



## Diet and Nutrition Can Play a Pivotal Role in Improving Outcomes among Minorities and Reducing Health Disparities

Improving dietary habits and ensuring access to healthy foods are important to reducing health disparities and improving outcomes among lower-income individuals and minorities, at-risk populations for developing kidney disease in the United States. This was the conclusion of two new studies presented at Kidney Week 2012 that demonstrated 1) increased intake of fruit and vegetables can ameliorate metabolic acidosis, and 2) an unhealthy diet lacking nutrients that indicate adherence to a DASH (Dietary Approaches to Stop Hypertension) diet—which is high in whole grains and fruits and vegetables—among individuals living in poverty can adversely impact their chances for developing CKD, some of whom already have an increased odds for disease progression. Both studies offer evidence that diet and nutrition present targets for reducing health disparities in individuals facing an increased risk for kidney disease.

Previous research into the effects of diet on CKD focused on limiting protein intake, most notably in the Modification of Diet in Renal Disease (MDRD) study, said Frank C. Brosius III, MD, of the University of Michigan Health System, who was not involved in either of the studies. The MDRD study, however, found no significant difference in outcomes based on diet, and despite interest in how nutrients and antioxidants impact kidney disease, “there have been no conclusive studies stating that dietary intervention leads to a statistically significant improvement in outcomes,” he said.

“This is why studies like these are exciting, because improving diet can be a low-cost high-safety intervention,” Brosius said. “The focus of this research is great, because if dietary changes can be shown to have an impact on progression of disease, particularly in those groups who are at highest risk for kidney disease, you can get the biggest bang for your buck.”

## Dietary habits of individuals living in poverty

Research has demonstrated that lower socioeconomic status is connected with reduced kidney function and an increased risk for progression to ESRD. To determine if dietary habits were contributing to this increased risk for CKD, Deidra Crews, MD, FASN, of the Johns Hopkins University School of Medicine, and her colleagues stud-

ied a large urban population to determine if adherence to a DASH-style diet was linked with reduced prevalence of kidney disease among those living in poverty.

Crews used the Healthy Aging in Neighborhoods of Diversity Across the Lifespan (HANDLS) cohort, an intramural study of the National Institute on Aging that focuses on the influence of socioeconomic status and race on health outcomes. A total of 2058 participants from diverse backgrounds in Baltimore were included, 42 percent of

whom were classified as living in poverty. The poverty group had a significantly higher number of black and uninsured individuals and tobacco users compared with the non-poverty group. Although participants were not instructed in the DASH diet, their report, via 24-hour dietary recall of intake of foods containing the macro- and micronutrients considered in DASH adherence scoring were used to assess their dietary habits. Kidney disease was defined by reduced eGFR and/or elevated urinary albumin-creatinine ratio.

## Omontys<sup>®</sup> peginesatide

Brief Summary of Prescribing Information for:  
OMONTYS (peginesatide) Injection for intravenous or subcutaneous use

**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.
- No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks [see *Warnings and Precautions*].
- Use the lowest OMONTYS dose sufficient to reduce the need for red blood cell (RBC) transfusions [see *Warnings and Precautions*].

### INDICATIONS AND USAGE

#### 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 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*].
- 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*].

### 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 – 11.3 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. 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<sup>®</sup> 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 ± 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).

#### 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.

#### 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.

#### 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.

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

#### 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.

#### 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%. The majority of patients with CKD will require supplemental iron during the course

The majority in both poverty and non-poverty groups in the HANDLS cohort were found to be non-adherent to a DASH-style diet (only 4.5 percent and 6.1 percent, respectively, were adherent). Despite this, those in the poverty group fared significantly worse in levels of nutrients (cholesterol, fiber, magnesium, calcium, and potassium) and had a significantly higher rate of CKD compared with the non-poverty group (5.6 percent versus 3.8 percent).

When the entire cohort was stratified

across tertiles of DASH adherence (lowest, middle, and highest) prevalence of CKD remained higher in the low and middle adherence tiers of the poverty group, while there was no statistically significant difference across the tiers in the non-poverty group. Logistic regression revealed similar findings, even after inclusion of sociodemographic, hypertension, diabetes, and tobacco use variables.

Given these results, could specific factors lead to increased risk for indi-

viduals in the poverty group? Crews said the reasons behind this relationship were unclear.

“The specific nutrient profiles could be the main drivers, as could additives in the foods of the poverty group (which we did not directly assess),” Crews said. “It is also possible that dietary habits do not play as much of a role in CKD risk for higher income individuals because their risk is largely mitigated by access to health care, access to recreation, and less psychological stress. On the

converse, dietary habits may play a big role in risk of CKD for poor individuals because they have so many risk ‘amplifiers’ (poor access to health care, limited access to recreation, significant stress, or discrimination), and thus when dietary habits are favorable, CKD risk might be lessened even in the setting of poverty.”

Brosius noted that although “it is a complex study, the results are consistent with the fact that the DASH diet tends to be more expensive, and the poverty group is more likely to be living in ‘food deserts’ where there is less access to DASH-style diets. However, those people in poverty groups who do adhere to DASH-style diets have a significantly reduced risk of CKD.” He added that a follow-up study would need to control for more than presence or absence of diabetes and hypertension, “but also how well these are being controlled. But in these groups, a DASH diet might be an effective preventative intervention.”

Crews is planning a tailored interventional study in a similar population, aimed at educating the participants on how to follow a DASH-style diet even with limited finances and limited access to healthy foods.

“As more evidence is revealed regarding the detrimental and costly effects of limited access to healthy foods we will see changes in policies on zoning and more incentives for full-service grocery stores opening in what are now food deserts,” Crews said. “I consider ours, and other studies of its kind, a call to action for members of the kidney community to get involved in public policy.”

## Fruits and vegetables can mitigate metabolic acidosis

Metabolic acidosis can commonly affect individuals with CKD and is associated with higher levels of angiotensin II, a pathway that powerfully promotes hypertension, a decline in renal function, and irreversible fibrosis of kidney tissue. This condition is exacerbated by a diet rich in fat and animal proteins, which generate a higher acid load than impaired kidneys can handle. Current clinical guidelines indicate alkali therapy for severe (<22 mM  $\text{PTCO}_2$ ) but not for milder (22–24 mM  $\text{PTCO}_2$ ) cases. To determine if patients with stage 3 CKD and less severe metabolic acidosis could also benefit from therapy, Nimrit Goraya, MD, of the Texas A&M College of Medicine and her co-workers investigated if adding fruits and vegetables (which generate a net alkaline load) or oral doses of sodium bicarbonate could reduce the decline in kidney function.

Building on their previous research, they performed a prospective trial with

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.

### 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*]
- Hypertension [see *Warnings and Precautions*]

### 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 0.07mg/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)
<b>Gastrointestinal Disorders</b>		
Diarrhea	18.4%	15.9%
Nausea	17.4%	19.6%
Vomiting	15.3%	13.3%
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Dyspnea	18.4%	19.4%
Cough	15.9%	16.6%
<b>Injury, Poisoning and Procedural Complications</b>		
Arteriovenous Fistula Site Complication	16.1%	16.6%
Procedural Hypotension	10.9%	12.5%
<b>Nervous System Disorders</b>		
Headache	15.4%	15.9%
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Muscle Spasms	15.3%	17.2%
Pain in Extremity	10.9%	12.7%
Back Pain	10.9%	11.3%
Arthralgia	10.7%	9.8%
<b>Vascular Disorders</b>		
Hypotension	14.2%	14.6%
Hypertension	13.2%	11.4%
<b>General Disorders and Administration Site Conditions</b>		
Pyrexia	12.2%	14.0%
<b>Metabolism and Nutrition Disorders</b>		
Hyperkalemia	11.4%	11.8%
<b>Infections and Infestations</b>		
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.

### 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.

### 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.

### USE IN SPECIFIC POPULATIONS

#### 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  $\geq 1$  mg/kg and the malformations (cleft palate and sternoschisis, and variations in blood vessels) were mostly evident at doses of  $\geq 10$  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  $\geq 0.5$  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.

#### 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.

#### Pediatric Use

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

#### 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.

#### OVERDOSAGE

OMONTYS overdosage 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. Cases of severe hypertension have been observed following overdose with ESAs [see *Warnings and Precautions*].

#### PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Medication Guide*).

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**Affymax, Inc.**  
Palo Alto, CA 94304

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**Takeda Pharmaceuticals America, Inc.**  
Deerfield, IL 60015

For more detailed information, see the full prescribing information for OMONTYS at [www.omontys.com](http://www.omontys.com) or contact Takeda Pharmaceuticals America, Inc.

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