

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OMONTYS® safely and effectively. See full prescribing information for OMONTYS.

OMONTYS® (peginesatide) Injection,
for intravenous or subcutaneous use
Initial U.S. Approval: 2012

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

See full prescribing information for complete boxed warning.

Chronic Kidney Disease:

- In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL (5.1).
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks (5.1).
- Use the lowest OMONTYS dose sufficient to reduce the need for red blood cell (RBC) transfusions (5.1).

INDICATIONS AND USAGE

OMONTYS is an erythropoiesis-stimulating agent (ESA) indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis (1.1).

Limitations of Use

OMONTYS is not indicated and is not recommended for use:

- In patients with CKD not on dialysis (1.2).
- In patients receiving treatment for cancer and whose anemia is not due to CKD (1.2).
- As a substitute for RBC transfusions in patients who require immediate correction of anemia (1.2).
- OMONTYS has not been shown to improve symptoms, physical functioning or health-related quality of life (1.2).

DOSAGE AND ADMINISTRATION

- Initial treatment: 0.04 mg/kg body weight administered once monthly (2.3).
- Conversion from another ESA: dose once monthly based on the total weekly epoetin or darbepoetin alfa dose at the time of conversion (2.4).

FULL PRESCRIBING INFORMATION—CONTENTS*

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

1 INDICATIONS AND USAGE

- 1.1 Anemia Due to Chronic Kidney Disease
- 1.2 Limitations of Use

2 DOSAGE AND ADMINISTRATION

- 2.1 Evaluation of Iron Stores and Nutritional Factors
- 2.2 Patients with Chronic Kidney Disease
- 2.3 Initiation of Treatment and Starting Dose
- 2.4 Conversion from epoetin alfa or darbepoetin alfa to OMONTYS in patients with CKD on dialysis
- 2.5 General Guidance including Dose Adjustments
- 2.6 Preparation and Administration of OMONTYS

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism
- 5.2 Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence in Patients with Cancer Receiving ESAs
- 5.3 Hypertension
- 5.4 Lack or Loss of Response to OMONTYS
- 5.5 Dialysis Management

DOSAGE FORMS AND STRENGTHS

Dosage Form	Strengths
Single use vials (preservative-free)	2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL
Single use pre-filled syringes (preservative-free)	1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL
Multiple use vials (with preservative)	10 mg/mL and 20 mg/2 mL

CONTRAINDICATIONS

- Uncontrolled hypertension (4).

WARNINGS AND PRECAUTIONS

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism: Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefits (5.1). Use caution in patients with coexistent cardiovascular disease and stroke (5.1).
- Hypertension: Control hypertension prior to initiating and during treatment with OMONTYS (5.3).

ADVERSE REACTIONS

The most common adverse events (≥ 10%) are dyspnea, diarrhea, nausea, cough, and arteriovenous fistula site complication (6).

To report SUSPECTED ADVERSE REACTIONS, contact Affymax, Inc. at 1-855-466-6689 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Exercise caution when OMONTYS is administered to a nursing woman (8.3).
- Pediatric Use: The safety and efficacy of OMONTYS in pediatric patients have not been established (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2012

5.6	Laboratory Monitoring
6	ADVERSE REACTIONS
6.1	Clinical Trials Experience
6.2	Immunogenicity
7	DRUG INTERACTIONS
8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy
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

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

FULL PRESCRIBING INFORMATION

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 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 [see *Warnings and Precautions (5.1)*].
- Use the lowest OMONTYS dose sufficient to reduce the need for red blood cell (RBC) transfusions [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE

1.1 Anemia Due to Chronic Kidney Disease

OMONTYS® is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

1.2 Limitations of Use

OMONTYS is not indicated and is not recommended for use:

- In patients with CKD not on dialysis because of safety concerns in this population [see *Warnings and Precautions (5.1)*].
- In patients receiving treatment for cancer and whose anemia is not due to CKD, because ESAs have shown harm in some settings and the benefit-risk factors for OMONTYS in this setting have not been evaluated [see *Warnings and Precautions (5.2)*].
- As a substitute for RBC transfusions in patients who require immediate correction of anemia.
- OMONTYS has not been shown to improve symptoms, physical functioning or health-related quality of life.

2 DOSAGE AND ADMINISTRATION

2.1 Evaluation of Iron Stores and Nutritional Factors

Evaluate the iron status in all patients before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia (e.g., vitamin deficiency, metabolic or chronic inflammatory conditions, bleeding, etc.) before initiating OMONTYS [see *Warnings and Precautions (5.6)*].

2.2 Patients with Chronic Kidney Disease

Individualize dosing and use the lowest dose of OMONTYS sufficient to reduce the need for RBC transfusions [see *Warnings and Precautions (5.1)*]. In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL. No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks. Physicians and patients should weigh the possible benefits of decreasing transfusions against the increased risks of death and other serious cardiovascular adverse events [see *Boxed Warning and Clinical Studies (14)*].

2.3 Initiation of Treatment and Starting Dose

Initiate OMONTYS treatment when the hemoglobin level is less than 10 g/dL.

The recommended starting dose for the treatment of anemia in patients who are not currently treated with an ESA is 0.04 mg/kg body weight administered as a single intravenous or subcutaneous injection once monthly.

2.4 Conversion from Epoetin Alfa or Darbepoetin Alfa to OMONTYS in Patients with CKD on Dialysis

OMONTYS is administered once monthly, either subcutaneously or intravenously.

In patients previously receiving epoetin alfa or darbepoetin alfa, estimate the starting monthly dose of OMONTYS for patients on the basis of the weekly dose of epoetin alfa or darbepoetin alfa at the time of substitution (see Table 1). Maintain the route of administration (intravenous or subcutaneous injection).

- For patients previously receiving epoetin alfa, the first dose of OMONTYS should be administered one week after the last epoetin alfa dose was administered.
- For patients previously receiving darbepoetin alfa, the first dose of OMONTYS should be administered at the next scheduled dose in place of darbepoetin alfa.

Table 1 Estimated OMONTYS Starting Doses for Patients Based on Previous Weekly ESA Dose

Previous Total Weekly Epoetin Alfa Dose (U/week)	Previous Weekly Darbepoetin Alfa Dose (mcg/week)	OMONTYS Dose Once Monthly (mg/month)
Less than 2,500	Less than 12	2
2,500 to less than 4,300	12 to less than 18	3
4,300 to less than 6,500	18 to less than 25	4
6,500 to less than 8,900	25 to less than 35	5
8,900 to less than 13,000	35 to less than 45	6
13,000 to less than 19,000	45 to less than 60	8
19,000 to less than 33,000	60 to less than 95	10
33,000 to less than 68,000	95 to less than 175	15
greater than or equal to 68,000	greater than or equal to 175	20

2.5 General Guidance including Dose Adjustments

Monitor hemoglobin levels at least every 2 weeks 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.
- If the hemoglobin rises rapidly (e.g., more than 1 g/dL in the 2 weeks prior to the dose or more than 2 g/dL in 4 weeks), reduce the dose of OMONTYS by 25% or more as needed to reduce rapid responses.
- If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of OMONTYS. After a dose has been withheld and once the hemoglobin begins to decrease, OMONTYS may be restarted at a dose approximately 25% below the previously administered dose.
- 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 OMONTYS 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 OMONTYS if responsiveness does not improve [see *Warnings and Precautions* (5.4)].
- If a dose of OMONTYS is missed, administer the missed dose as soon as possible and restart OMONTYS at the prescribed once monthly dosing frequency.

When treating dialysis patients who have chronic kidney disease and cancer, physicians should refer to *Warnings and Precautions* (5.1 and 5.2).

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

2.6 Preparation and Administration of OMONTYS

OMONTYS is packaged as single use vials, single use pre-filled syringes, and multiple use vials. OMONTYS packaged in single use vials and single use pre-filled syringes contains no preservatives. OMONTYS is administered either subcutaneously or intravenously.

- Use the single use vial or single use pre-filled syringe only one time. Discard unused portion of OMONTYS in single use vials.
- Store unused portions of OMONTYS in multiple use vials at 36 °F to 46 °F (2 °C to 8 °C). Discard 28 days after first use.
- Protect OMONTYS from light. Store OMONTYS vials or pre-filled syringes in their cartons until time of use.
- Do not use if tamper-evident seal on carton is broken or missing.
- Do not dilute OMONTYS and do not administer in conjunction with other drug solutions.
- OMONTYS should be inspected visually for particulate matter and coloration prior to administration. Do not use any vials or pre-filled syringes of OMONTYS exhibiting particulate matter or a coloration other than colorless to slightly yellow.

3 DOSAGE FORMS AND STRENGTHS

Dosage Form	Strengths
Single use vials (preservative-free)	2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL
Single use pre-filled syringes (preservative-free)	1 mg/0.5 mL, 2 mg/0.5 mL, 3 mg/0.5 mL, 4 mg/0.5 mL, 5 mg/0.5 mL, and 6 mg/0.5 mL
Multiple use vials (with preservative)	10 mg/mL and 20 mg/2 mL

4 CONTRAINDICATIONS

OMONTYS is contraindicated in patients with:

- Uncontrolled hypertension [see *Warnings and Precautions* (5.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism

- In controlled clinical trials of other ESAs in patients with CKD comparing higher hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL) (see Table 2), increased risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events was observed 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 [see *Dosage and Administration* (2.2)]. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality than other patients. A rate of hemoglobin rise of greater than 1 g/dL over 2 weeks may contribute to these risks.
- In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions was observed. 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 deep venous thrombosis (DVT) was observed in patients undergoing orthopedic procedures.

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

Table 2 Adverse Cardiovascular Outcomes in Randomized Controlled Trials Comparing Higher and Lower Hemoglobin Targets in Patients with CKD

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

Patients with Chronic Kidney Disease Not on Dialysis

OMONTYS is not indicated and is not recommended for the treatment of anemia in patients with CKD who are not on dialysis.

A higher percentage of patients (22%) who received OMONTYS experienced a composite cardiovascular safety endpoint event compared to 17% who received darbepoetin alfa in two randomized, active-controlled, open-label, multi-center trials of 983 patients with anemia due to CKD who were not on dialysis. The trials had a pre-specified, prospective analysis of a composite safety endpoint consisting of death, myocardial infarction, stroke, or serious adverse events of congestive heart failure, unstable angina or arrhythmia (hazard ratio 1.32, 95% CI: 0.97, 1.81).

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

OMONTYS is not indicated and is not recommended for reduction of RBC transfusions in patients receiving treatment for cancer and whose anemia is not due to CKD because ESAs have shown harm in some settings and the benefit-risk factors for OMONTYS in this setting have not been evaluated.

The safety and efficacy of OMONTYS have not been established for use in patients with anemia due to cancer chemotherapy. Results from clinical trials of ESAs in patients with anemia due to cancer therapy showed decreased locoregional control, progression-free survival and/or decreased overall survival. The findings were observed in clinical trials of other ESAs administered to patients with: breast cancer receiving chemotherapy, advanced head and neck cancer receiving radiation therapy, lymphoid malignancy, cervical cancer, non-small cell lung cancer, and with various malignancies who were not receiving chemotherapy or radiotherapy.

5.3 Hypertension

OMONTYS is contraindicated in patients with uncontrolled hypertension.

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

5.4 Lack or Loss of Response to OMONTYS

For lack or loss of hemoglobin response to OMONTYS, 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 the patient for the presence of antibodies to peginesatide. In the absence of antibodies to peginesatide, follow dosing recommendations for management of patients with an insufficient hemoglobin response to OMONTYS therapy [see *Dosage and Administration* (2.2)].

Contact Affymax, Inc. (1-855-466-6689) to perform assays for binding and neutralizing antibodies.

5.5 Dialysis Management

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

5.6 Laboratory Monitoring

Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20% [see *Dosage and Administration* (2.1)]. The majority of patients with CKD will require supplemental iron during the course of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin every 2 weeks until the hemoglobin is stable and sufficient to minimize the need for RBC transfusion. Thereafter, hemoglobin should be monitored at least monthly provided hemoglobin levels remain stable.

6 ADVERSE REACTIONS

The following serious adverse reactions observed during clinical trials with OMONTYS are discussed in greater detail in other sections of the labeling:

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism [see *Warnings and Precautions* (5.1)]
- Hypertension [see *Warnings and Precautions* (5.3)]

6.1 Clinical Trials Experience

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

Patients with Chronic Kidney Disease

Adverse reactions were determined based on pooled data from two active controlled studies of 1066 dialysis patients treated with OMONTYS and 542 treated with epoetin, including 938 exposed for at least 6 months and 825 exposed for greater than one year to OMONTYS. The population for OMONTYS was 20 to 93 years of age, 58.5% male, and the percentages of Caucasian, Black (including African Americans), and Asian patients were 57.9%, 37.4%, and 3.1%, respectively. The median weight adjusted dose of OMONTYS was 0.07 mg/kg and 113 U/week/kg of epoetin.

Table 3 summarizes the most frequent adverse reactions ($\geq 10\%$) in dialysis patients treated with OMONTYS.

Table 3 Adverse Reactions Occurring in $\geq 10\%$ of Dialysis Patients treated with OMONTYS

Adverse Reactions	Dialysis Patients Treated with OMONTYS (N = 1066)	Dialysis Patients Treated with Epoetin (N = 542)
Gastrointestinal Disorders		
Diarrhea	18.4%	15.9%
Nausea	17.4%	19.6%
Vomiting	15.3%	13.3%
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	18.4%	19.4%
Cough	15.9%	16.6%
Injury, Poisoning and Procedural Complications		
Arteriovenous Fistula Site Complication	16.1%	16.6%
Procedural Hypotension	10.9%	12.5%
Nervous System Disorders		
Headache	15.4%	15.9%
Musculoskeletal and Connective Tissue Disorders		
Muscle Spasms	15.3%	17.2%
Pain in Extremity	10.9%	12.7%
Back Pain	10.9%	11.3%
Arthralgia	10.7%	9.8%
Vascular Disorders		
Hypotension	14.2%	14.6%
Hypertension	13.2%	11.4%
General Disorders and Administration Site Conditions		
Pyrexia	12.2%	14.0%
Metabolism and Nutrition Disorders		
Hyperkalemia	11.4%	11.8%
Infections and Infestations		
Upper Respiratory Tract Infection	11.0%	12.4%

Seizures have occurred in patients participating in OMONTYS clinical studies. During the first several months following initiation of OMONTYS, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely.

Advise patients to contact their healthcare practitioner for new-onset seizures, premonitory symptoms, or change in seizure frequency.

Allergic reactions have been reported in patients treated with OMONTYS. Discontinue OMONTYS and administer appropriate therapy if a serious allergic, anaphylactic or infusion-related reaction occurs.

6.2 Immunogenicity

Of the 2357 patients tested, 29 (1.2%) had detectable levels of peginesatide-specific binding antibodies. There was a higher incidence of peginesatide-specific binding antibodies in patients dosed subcutaneously (1.9%) as compared to those dosed intravenously (0.7%). Peginesatide neutralizing antibodies were detected *in vitro* using a cell-based functional assay in 21 of these patients (0.9%). In approximately half of all antibody-positive patients, the presence of antibodies was associated with declining hemoglobin levels, the requirement for increased doses of OMONTYS to maintain hemoglobin levels, and/or transfusion for anemia of CKD. No cases of pure red cell aplasia (PRCA) developed in patients receiving OMONTYS during clinical trials.

7 DRUG INTERACTIONS

No formal drug/drug interaction studies have been performed. Peginesatide does not bind to serum albumin or lipoproteins as demonstrated in *in vitro* protein binding studies in rat, monkey and human sera. *In vitro* studies conducted with human hepatocytes or microsomes have shown no potential for peginesatide to induce or inhibit CYP450 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Peginesatide was teratogenic and caused embryofetal lethality when administered to pregnant animals at doses and/or exposures that resulted in polycythemia. OMONTYS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of peginesatide by intravenous injection to rats and rabbits during organogenesis was associated with embryofetal toxicity and malformations. Dosing was every third day in rats for a total of 5 doses and every fifth day in rabbits for a total of 3 doses (0.01 to 50 mg/kg/dose). In rats and rabbits, adverse embryofetal effects included reduced fetal weight, increased resorption, embryofetal lethality, cleft palate (rats only), sternum anomalies, unossification of sternebrae and metatarsals, and reduced ossification of some bones. Embryofetal toxicity was evident in rats at peginesatide doses of ≥ 1 mg/kg and the malformations (cleft palate and sternoschisis, and variations in blood vessels) were mostly evident at doses of ≥ 10 mg/kg. The dose of 1 mg/kg results in exposures (AUC) comparable to those in humans after intravenous administration at a dose of 0.35 mg/kg in patients on dialysis. In a separate embryofetal developmental study in rats, reduced fetal weight and reduced ossification were seen at a lower dose of 0.25 mg/kg. Reduced fetal weight and delayed ossification in rabbits were observed at ≥ 0.5 mg/kg/dose of peginesatide. In a separate embryofetal developmental study in rabbits, adverse findings were observed at lower doses and included increased incidence of fused sternebrae at 0.25 mg/kg. The effects in rabbits were observed at doses lower (5% - 50%) than the dose of 0.35 mg/kg in patients.

8.3 Nursing Mothers

It is not known whether peginesatide is excreted in human milk. Because many drugs are excreted into human milk, caution should be exercised when OMONTYS is administered to a nursing woman.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of dialysis patients in Phase 3 clinical studies of OMONTYS, 32.5% were age 65 and over, while 13% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

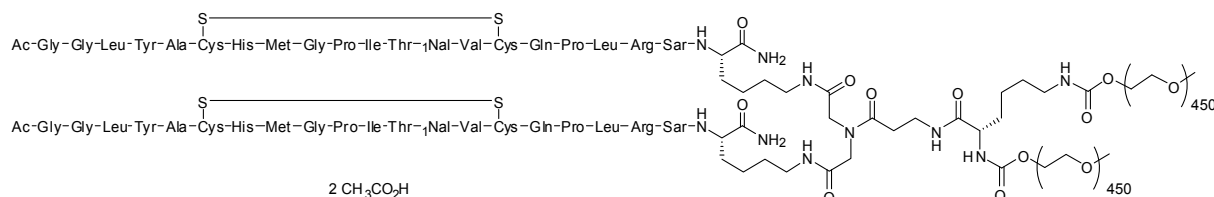
10 OVERDOSAGE

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

11 DESCRIPTION

Peginesatide is an ESA that is a synthetic, pegylated dimeric peptide comprised of two identical, 21-amino acid chains covalently bonded to a linker derived from iminodiacetic acid and β -alanine. Peginesatide is manufactured as an acetate salt. The dimeric peptide (approximate MW 4,900 daltons) is covalently linked to a single lysine-branched bis-(methoxypoly(ethylene glycol)) (PEG) chain (approximate MW 40,000 daltons). The structure is provided in Figure 1; peginesatide has no amino acid sequence homology to erythropoietin. The empirical formula is $C_{2031}H_{3950}N_{62}O_{958}S_6$ (free base). The total molecular weight is approximately 45,000 daltons.

Figure 1: Structure of peginesatide acetate



OMONTYS (peginesatide) Injection is formulated as a sterile, colorless to slightly yellow preservative-free solution and a sterile, colorless to slightly yellow preserved solution for intravenous or subcutaneous administration.

Single use, preservative-free injectable solutions of OMONTYS in vials and pre-filled syringes are supplied in multiple strengths. Each 0.5 mL vial or pre-filled syringe contains peginesatide, 23.5 mg sorbitol, 1.5 mg sodium phosphate monobasic (dihydrate), 0.06 mg sodium phosphate dibasic, 0.02 mg polysorbate 20, and water for injection, USP. Sodium hydroxide added to adjust pH. The pH is 6.0 ± 0.3 .

Multiple use, preserved injectable solutions of OMONTYS in vials are supplied in two fill volumes: 1 mL and 2 mL. Each mL contains 10 mg peginesatide, 47 mg sorbitol, 5 mg phenol, 1.5 mg L-methionine, 0.6 mg glacial acetic acid, and water for injection, USP. Sodium hydroxide added to adjust pH. The pH is 5.4 ± 0.5 .

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Peginesatide binds to and activates the human erythropoietin receptor and stimulates erythropoiesis in human red cell precursors *in vitro*.

12.2 Pharmacodynamics

Peginesatide increases the reticulocyte count, followed by increases in hemoglobin. The rate of hemoglobin increase varies among patients and is dependent upon the dose of peginesatide administered.

Effect on Cardiac Repolarization

The effect of OMONTYS (0.1 mg/kg intravenously) on QTc interval was evaluated in a randomized, double-blind, double-dummy, three-period crossover thorough QT study in 56 healthy subjects. A dose of 0.1 mg/kg administered intravenously did not delay cardiac repolarization compared to placebo. The dose of 0.1 mg/kg is adequate to represent the median dose (0.07 mg/kg) in the phase 3 trials, however is not sufficient to represent doses higher than 0.1 mg/kg in the intended patients.

12.3 Pharmacokinetics

Following single intravenous and subcutaneous injections at doses ranging from 0.03 to 0.1 mg/kg to dialysis patients, maximal plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) increase with dose. Following subcutaneous administration, the maximum concentrations of peginesatide are reached in approximately 48 hours. The bioavailability of peginesatide following subcutaneous administration is approximately 46%.

No mass balance study has been conducted in humans. Preclinical radiolabeled peginesatide study indicated that peginesatide is not metabolized and that urinary excretion was the predominant route of elimination following either intravenous or subcutaneous dosing.

The mean half-life is 25.0 ± 7.6 hours following intravenous administration and 53.0 ± 17.7 hours following subcutaneous administration in healthy subjects. The mean half-life in dialysis patients is 47.9 ± 16.5 hours following intravenous administration. Mean systemic clearance is 0.5 ± 0.2 mL/hr·kg and mean volume of distribution is 34.9 ± 13.8 mL/kg following intravenous administration in dialysis patients. No accumulation is observed following administration every 4 weeks following intravenous or subcutaneous administration. The pharmacokinetics of peginesatide in patients with CKD on dialysis are not altered by age, gender or race based on population pharmacokinetic analyses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Peginesatide was not carcinogenic in a 2-year study in rats at doses up to 0.25 mg/kg administered every 3 weeks by intravenous injection. This dose is approximately 14% the human exposure (AUC) at a dose of 0.35 mg/kg in patients on dialysis. Peginesatide was not carcinogenic in a 26-week study in rasH2 transgenic mice when administered by intravenous injection at doses of 0.1, 0.25, or 0.5 mg/kg/dose every 3 weeks.

Peginesatide was not mutagenic or clastogenic in the *in vitro* Ames assay, *in vitro* mammalian chromosome aberration assay, and an *in vivo* mouse erythrocyte micronucleus assay.

When peginesatide was administered intravenously to male and female rats at weekly intervals prior to and during mating, and treated rats mated, fertility was reduced at ≥ 0.1 mg/kg (approximately 5% of the dose of 0.35 mg/kg in patients) and was most evident at doses

≥ 1.0 mg/kg of peginesatide. Adverse effects in males included reduced weight of seminal vesicles and prostate. Decreased viable fetuses at ≥ 0.1 mg/kg in females appeared to be due to pre- and post-implantation losses. There was no apparent drug-related effect on estrous cycles or number of corpora lutea.

14 CLINICAL STUDIES

The efficacy and safety of OMONTYS in patients with CKD on dialysis were demonstrated in two randomized, active-controlled, open-label, multi-center clinical studies that evaluated OMONTYS in the maintenance of hemoglobin concentrations in patients who were being treated with another ESA (epoetin alfa or epoetin beta) at the time of study entry. The primary efficacy endpoint for each study was the change in hemoglobin from Baseline to the Evaluation Period (Weeks 29 to 36) using a non-inferiority comparison with epoetin. In Study 1, patients received epoetin via the intravenous route of administration and continued to use this route after randomization to either OMONTYS or epoetin. The average patient exposure year [PEY] per patient was 1.14 years for OMONTYS and the average PEY per patient was 1.25 years for epoetin. In Study 2, the route of administration previously used for epoetin (intravenous or subcutaneous) was used. The average PEY per patient was 1.17 years for OMONTYS and the average PEY per patient was 1.16 years for epoetin. The median dose of OMONTYS was 0.07 mg/kg administered once monthly and the median dose of epoetin was 113 units/kg administered weekly (in 1 to 3 doses).

Patients were randomized (2 to 1) to receive OMONTYS once monthly, or to continue on their current ESA treatment 1 to 3 times per week. The OMONTYS starting dose was based on the patient's total weekly ESA dose during the last week of the screening period. As shown in Table 4, treatment with OMONTYS once monthly and treatment with epoetin 1-3 times per week maintained hemoglobin concentrations within the study pre-specified hemoglobin range (10 to 12 g/dL). In both studies, the proportion of patients receiving transfusions was similar in each treatment group.

Table 4: Clinical Studies in Dialysis Patients

Group (N)	Mean baseline Hemoglobin	Change from Baseline to Weeks 29-36	Between group difference, Least Squares Mean g/dL (95% CI)
Study 1			
OMONTYS (524)	11.3 g/dL	-0.24 g/dL	-0.15 g/dL (-0.30, -0.01)
Epoetin (269)	11.3 g/dL	-0.09 g/dL	
Study 2			
OMONTYS (542)	11.2 g/dL	-0.07 g/dL	0.10 g/dL (-0.05, 0.26)
Epoetin (273)	11.2 g/dL	-0.17 g/dL	

Studies 1 and 2 had a pre-specified, prospective, pooled analysis of a composite cardiovascular safety endpoint consisting of death, myocardial infarction, stroke, or serious adverse events of congestive heart failure, unstable angina or arrhythmia. In patients receiving OMONTYS, 22.8% experienced one of these events compared to 24.4% receiving epoetin (hazard ratio 0.95, 95% CI 0.77, 1.17).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

OMONTYS is available in single use vials, single use pre-filled syringes, and multiple use vials. The vial caps and plungers of the pre-filled syringes are designated with unique colors for each dosage strength. The single use pre-filled syringes are supplied with a 27 gauge, ½ inch needle.

To reduce the risk of accidental needle sticks after application, each single use pre-filled syringe is equipped with a safety device that activates and covers the needle once the dose has been given.

OMONTYS is available in the following pack sizes:

Single use vials	Single use pre-filled syringes with a 27 gauge, ½ inch needle with an UltraSafe Passive® Needle Guard	Multiple use vials
1 Vial/Carton	1 Syringe/Carton	1 Vial/Carton
2 mg/0.5 mL (NDC 64764-602-05)	1 mg/0.5 mL (NDC 64764-601-99)	10 mg/mL (NDC 64764-610-10)
3 mg/0.5 mL (NDC 64764-603-05)	2 mg/0.5 mL (NDC 64764-602-99)	20 mg/2 mL (NDC 64764-620-20)
4 mg/0.5 mL (NDC 64764-604-05)	3 mg/0.5 mL (NDC 64764-603-99)	
5 mg/0.5 mL (NDC 64764-605-05)	4 mg/0.5 mL (NDC 64764-604-99)	
6 mg/0.5 mL (NDC 64764-606-05)	5 mg/0.5 mL (NDC 64764-605-99)	
	6 mg/0.5 mL (NDC 64764-606-99)	

16.2 Stability and Storage

The recommended storage temperature is refrigerated at 2 °C to 8 °C (36 °F to 46 °F). Protect from light. Retain in carton until time of use.

Storage of single use vials, single use pre-filled syringes or multiple use 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 30 days.

After first use, the multiple use vials should be stored at 2 °C to 8 °C, and then discarded after 28 days.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

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

Inform patients:

- To read the Medication Guide and to review and discuss any questions or concerns with their healthcare provider before starting OMONTYS and at regular intervals while receiving OMONTYS.
- Of the increased risks of mortality, serious cardiovascular reactions, thromboembolic reactions, stroke, and tumor progression [see *Warnings and Precautions* (5.1, 5.2)].
- To undergo regular blood pressure monitoring, adhere to prescribed anti-hypertensive regimen and follow recommended dietary restrictions.

- To contact their healthcare provider for new-onset neurologic symptoms or change in seizure frequency.
- Of the need to have regular laboratory tests for hemoglobin.

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

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

Marketed by:
Affymax, Inc.
Palo Alto, CA 94304

Distributed and Marketed by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

OMONTYS is a trademark of Affymax, Inc. registered in the U.S. Patent and Trademark Office and used under license by Takeda Pharmaceuticals America, Inc.

All other trademarks are the property of their respective owners.

PEG096 R1