) through formation of a chemical bond between either the N-terminal amino group or the ε-amino group of any lysine present in EPO, 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.

- Methoxy polyethylene glycol-epoetin beta is produced in Chinese hamster ovary cells using recombinant DNA technology.
- MIRCERA (methoxy polyethylene glycol-epoetin beta) is formulated as a sterile, preservative-free protein solution for intravenous or subcutaneous administration.
- MIRCERA (methoxy polyethylene glycol-epoetin beta) is formulated in an aqueous solution containing mannitol (9 mg), methionine (0.447 mg), poloxamer 188 (0.03 mg), sodium phosphate monobasic monohydrate (0.414 mg), and sodium sulfate (1.704 mg).
- The solution is clear, colorless to slightly yellowish, and the pH is 6.2±0.2.

3.2 Clinical Pharmacology[1]

3.2.1 Mechanism of Action

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

3.2.2 Pharmacodynamics

Following a single-dose of MIRCERA in adult patients with CKD, the onset of hemoglobin increase (defined as an increase more than 0.4 g/dL from baseline) was observed 7 to 15 days following initial dose administration.

3.2.3 Pharmacokinetics

The pharmacokinetics of methoxy polyethylene glycol-epoetin beta were studied in adult anemic patients with CKD, including patients on dialysis and those not on dialysis. Parameters are presented as the geometric mean (% coefficient of variation [% CV]) unless otherwise specified.

Methoxy polyethylene glycol-epoetin beta did not accumulate following administration every 4 weeks. However, when MIRCERA was administered every 2 weeks, serum concentrations at steady state increased by 12%. Multiple dosing had no effect on clearance, volume of distribution, or bioavailability of methoxy polyethylene glycol-epoetin beta.

Absorption

Following the subcutaneous administration of MIRCERA, the maximum serum concentrations of methoxy polyethylene glycol-epoetin beta were observed at a median (min, max) time of 72 (24-192) hours. The absolute bioavailability of MIRCERA after subcutaneous administration was 62%.

Distribution

The volume of distribution at steady state was 61 (46%) mL/kg.

Elimination

Following an intravenous administration of MIRCERA 0.4 mcg/kg body weight to patients with CKD receiving peritoneal dialysis, the observed terminal half-life was 119 (55%) hours, and the total systemic clearance was 0.47 (35%) mL/h/kg. Following a subcutaneous administration of MIRCERA 0.8 mcg/kg to patients with CKD receiving peritoneal dialysis, the terminal half-life was 124 (57%) hours.

Specific Populations

The pharmacokinetics of methoxy polyethylene glycol-epoetin beta were not altered by age (range: 6-89 years), gender, race, severe hepatic impairment (Child-Pugh Class C), site of subcutaneous injection (abdomen, arm, or thigh), or the use of dialysis.

Pharmacokinetics in Pediatric Patients

The pharmacokinetics of methoxy polyethylene glycol-epoetin beta were studied in 64 pediatric patients with CKD (ages 5-17 years) who were on hemodialysis and who were previously receiving another ESA (epoetin alfa/beta or darbepoetin alfa). At steady state (following the third intravenous administration of MIRCERA), the observed C_{max} was 66 (150%) ng/mL, and the $AUC_{0\text{-}tau}$ was 7170 (140%) ng·h/mL in the group who were dosed using the recommended conversion factor. Methoxy polyethylene glycol-epoetin beta serum concentrations declined with an apparent half-life of 121 (44%) hours, and a total systemic clearance of 0.51 (96%) mL/h/kg.

Section 4: SUPPLY AND STORAGE

4.1 How MIRCERA is Supplied[1]

MIRCERA (methoxy polyethylene glycol-epoetin beta) injection is available in single-dose prefilled syringes.

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

Table 7: MIRCERA NDC Numbers and Available Strengths

Strength	10-digit NDC[1]	11-digit NDC
30 mcg/0.3mL	59353-400-09	59353-0400-09
50 mcg/0.3mL	59353-401-09	59353-0401-09
75 mcg/0.3mL	59353-402-09	59353-0402-09
100 mcg/0.3mL	59353-403-09	59353-0403-09
150 mcg/0.3mL	59353-404-09	59353-0404-09
200 mcg/0.3mL	59353-405-09	59353-0405-09

NDC=National Drug Code

4.2 Storage and Handling[1]

Store MIRCERA refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake.

The end-user may store the product at room temperature up to 25°C (77°F) in the original carton up to 30 days. Discard after 30 days.

MIRCERA®
methoxy polyethylene glycol-epoetin beta

KEY ABBREVIATIONS

%CV	% coefficient of variation
AR	adverse reaction
AUC	area under the curve
BL	baseline
CABG	coronary artery bypass graft surgery
CERA	continuous erythropoietin receptor activator
CI	confidence interval
CKD	chronic kidney disease
CRP	C-reactive protein
DA	darbepoetin alfa
DVT	deep venous thrombosis
ELISA	enzyme-linked immunosorbent assay
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
FDA	US Food and Drug Administration
ITT	intent-to-treat
IV	intravenous

KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
MI	myocardial infarction
ND-CKD	non-dialysis chronic kidney disease
NDC	National Drug Code
NKF	National Kidney Foundation
PEG	polyethylene glycol
PRCA	pure red cell aplasia
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QW	once every week
RBC	red blood cell
SC	subcutaneous
SD	standard deviation
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis
TIW	3 times weekly

MIRCERA®
methoxy polyethylene glycol-epoetin beta

REFERENCES

1. MIRCERA® [prescribing information]. St. Gallen, Switzerland: Vifor (International) Inc; June 2018. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=22c56f2a-f73c-60e7-e054-00144ff88e88. Accessed May 31, 2019.
2. National Institute for Health and Care Excellence (NICE), National Clinical Guideline Centre. Anaemia management in chronic kidney disease: partial update 2015. https://www.nice.org.uk/guidance/ng8/evidence/full-guideline-pdf-70545136. Published June 3rd 2015. Accessed May 31, 2019.
3. McClellan W, Aronoff SL, Bolton WK, et al. The prevalence of anemia in patients with Chronic Kidney Disease. *Curr Med Res Opin*. 2004;20(9):1501-1510.
4. Kidney Disease Improving Global Outcomes (KDIGO). Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Int. Suppl 2012;2: 292-298.
5. National Kidney Foundation: KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis.* 47:S11-S145, 2006 (suppl 3).
6. Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Anemia in CKD. *Am J Kidney Dis.* 2013;62(5):849-859.
7. Macdougall IC, Walker R, Provenzano R, et al. C.E.R.A. corrects anemia in patients with Chronic Kidney Disease not on dialysis: results of a randomized clinical trial. *Clin J Am Soc Nephrol*. 2008;3(2):337-347.
8. Klinger M, Arias M, Vargemezis V, et al. Efficacy of intravenous methoxy polyethylene glycol-epoetin beta administered every 2 weeks compared with epoetin administered 3 times weekly in patients treated by hemodialysis or peritoneal dialysis: a randomized trial. *Am J Kidney Dis.* 2007;50(6):989-1000.
9. Levin NW, Fishbane S, Cañedo FV, et al. Intravenous methoxy polyethylene glycol-epoetin beta for haemoglobin control in patients with chronic kidney disease who are on dialysis: a randomised non-inferiority trial (MAXIMA). *Lancet.* 2007;370(9596):1415-1421.
10. Sulowicz W, Locatelli F, Ryckelynck JP, et al. Once-monthly subcutaneous C.E.R.A. maintains stable hemoglobin control in patients with chronic kidney disease on dialysis and converted directly from epoetin one to three times weekly. *Clin J Am Soc Nephrol.* 2007;2(4):637-646.
11. Canaud B, Mingardi G, Braun J, et al. Intravenous C.E.R.A. maintains stable haemoglobin levels in patients on dialysis previously treated with darbepoetin alfa: results from STRIATA, a randomized phase III study. *Nephrol Dial Transplant.* 2008;23(11):3654-3661.
12. Spinowitz B, Coyne DW, Lok CE, et al. C.E.R.A. maintains stable control of hemoglobin in patients with chronic kidney disease on dialysis when administered once every two weeks. *Am J Nephrol.* 2008;28(2):280-289.
13. Fischbach M, Wuhl E, Reigner SCM, Morgan Z, Schaefer F. Efficacy and long-term safety of C.E.R.A. maintenance in pediatric hemodialysis patients with anemia of CKD. *Clin J Am Soc Nephrol.* 2018;13(1):81-90.

IMPORTANT SAFETY INFORMATION[1]

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

Chronic Kidney Disease:

- **In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to target a hemoglobin level of greater than 11 g/dL.**
- **No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.**
- **Use the lowest Mircera dose sufficient to reduce the need for red blood cell (RBC) transfusions.**

Cancer:

- **Mircera is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircera was terminated early because of more deaths among patients receiving Mircera than another ESA.**
- **ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers.**

CONTRAINDICATIONS

Mircera is contraindicated in patients with:

- Uncontrolled hypertension
- Pure red cell aplasia (PRCA) that begins after treatment with Mircera or other erythropoietin protein drugs
- History of serious or severe allergic reactions to Mircera (e.g., anaphylactic reactions, angioedema, bronchospasm, pruritus, skin rash, and urticaria).

INCREASED MORTALITY, MYOCARDIAL INFARCTION, STROKE, AND THROMBOEMBOLISM

- In controlled clinical trials of patients with CKD comparing higher hemoglobin targets (13 to 14 g/dL) to lower targets (9 to 11.3 g/dL), ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups.
- Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with coexistent cardiovascular disease and stroke. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.
- In controlled clinical trials of patients with cancer, ESAs increased the risks for death and serious adverse cardiovascular reactions. These adverse reactions included myocardial infarction and stroke.
- In controlled clinical trials, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and the risk of deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

MIRCERA®
methoxy polyethylene glycol-epoetin beta

Please see full Prescribing Information, including Boxed WARNING, and Medication Guide for Mircera (methoxy polyethylene glycol-epoetin beta) Injection, for Intravenous or Subcutaneous Use.

IMPORTANT SAFETY INFORMATION (continued)

INCREASED MORTALITY AND/OR INCREASED RISK OF TUMOR PROGRESSION OR RECURRENCE IN PATIENTS WITH CANCER

- Mircera is not indicated and is not recommended for use in the treatment of anemia due to cancer chemotherapy. A dose-ranging trial of Mircera in 153 patients who were undergoing chemotherapy for non-small cell lung cancer was terminated prematurely because more deaths occurred among patients receiving Mircera than another ESA.
- ESAs resulted in decreased locoregional control/progression-free survival and/or overall survival. These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy, in patients receiving chemotherapy for metastatic breast cancer or lymphoid malignancy, and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy.

HYPERTENSION

- Mircera is contraindicated in patients with uncontrolled hypertension.
- In Mircera clinical studies, approximately 27% of patients with CKD, including patients on dialysis and patients not on dialysis, required intensification of antihypertensive therapy. Hypertensive encephalopathy and/or seizures have been observed in patients with CKD treated with Mircera.
- Appropriately control hypertension prior to initiation of and during treatment with Mircera. Reduce or withhold Mircera if blood pressure becomes difficult to control. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions.

SEIZURES

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

LACK OR LOSS OF HEMOGLOBIN RESPONSE TO MIRCERA

- For lack or loss of hemoglobin response to Mircera, initiate a search for causative factors (e.g., iron deficiency, infection, inflammation, bleeding).
- If typical causes of lack or loss of hemoglobin response are excluded, evaluate for PRCA. In the absence of PRCA, follow dosing recommendations for management of patients with an insufficient response to Mircera therapy.

PURE RED CELL APLASIA

- Cases of PRCA and of severe anemia, with or without other cytopenias that arise following the development of neutralizing antibodies to erythropoietin have been reported in the postmarketing setting in patients treated with Mircera. This has been reported predominantly in patients with CKD receiving ESAs by subcutaneous administration. PRCA was not observed in clinical studies of Mircera.
- PRCA has also been reported in patients receiving ESAs for anemia related to hepatitis C treatment (an indication for which Mircera is not approved).
- If severe anemia and low reticulocyte count develop during treatment with Mircera, withhold Mircera and evaluate patients for neutralizing antibodies to erythropoietin. Serum samples should be obtained at least a month after the last Mircera administration to prevent interference of Mircera with the assay. **Contact Vifor at 1-800-576-8295 to perform assays for binding and neutralizing antibodies.** Permanently discontinue Mircera in patients who develop PRCA following treatment with Mircera or other erythropoietin protein drugs. Do not switch patients to other ESAs as antibodies may cross-react.

IMPORTANT SAFETY INFORMATION (continued)

SERIOUS ALLERGIC REACTIONS

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

SEVERE CUTANEOUS REACTIONS

- Blistering and skin exfoliation reactions including Erythema multiforme and Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with ESAs (including Mircera) in the postmarketing setting. Discontinue Mircera therapy immediately if a severe cutaneous reaction, such as SJS/TEN, is suspected.

DIALYSIS MANAGEMENT

- Patients may require adjustments in their dialysis prescription after initiation of Mircera. Patients receiving Mircera may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

ADVERSE EVENTS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

- Most frequent adverse reactions (>5%) in adult patients with CKD treated with Mircera were hypertension, diarrhea, nasopharyngitis, upper respiratory tract infection, headache, muscle spasms, procedural hypotension, fluid overload, vomiting, back pain, cough, hypotension, constipation, urinary tract infection, pain in extremity, arteriovenous fistula thrombosis, arteriovenous fistula site complication.
- In pediatric patients on hemodialysis, all reported adverse reactions regardless of causality (more than 5% incidence) were headache, nasopharyngitis, hypertension, vomiting, bronchitis, abdominal pain, arteriovenous fistula thrombosis, cough, device related infection, hyperkalemia, pharyngitis, pyrexia, thrombocytopenia, and thrombosis in device.

INDICATIONS AND LIMITATIONS OF USE

- Mircera is indicated for the treatment of anemia associated with chronic kidney disease (CKD) in adult patients on dialysis and adult patients not on dialysis, and pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin level was stabilized with an ESA.
- Mircera is not indicated and is not recommended for use in the treatment of anemia due to cancer chemotherapy, or as a substitute for RBC transfusions in patients who require immediate correction of anemia.
- Mircera has not been shown to improve quality of life, fatigue, or patient well-being.

Please see full Prescribing Information, including BOXED WARNING and Medication Guide for Mircera (methoxy polyethylene glycol-epoetin beta) Injection, for Intravenous or Subcutaneous Use.

VIFOR PHARMA

HQ-MIR-1900008 08/19

MIRCERA®
methoxy polyethylene glycol-epoetin beta