Reducing the burden of ESA administration

Consider the first once-monthly, non-EPO ESA offering less-frequent dose administration.

INDICATION AND LIMITATIONS OF USE
OMONTYS® ( peginesatide ) Injection is indicated for the treatment of anemia due to chronic kidney disease ( CKD ) in adult patients on dialysis.

OMONTYS is not indicated and is not recommended for use in patients with CKD not on dialysis, in patients receiving treatment for cancer and whose anemia is not due to CKD, or as a substitute for red blood cell ( 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.

IMPORTANT SAFETY INFORMATION

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOSIS, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, ESRD, AND DEATH FROM THROMBOEMBOLISM. 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 OMONTYS dose sufficient to reduce the need for RBC transfusions.

Contraindications OMONTYS is contraindicated in patients with uncontrolled hypertension and in patients who have had serious allergic reactions to OMONTYS.

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 benefit. Use caution in patients with persistent 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. A rate of hemoglobin rise of >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 including myocardial infarction and stroke was observed.
- There is increased mortality and/or increased risk of tumor progression or recurrence in patients with cancer receiving ESAs.
- In controlled clinical trials of ESAS, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery ( CABG ) and deep venous thrombosis ( DVT ) in patients undergoing orthopedic procedures.

Dialysis management: Patients receiving OMONTYS may require adjustments to dialysis prescriptions and/or increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

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 mg/L, or when serum transferrin saturation is less than 20%. Monitor hemoglobin every 2 weeks until stable and the need for RBC transfusions is minimized. Then, monitor monthly.

Adverse reactions Most common adverse reactions in clinical studies in patients with CKD on dialysis treated with OMONTYS were dyspnea, diarrhea, nausea, cough, and arteriovenous fistula site complication.

Please see accompanying Brief Summary.

OMONTYS® peginesatide

CBB plus ARB Improves Outcomes in Hypertension and CKD

In high-risk older adults with hypertension and chronic kidney disease ( CKD ), adding a calcium channel blocker ( CCB ) to high-dose angiotensin II receptor blocker ( ARB ) yields further reductions in cardiovascular events, reports a trial in Kidney International.

The multicenter “OlmecSartan and Calcium Antagonists Randomized” ( OSCAR ) trial included 1078 older Japanese adults with hypertension and baseline cardiovascular disease and/or diabetes. In the main trial, patients were randomly assigned to upward titration of ARB or to the addition of a CCB to ARB therapy. The current study was a prespecified subgroup analysis assessing treatment responses according to baseline estimated GFR ( eGFR ).

On the basis of an eGFR of less than 60 mL/min/1.73 m², 355 patients had CKD; in almost all, eGFR was 30–59 mL/min/1.73 m². In patients with or without CKD, blood pressure was lower with CCB plus ARB than with high-dose ARB.

Among CKD patients, the primary composite outcome of cardiovascular events and noncardiovascular death was about twice as high in the high-dose ARB group: 30 versus 16 events, hazard ratio 2.25. In particular, the rates of cerebrovascular and heart failure events were higher in CKD patients receiving high-dose ARB, compared with CCB plus ARB. By contrast, for patients without CKD, the primary event rate was similar between treatment groups. The subgroup interaction was significant, with high-dose ARB being an independent prognostic factor for primary events among
The risk of angioedema appears higher for patients taking angiotensin-converting enzyme inhibitors (ACEs) compared with other drugs targeting the renin-angiotensin-aldosterone system, according to a study in the *Archives of Internal Medicine*. The retrospective analysis included adult patients from 17 health plans contributing data to the Mini-Sentinel program. From 2001 through 2010, more than 1.8 million patients started treatment with an ACEI, 467,313 with an angiotensin receptor blocker (ARB), and 4867 with the direct renin inhibitor aliskiren. A propensity score approach was used to compare the risk of angioedema between these three groups and with 1.6 million patients starting treatment with a β-blocker.

The "real-world" study showed an overall low rate of angioedema, with a total of 4511 events during follow-up. However, risk was elevated with ACEIs or aliskiren. The cumulative incidence per 1000 patients was 1.79 with ACEIs and 1.44 with aliskiren, compared with 0.62 with ARBs and 0.58 with β-blockers. The incidence rates per 1000 person-years were 4.38 for ACEIs and 4.67 for aliskiren, compared with 1.66 for ARBs and 1.67 for β-blockers. The adjusted hazard ratio for angioedema (compared with β-blockers) was 3.04 with ACEIs and 2.85 for aliskiren. The risk of serious angioedema causing airway obstruction was low, but higher with ACEIs.

Some reports have linked drugs targeting the renin-angiotensin-aldosterone system to an increased risk of angioedema, but few have addressed the magnitude of this risk or the differences in risk between drug classes. The new study suggests that angioedema risk, though low overall, is elevated threefold in patients taking ACEIs compared with β-blockers. Aliskiren may also increase risk, according to studies based on a small number of cases; risk may differ for individual ARBs as well [Telò S, et al. Comparitive risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med* 2012; 172:1582–1589].

### ACEIs Linked to Increased Angioedema Risk

<table>
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<tr>
<th>Patients with CKD who were on dialysis with concomitant CHF or CAD, compared with patients who were not on dialysis</th>
<th>14.0% vs. 5.0%</th>
<th>13.5% vs. 11.3%</th>
<th>13.0% vs. 8.8%</th>
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### Indicators of Use

**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.

**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].

- In patients receiving treatment for cancer and whose anemia is not due to CKD, because ESA have shown harm in some settings and the benefit-risk factors for *OMONTYS* in this setting have not been studied [see Warnings and Precautions].

- 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.

### CONTRAINDICATIONS

- *OMONTYS* is contraindicated in patients with:
  - Uncontrolled hypertension [see Warnings and Precautions].
  - Serious allergic reactions to *OMONTYS* [see Warnings and Precautions].

### WARNINGS AND PRECAUTIONS

#### 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 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 group.

- Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not shown to provide additional benefit. Use caution in patients with covariant 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 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, ESA 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.

#### Increased Incidence in Renal Insufficiency (CHOIR) and Trial to Reduce Cardiovascular Events with ARBs (TREAT).”

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