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Truvada™: A New Indication for HIV Pre-exposure Prophylaxis

In July 2012, Truvada™ became the first medication to be FDA approved for use in conjunction with safe sex practices as pre-exposure prophylaxis to reduce the risk of sexually acquired disease in high-risk adults.

Peginesatide (Omontys®): A New Erythropoiesis Stimulating Agent for Anemia of Chronic Kidney Disease

It is estimated that more than 20 million people in the United States have CKD, with anemia being a common complication. Peginesatide (Omontys®) is the newest erythropoiesis stimulating agent to be approved by the FDA for use in anemia associated with chronic kidney disease.

Ondansetron 32 mg Withdrawn from Market

The FDA has notified health care professionals that the 32 mg, single intravenous (IV) dose of the anti-nausea drug Zofran (ondansetron hydrochloride) will no longer be marketed in the U.S. because of the potential for serious cardiac risks.
Diabetic Foot Infection: 2012 Update to the IDSA Guidelines

Christina York, PharmD

The Infectious Disease Society of America (IDSA) released diabetic foot infection updated guidelines in June 2012. The guidelines were compiled by a panel of experts using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system. Updated information includes, but is not limited to, use of a validated classification system for diagnosis and additional antimicrobial agents indicated for diabetic foot infection since the 2004 guidelines were published.¹

Diabetic foot infection contributes significantly to healthcare cost and morbidity, as most patients require some form of surgical intervention ranging from debridement to amputation. There is also a risk of developing osteomyelitis which requires a prolonged course of antibiotics.

Diagnosis

The guidelines strongly recommend that an ulcer should not be considered infected without the presence of inflammation or purulence. Inflammation is defined by the presence of two or more of the following: erythema, warmth, swelling, tenderness, or pain.

Use of the International Working Group on the Diabetic Foot (IWGDF) - IDSA System to classify infection as uninfected (grade 1), mild (grade 2), moderate (grade 3), or severe (grade 4) is also strongly recommended. This system, which was validated since the 2004 guidelines were published, uses disease classification to predict clinical outcomes, such as hospitalization, osteomyelitis or amputation.²

The guidelines recommend obtaining a deep tissue culture by biopsy or curettage after debridement if clinical signs and symptoms are present. A swab of the wound is not considered adequate. An exception is made for mild infection in patients not recently treated with antibiotics, in which case empiric therapy may be sufficient. A newer approach using molecular diagnostics is also recognized as effective if available.

Plain radiographic imaging should be performed on all patients with infection to identify soft tissue gas, bony involvement, or foreign body presence. A MRI is preferred if further evaluation is needed. If MRI is contraindicated or unavailable, a nuclear bone scan in conjunction with radio-labeled white blood cells is an appropriate option, particularly in suspected osteomyelitis.³

Diagnosis of osteomyelitis should be based on a probe-to-bone (PTB) test, imaging, and bone culture and histology collected during debridement.⁴ If osteomyelitis is suspected based on these findings, a bone biopsy is preferred for culture and histology. Needle aspiration of deep tissue near the bone is considered inferior to a biopsy, with
one study finding only a 30% correlation between needle aspiration and bone biopsy culture. However, because of the invasiveness of a bone biopsy, empiric treatment guided by soft tissue culture may be appropriate if diagnosis is fairly certain and the patient is responding to therapy.

**Treatment**

An interprofessional team approach is strongly emphasized within the guidelines, including recommendations to consult a surgeon, a specialized infectious disease or microbiology clinician, and a wound care specialist. Telemedicine is a new approach which may be useful for clinicians in communities without direct access to these resources.

The combination of appropriate antibiotics and wound care should be initiated in all patients with infection. Patients should be hospitalized if they have severe infection, moderate infection with comorbidities, or if unable to improve at home due to clinical or social etiologies. Medically treated osteomyelitis alone is not an acceptable reason for hospitalization.

Empiric therapy should be based on presentation (Table 1). Agents which are recommended for uncomplicated mild infection cover gram positive cocci and include dicloxacillin, clindamycin, or cephalexin; past antibiotic exposure or chronic infection may require levofloxacain or amoxicillin-clavulanate. A penicillin with beta-lactamase inhibitor or a fluoroquinolone is appropriate for uncomplicated moderate to severe infection; past antibiotic exposure or chronic infection may require cefoxitin, ceftriaxone, ertapenem, imipenem-cilastatin, tigecycline, or the addition of clindamycin. Ertapenem received FDA approval for the treatment of diabetic foot infection since the 2004 guidelines. Meropenem, which is the carbapenem on formulary at UMMC, also has approval for complicated skin and skin structure infections.

Multi-drug resistant pathogens may be considered if local resistance is high, regardless of past exposure. The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) ranges from 10-30% in literature, but the incidence has been rising nationwide. According to the most recent antibiogram, 59% of all *Staphylococcus aureus* cultured at UMMC is methicillin-resistant. Suspected MRSA should be covered with doxycycline, sulfamethoxazole-trimethoprim, vancomycin, linezolid, or daptomycin. Pseudomonas should be considered if there is a particularly high local incidence or the patient has frequent exposure of the foot to moisture which can occur in warm, humid climates. There is an estimated 3-10% incidence of pseudomonas diabetic foot infection reported in the literature. UMMC may have a higher incidence, however, with the most recent antibiogram at UMMC showing *Pseudomonas aeruginosa* as the second most common gram negative organism isolated from culture. If pseudomonas is suspected, the recommended therapy is piperacillin-tazobactam, and this is supported by our
antibiogram with 86% susceptibility at UMMC. Both linezolid and piperillin-tazobactam have received FDA approval for treatment of diabetic foot infection since the 2004 guidelines. Although the guidelines do not address penicillin-allergy, an aminoglycoside would be the best alternative empiric therapy for pseudomonas at UMMC according to our antibiogram.

Of the agents previously mentioned, a few require special consideration. Tigecycline should be reserved for alternate therapy due to the FDA warning regarding increased risk of mortality compared to other agents in treatment of pneumonia and complicated skin and skin structure infections. Both linezolid and daptomycin are restricted medications at UMMC and should only be used in diabetic foot infection if a patient has resistance or allergy to vancomycin. Also, tigecycline and imipenem-cilastatin are considered very broad spectrum agents. It is important to use the narrowest spectrum possible and to restrict use of these broad spectrum agents to special cases to prevent the emergence of resistance.

Clinical judgment, culture results, and patient response to therapy should be used to modify or guide empiric therapy. Criteria for hospital discharge include clinical stability and completion of urgent surgical procedures. Prior to discharge, a plan should be established for continuation of antibiotics, wound care, and close follow up.

Mild infection will generally be treated for 1-2 weeks and moderate to severe infection for 2-3 weeks, but duration should ultimately be dictated by resolution of signs and symptoms of infection. There is no evidence to suggest benefit in treating until the wound has completely healed.

For medical treatment of osteomyelitis, antibiotics should be continued for at least 4 weeks. If necrotic bone is present, a much longer course, often for 3 months or more, is generally required. There is no evidence to recommend a particular agent or to recommend the parenteral route over the oral route. The regimen should be empirically designed to cover staphylococci, and definitive therapy should be guided by culture. Clinical response is monitored by a decrease in inflammatory markers such as erythrocyte sedimentation rate, response of concomitant soft tissue infection, wound healing, and imaging.

For infections not adequately responding to antimicrobials alone, hyperbaric oxygen therapy is still the only adjuvant with moderate-quality evidence and a strong recommendation from the panel. Granulocyte colony-stimulating factor (GCSF), bioengineered skin equivalents, and growth factors carry a weak recommendation with moderate-quality evidence. The adjuvant carrying the weakest recommendation is negative pressure wound therapy.
Conclusion

A team approach is critical for the appropriate management of a patient with a diabetic foot infection. Diagnosis should be on the basis of inflammation or purulence and classified using the IWGDF-IDSA classification system to guide empiric therapy. Deep tissue culture and imaging should be performed at the time of diagnosis. For empiric therapy, MRSA infection should be considered at UMMC since frequency has been increasing. Pseudomonas may also be a concerning pathogen in our region. Along with previously available therapy, ertapenem, linezolid, and piperillin-tazobactam are newly approved for diabetic foot infection but use of the first two agents should be limited to special situations. Culture directed therapy should continue for as long as signs and symptoms of infection are present.

References

11. FDA Drug Safety Communication: Increased risk of death with Tygacil® (tigecycline) compared to other antibiotics used to treat similar infections. http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm
Belviq® and Qsymia™: Two New FDA Approved Weight Loss Medications

Bradley Wagner, PharmD

Nationally, the CDC estimates that 35.7% of Americans are obese. This is thought to cost $147 billion annually in medical expenses. Locally, Mississippi has had the highest obesity rate in the United States for seven consecutive years. Obesity is clearly associated with diseases of significant morbidity and mortality such as diabetes, cardiovascular disease, hypertension, and dyslipidemia. A loss of 5-10% of total body weight can significantly improve obesity related diseases. Surrogate markers of glycem, blood pressure, and dyslipidemia seem to indicate an improvement in overall health and quality of life. Past efforts to reduce the rate of obesity have been inadequate. Newer weight loss medications with fewer severe side effects would be a welcome addition to use in conjunction with lifestyle and behavior modification to attain and maintain weight loss.

Historically, fenfluramine and dexfenfluramine were both prescription weight loss agents that were withdrawn by the FDA in 1997. These two agents were associated with cardiac valvulopathy. The valve problem was noted on echocardiogram in as many as 30% of patients. It is thought that the affinity and agonism of a particular serotonin subtype (5HT-2b) was the culprit.

Currently approved pharmacologic weight loss treatments include orlistat, phentermine, and diethylpropion. Orlistat is a lipase inhibitor available OTC (Alli™ 60 mg) and by prescription (Xenical™ 120 mg) that reduces the body’s fat absorption by one-fourth to one-third, respectively, resulting in an average of 13 pounds of weight loss in 1 year with Xenical™. Embarrassing side effects include fecal urgency and “flatus with discharge.” Diethylpropion and phentermine, both short term appetite suppressants, work as sympathomimetics to “jump-start” a diet by promoting satiety. Side effects include tachycardia, insomnia and, again, possible valvular heart disease.

This year marks the first time the FDA has approved prescription weight loss medications since 1999. Belviq® (lorcaserin) was approved in June 2012 and is
expected to be available early 2013. Qsymia,™ (phentermine/topiramate extended release) a schedule IV medication, was approved in July 2012 and is now available. It must be obtained through certified Risk Evaluation and Mitigation Strategy (REMS) mail order pharmacies due to its risk for fetal toxicity.

Both medications were approved as an adjunct to reduced calorie diet and increased exercise for chronic weight management in obesity (BMI ≥ 30 kg/m²) or in overweight patients (BMI ≥ 27 kg/m²) with at least one weight-related comorbidity (hypertension, type 2 diabetes, or dyslipidemia).

Qsymia™ is a combination sympathomimetic, phentermine and an antiepileptic medication, topiramate which has been noted to have a side effect of weight loss. Phentermine works by increasing norepinephrine release in the hypothalamus leading to increased satiety. Topiramate’s weight loss mechanism is unknown, but is believed to be due to increased satiety and decreased appetite through carbonic anhydrase inhibition, agonism at GABA receptors and inhibition of an excitatory neurotransmitter, AMPA (2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid)/ kainite.

This is not the first time phentermine has been used in combination with another medication as a weight loss method. “Fen-phen” or fenfluramine/phentermine was used for weight loss before the FDA withdrew fenfluramine due to previously stated valvulopathy problems. However, it was not available as a single drug product, but was used as the two individual entities.

Qsymia™ is available in four prescription strengths (see Table 1). The phentermine 3.75 mg/ topiramate 23 mg starting dose should be titrated up to the 7.5/46 mg strength after the initial 14 days. If after 12 weeks on this dose, patients do not see a 5% total weight loss the medication should either be discontinued or further increased to 11.25/69 mg strength for 14 days followed by 15/92 mg thereafter.

Qsymia’s™ 7.5/46 mg and 15/92 mg doses demonstrated the greatest weight loss, but, also, the most troublesome side effect profile. Patients weighing an average of 235 pounds (BMI 37.4) lost 20-25 pounds (8.6-10.6%) with Qsymia™ compared to patients with a weight loss of 4 pounds with placebo (see Table 3). Patients began to see weight loss within 4 weeks after starting Qsymia.™ The SEQUEL trial demonstrated mean heart rate increases of 1.3 bpm and 1.7 bpm in the 7.5/46 mg and 15/92 mg groups, respectively. More than 75% of patients on these doses, however, had at least one follow-up with > 5 bpm increase from baseline. Nearly 20% in the 15/92 mg group had at least one follow-up with > 20 bpm increase. Sustained heart rate increases require down titration of the dose or discontinuation of the medication altogether. In patients with known cardiac or cerebrovascular diseases, the risk-benefit ratio must be strongly considered before prescribing Qsymia.™
dropout rates in conquer and equip, two 56-week studies, were 35% in patients taking qsymia™. qsymia’s most common side effects include paresthesias (16-20%), dizziness (7%) and dysgeusia (7%). the topiramate moiety can cause cognitive impairment (5%), oligohydrosis and hyperthermia, and possible suicidal ideation. phentermine’s serious side effects include tachycardia, possible valvular heart disease and rarely primary pulmonary hypertension.

qsymia™ is contraindicated in pregnancy, glaucoma, hyperthyroidism, and within 14 days of using a monoamine oxidase inhibitor. qsymia should not be discontinued abruptly as this lowers the seizure threshold and may cause seizures. dose adjustment is required in renal and hepatic impairment (see table 1).

belviq® (lorcaserin) is a novel compound that promotes satiety by acting as an agonist at the serotonin 2c receptor of the anorexigenic pro-opiomelanocortin neuron, a neuron that inhibits food intake and regulates energy homeostasis in the brain’s hypothalamus. lorcaserin is different from dextenfluramine and fenfluramine of its selectivity for the 2c receptor subtype. it has not shown any significant increase of cardiac valvulopathy during clinical trials compared to placebo.

schematic of the mediobasal hypothalamus.
arc, arcuate nucleus; vmn, ventromedial hypothalamic nucleus. hormones secreted in proportion to body fat mass, insulin and leptin act in the arc to stimulate pomic neurons and to inhibit npy/agrp neurons. both pomic and bdnf neurons can inhibit food intake, whereas npy/agrp neurons increase intake. new evidence from xu et al.3 suggests that pomic neurons reduce food intake via activation of bdnf neurons in the vmn.

abbreviations: pomic = pro-opiomelanocortin; bdnf = brain derived neurotrophic factor
figure from . wisse, b. schwartz m. the skinny on neurotrophins. nature neuroscience 2003:6, 655 – 656. (reference 16) used with permission

belviq® demonstrated a roughly 12 pound (5.4%) mean weight loss in patients weighing an average of 220 pounds (bmi 36). patients began to see weight loss by approximately 6 weeks after initiating belviq®. in the bloom-dm trial, a trial in type 2 patients with diabetes on either metformin (92%), a sulfonylurea (50%) or both (42%), patients on lorcaserin achieved a weight loss of 9.9 pounds versus 3.3 pounds on
placebo (p<0.001). Percent of patients attaining their HbA1c goal of ≤ 7% were 50% in the lorcaserin group and 26% in the placebo group.

In the three pivotal lorcaserin trials, BLOOD, BLOOD-DM, and BLOSSOM only 55%, 72%, and 58%, respectively, remained on lorcaserin at one year. The BLOOD trial showed those who switched from lorcaserin to placebo after one year lost the same amount of weight as those who took placebo for two years (see Table 2). Considering the high dropout rates and the return to placebo effect once stopping lorcaserin, the weight loss benefit is limited to those able to continue lorcaserin long term.

Lorcaserin is contraindicated in pregnancy, and use in severe hepatic or renal impairment is not recommended. Lorcaserin’s most common side effects include headache (16%), nausea (8%), and possibility of serotonin syndrome on concomitant serotonin boosting agents, cardiac valvulopathy (2-3%), and cognitive dysfunction (2%).

The cost of Belviq® has not been released, although the CEO of Arena Pharmaceuticals, maker of Belviq®, stated the cost will be about the same as a “Starbucks venti latte in New York” (roughly $4). Qsymia™ ranges from approximately $140 to $220 for a 30 day supply depending on the strength. Third party prescription coverage of these weight loss medications is estimated to be approximately 30%, however; Mississippi Medicaid will not cover either medication, as it excludes any weight loss medication. Blue Cross Blue Shield of Mississippi does not cover either medication as of this printing.

Overall, Qsymia™ has demonstrated greater weight loss, but with a more serious side effect profile than Belviq®. Patients with cardiovascular or cerebrovascular pathology taking Qsymia™ must be closely monitored for heart rate increases, possible cognitive impairment and oligohydrosis. Belviq’s® modest weight loss was only seen in those who continued long term therapy, while those who stopped Belviq® after 1 year showed no difference from placebo at two years. Neither of these medications will cure the obesity epidemic affecting the United States and Mississippi, in particular. Only eliminating calories, ingesting quality foods, and consistently exercising can hope to make a lasting impact. However, these may become useful tools to assist in the fight against obesity. These agents seem to be best reserved for those who have seen suboptimal weight loss and comorbid disease management with lifestyle changes, and can tolerate long term use of these agents.

Tables on next 3 pages
<table>
<thead>
<tr>
<th>Weight Loss Medication &amp; Mechanism of Action</th>
<th>Availability/Dosing</th>
<th>Side Effects/Warnings</th>
<th>Special Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belviq® (lorcaserin) 5HT-2c agonist</td>
<td>10 mg tablets; 10 mg orally twice daily</td>
<td>Headache (16%); Dizziness (9%); Nausea (8%); Serotonin syndrome/NMS like reaction</td>
<td>Monitor for hypoglycemia, heart valvulopathy; Contraindicated in Pregnancy</td>
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<tr>
<td>1 year weight loss: 12 lbs</td>
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<td>Duration of therapy:</td>
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<tr>
<td>Chronic</td>
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<tr>
<td>Stop if &lt; 5% wt loss in 12 weeks</td>
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<tr>
<td>Qsymia™ (phentermine/topiramate ER)</td>
<td>3.75 mg/23 mg 7.5 mg/46 mg 11.25 mg/69 mg 15 mg/92 mg 3.75/23 mg orally once daily x 14 days, then increase to 7.5/46 mg daily</td>
<td>Paresthesias (14-20%); Constipation (15%); Sinusitis (7%); Xerostomia (13-19%); Upper respiratory tract infection (12%)</td>
<td>Do not abruptly discontinue (seizures); Monitor heart rate/BP; Contraindicated: -Pregnancy; -Within 14 days of using a MAOI; -Hyperthyroidism; -Glaucoma</td>
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<tr>
<td>Sympathomimetic/Agonizes GABA, inhibits AMPA/kainite- an excitatory neurotransmitter</td>
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<tr>
<td>1 year weight loss: 20-25 lbs</td>
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<td>Duration of therapy:</td>
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<td>Chronic</td>
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<tr>
<td>Stop if &lt; 5% wt loss with 15/92mg x 12 weeks</td>
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</tbody>
</table>

NMS: neuroleptic malignant syndrome; ER: extended release; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; MAOI: monoamine oxidase inhibitor
### Table 2 Clinical Efficacy

<table>
<thead>
<tr>
<th>Belviq,® Trial</th>
<th>Duration</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>BLOOM, 2010</td>
<td>2 years</td>
<td>N=3182 (year 1) 1599 (year 2) BMI ≥ 30 OR BMI ≥ 27 + coexisting comorbidity (HTN, DLD, CVD, etc.) Average participant 44 years old 100 kg BMI 36 Demographics 67% white 83% female</td>
<td><strong>YEAR ONE</strong> Lorcaserin 10 mg BID or Placebo BID <strong>YEAR TWO</strong> Placebo continued Lorcaserin group split 2/3 continued lorcaserin 1/3 changed to placebo</td>
<td><strong>YEAR ONE</strong> Lorcaserin : Placebo ≥5% wt loss: 47.5% : 20.3% P&lt;0.001 Change in wt: 5.81kg : 2.16 kg P&lt;0.001 ≥10% wt loss: 22.6 : 7.7% P&lt;0.001</td>
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All pts received lifestyle modification therapy

Incidence of valvulopathy

Placebo : 2.3%

Lorcaserin: 2.7% (P = 0.70)
<table>
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<tr>
<th>Qsymia™ Trial</th>
<th>Duration</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>SEQUEL, 2012</td>
<td>2 years</td>
<td>N=866</td>
<td>Qsymia™ 7.5/46 mg</td>
<td><strong>Mean wt loss</strong></td>
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<td>BMI ≥ 27 but ≤ 45</td>
<td>Qsymia™ 15/92 mg</td>
<td>Placebo: -1.8%</td>
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<td>+ ≥ 2 weight-related comorbidites:</td>
<td>Placebo</td>
<td>7.5/46 mg: -9.3%</td>
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<td>-HTN, DLD, IFG</td>
<td>All pts received lifestyle modification therapy</td>
<td>15/92 mg: -10.5% (P&lt;.0001)</td>
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<tr>
<td></td>
<td></td>
<td>-diabetic on metformin or lifestyle controlled</td>
<td>Note: Intent to treat with last observation carried forward</td>
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<tr>
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<td>Average participant</td>
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<td>≥ 5% wt loss</td>
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<td>51 years old</td>
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<td>Placebo: 30%</td>
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<td>101 kg</td>
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<td>7.5/46 mg: 75.2%</td>
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<td>BMI 36</td>
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<td>15/92 mg: 79.3% (P&lt;.0001)</td>
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<td>Demographics</td>
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<td></td>
<td>86% white</td>
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<tr>
<td></td>
<td></td>
<td>66% female</td>
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HTN: hypertension; DLD: dyslipidemia; IFG: impaired fasting glucose

**References**


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Truvada™: A New Indication for HIV Pre-exposure Prophylaxis

Leslie Kruse, PharmD

The human immunodeficiency virus (HIV) continues to affect millions worldwide, even decades after its discovery. In 2011, 9,907 Mississipians were living with HIV/AIDS. The Centers for Disease Control and Prevention (CDC) reports that at the end of 2008, approximately 1,178,350 people age 13 and older were living with HIV in the United States. From 1999-2008, there was an average of 38,279 AIDS diagnoses annually, representing a decline in new cases that may be attributed to the introduction of antiretroviral therapy. In 2009, 48,100 new cases of HIV were diagnosed in the United States, a number comparable to that of the previous 4 years. In spite of the decline in new cases and new therapy options, HIV/AIDS remains a public health concern.

Sexual contact, injection drug use, birth to an HIV-positive mother, and occupational exposures are among the risk factors that have recommendations for post-exposure prophylaxis from the CDC. Behavioral modifications to prevent non-occupational exposures are preferred, but recommendations for post-exposure prophylaxis are available. In the context of occupational exposures, prevention of exposure to blood and body fluids is preferred; however, the availability of post-exposure prophylaxis for such exposures is an important element of workplace safety for healthcare providers. Recommendations for post-exposure prophylaxis are summarized in Table 1.

Sexual contact is the most frequently reported risk factor, including male-to-male sexual contact as well as high-risk heterosexual contact. Ultimately, all sexual transmission of the disease occurs in a discordant couple; that is, a couple that includes one HIV-positive person and one HIV-negative person. To decrease sexual transmission, condom use and other behavioral modifications are recommended in patients with HIV to prevent transmission to sexual partners. The HPTN 052 study, published in the New England Journal of Medicine in 2011, found that early initiation of antiretroviral therapy (ART) in HIV-positive patients reduced sexual transmission to uninfected sexual partners, providing evidence that antiretroviral therapy can be effective in reducing the risk of transmission of HIV.

Pre-exposure prophylaxis (PrEP) has emerged as an alternate method to combat the spread of HIV. This concept is derived from animal studies as well as from information on the efficacy of antiretrovirals in preventing viral transmission from an HIV-positive mother when treating newborns and breastfed infants. The proposed mechanism of PrEP is through prevention of replication of the virus when it first enters the body, thus preventing the virus from establishing permanent infection in the host. In July 2012, Truvada™ became the first medication to be FDA approved for use in conjunction with safe sex practices as pre-exposure prophylaxis to reduce the risk of sexually acquired disease in high-risk adults.
Truvada™ is a combination of the nucleoside analog HIV-1 reverse transcriptase inhibitors emtricitabine and tenofovir. While many regimens for treatment of HIV result in a high pill burden, this combination tablet may be taken by mouth once daily, with or without food. Truvada™ is indicated for treatment or prevention of HIV-1 infection in patients aged 12 years and older. This therapy has demonstrated decrease in viral replication, improved survival, and reduction in viral load of genital secretions. It is recommended as part of all preferred initial treatment regimens for treatment naïve patients, except in those who are pregnant. The medication is pregnancy category B. Adverse effects seen with the medication include new onset or worsening of renal impairment, decrease in bone mineral density, and fat redistribution. Patients should be reminded that the medication is not to be taken only before or after contact, but daily. Additionally, patients should understand that intermittent use will not confer protection against the virus and could possibly make it more difficult to treat HIV if the virus is contracted.

A boxed warning accompanies the new indication, stating that it may only be prescribed for PrEP to those who are confirmed to be HIV-negative immediately prior to initial use as well as periodically during use of the medication. This warning resulted from the identification of drug-resistant HIV-1 variants following use of emtricitabine-tenofovir for PrEP in patients with undetected HIV-1. The boxed warnings for lactic acidosis, severe hepatomegaly with steatosis, and post-treatment exacerbation of hepatitis B should also be noted for those using the medication for PrEP. With the new indication for PrEP, the FDA placed emtricitabine-tenofovir in the risk evaluation and mitigation strategy (REMS) program. The FDA identifies REMS as a way to minimize risk of acquiring HIV and reduce the risk of the development of drug-resistant HIV variants. As with other REMS medications, training and education for prescribers as well as medication guides for patients are key components. The medication guide, although developed with the advent of the new indication, applies to all users of the medication. For further information regarding this medication, see Table 2.

Several trials have studied the use of antiretroviral therapy in preventing transmission of HIV. The HPTN 052 study evaluated the use of antiretroviral therapy in HIV-positive patients for preventing transmission to HIV-negative partners. The study enrolled 1763 discordant couples and randomized them to early antiretroviral therapy (immediately after enrollment) or delayed antiretroviral therapy (after two consecutive CD4 counts < 250 cells per cubic millimeter) and followed them for a median of 1.7 years. The study demonstrated a 96% relative reduction in linked HIV-1 transmission in those receiving early therapy compared to delayed therapy. The study demonstrated that antiretroviral therapy can be useful in preventing transmission of the virus and suggested the use of antiretroviral medications as a public health strategy to reduce transmission. The iPrEx trial, published in the New England Journal of Medicine in 2010, followed 2499 HIV-negative men or transgender women who had sex with men and had evidence of high-
risk behavior in the six months prior to screening for a mean of 1.2 years. The participants received emtricitabine and tenofovir or placebo once daily, in addition to HIV testing, risk-reduction counseling, condoms, and management services for sexually transmitted diseases. The primary outcome was HIV seroconversion. Among patients taking study medication, 36 experienced HIV-1 seroconversion. There were 64 seroconversions among participants taking placebo. These values correspond to a 44% risk reduction. Risk reduction was found to be greatest in those with detectable intracellular tenofovir, indicating that efficacy is correlated to adherence. The Partners PrEP study, published in the New England Journal of Medicine in July 2012, evaluated the use of tenofovir alone versus emtricitabine-tenofovir combination versus placebo for PrEP in discordant couples. Tenofovir had a 67% risk reduction compared to placebo, while emtricitabine-tenofovir had a 75% risk reduction compared to placebo; however, the difference in risk reduction was not statistically significant (p=0.23). Along with medications, patients received other HIV prevention services, including risk reduction counseling, screening and treatment for other sexually transmitted infections, free condoms with training and counseling, and referral for male circumcision. Among a random sample of the 4747 couples studied, tenofovir serum concentrations were detectable in 82% of patients, corresponding to a reduction of relative risk of HIV-1 infection of more than 85%. The authors suggested that the risk reduction associated with antiretroviral therapy for PrEP could be especially valuable for couples wishing to have children in spite of discordant HIV status.

A systematic review published in July 2012 reviewed six randomized controlled trials with a total of 9849 patients to evaluate the efficacy of oral antiretroviral prophylaxis to prevent HIV infection. The trials evaluated daily emtricitabine-tenofovir versus placebo or tenofovir versus placebo. The HIV-negative patients included commercial sex workers, individuals in serodiscordant relationships, injection drug users, men who have sex with men, and sexually active young adults. Four trials compared emtricitabine-tenofovir to placebo and demonstrated a 49% reduction in risk of acquisition of HIV. Two trials evaluated tenofovir alone versus placebo and exhibited a 62% risk reduction. Although the trials evaluating tenofovir alone showed a greater risk reduction, it should be noted that more data is available supporting the combination therapy for PrEP.

While the literature is encouraging regarding the benefit of emtricitabine-tenofovir for PrEP prophylaxis, not all publicity for this indication has been positive. In a Pittsburgh Post-Gazette article, several barriers to the effectiveness of this effort are highlighted. Expense, insurance issues, and behavioral barriers are among the problems identified. The estimated cost of one year of treatment with emtricitabine-tenofovir is $13,900. It is still unclear whether insurance companies will be willing to cover PrEP. Current legislation funds medications for uninsured patients who have HIV, but not those at risk. The manufacturer of Truvada™, Gilead Sciences, Inc., has an assistance program that enrolls approximately 10,000 of the 1 million-plus Americans with HIV. The regimen
itself, though simple compared to many used for HIV-positive patients, may not be feasible in many patients considered to be at-risk. Some of the high-risk populations who may have problems taking the medication consistently include the homeless, mentally ill, intravenous drug users, and alcohol abusers. Adverse effects, such as renal impairment, fat redistribution, and decreased bone mineral density, require monitoring and are important factors to consider. While patients who are HIV-positive may have high motivation to take this medication, patients who are at-risk but currently HIV-negative may not perceive that the benefits of prevention outweigh the risk of adverse effects. It is also recommended that patients taking the medication for PrEP be screened for HIV-1 every 3 months, presenting another possible barrier to use.

The new indication for emtricitabine-tenofovir represents the efforts of many to prevent the spread of HIV. Providing a prophylactic treatment option to be used in conjunction with behavioral modification offers the possibility to decrease transmission among couples with discordant HIV status. Patients who utilize PrEP should be encouraged to adhere to the prescribed regimen and utilize additional preventive methods to achieve higher success rates. In spite of the potential for preventing transmission, behavioral and monetary barriers may hinder availability of this option and limit benefit.

### Table 1: Post-Exposure Prophylaxis Against HIV

<table>
<thead>
<tr>
<th>Type of Exposure</th>
<th>Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonoccupational exposure to blood, genital secretions, or other potentially infected body fluids of a person known to be HIV-positive⁴</td>
<td>Efavirenz + lamivudine or emtricitabine + zidovudine or tenofovir</td>
</tr>
<tr>
<td></td>
<td>Lopinavir/ritonavir + lamivudine or emtricitabine + zidovudine</td>
</tr>
<tr>
<td>Occupational exposure⁵</td>
<td>Zidovudine or tenofovir + lamivudine or emtricitabine</td>
</tr>
<tr>
<td></td>
<td>*If a third medication is desired, lopinavir/ritonavir, atazanavir ± ritonavir, fosamprenavir ± ritonavir, indinavir ± ritonavir, saquinavir ± ritonavir, or efavirenz may be added</td>
</tr>
<tr>
<td>Birth to an HIV+ mother¹⁶</td>
<td>Zidovudine + lamivudine</td>
</tr>
</tbody>
</table>

Regimens listed are preferred regimens. Alternative regimens are available in the guidelines.
### Truvada™ (emtricitabine-tenofovir) Medication Information

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Inhibits HIV-1 reverse transcriptase by competing with the natural substrate and by being incorporated into viral DNA, resulting in chain termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Concentrations not affected by high fat or light meal</td>
</tr>
<tr>
<td></td>
<td>May be given with or without food</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Very little hepatic metabolism</td>
</tr>
<tr>
<td></td>
<td>Potential for CYP mediated interactions with other medicinal products is low</td>
</tr>
<tr>
<td>Excretion</td>
<td>86% emtricitabine in urine, only 13% as metabolites</td>
</tr>
<tr>
<td></td>
<td>70-80% tenofovir in urine, unchanged</td>
</tr>
<tr>
<td>Medication Interactions</td>
<td>Didanosine may be increased by tenofovir, which may result in didanosine-associated adverse reactions and may require discontinuation</td>
</tr>
<tr>
<td></td>
<td>Atazanavir and lopinavir/ritonavir may increase tenofovir and result in tenofovir-associated adverse reactions. Atazanavir without ritonavir should not be given with Truvada™</td>
</tr>
<tr>
<td></td>
<td>Acyclovir, adefovir, dipivoxil, cidofovir, ganciclovir, valacyclovir, and valganciclovir: also eliminated by active tubular secretion in the kidneys; may increase concentrations of emtricitabine, tenofovir, or the coadministered medication</td>
</tr>
<tr>
<td></td>
<td>Medications that decrease renal function may increase concentrations of emtricitabine and/or tenofovir</td>
</tr>
<tr>
<td></td>
<td>Do not administer with other medications containing emtricitabine, tenofovir, lamivudine, or adefovir.</td>
</tr>
</tbody>
</table>

### Boxed Warnings

- Lactic acidosis/severe hepatomegaly with steatosis
- Severe acute exacerbations of hepatitis B
- May only be prescribed for pre-exposure prophylaxis in patients confirmed to be HIV-negative prior to and periodically during the use of the medication

### Warnings/Precautions

- New onset or worsening renal impairment
- Decrease in bone mineral density
- Immune reconstitution syndrome in HIV-positive patients
<table>
<thead>
<tr>
<th><strong>Adverse Reactions</strong></th>
<th>Diarrhea, nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, rash (exfoliative, generalized, macular, maculopapular, pruritic, or vesicular), skin discoloration (hyperpigmentation of the palms and/or soles)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Reactions</strong></td>
<td>Sinusitis, upper respiratory tract infections, nasopharyngitis</td>
</tr>
<tr>
<td>≥ 10%</td>
<td></td>
</tr>
<tr>
<td>≥ 5%</td>
<td></td>
</tr>
<tr>
<td><strong>Increased Laboratory Parameters</strong></td>
<td>Bilirubin, serum glucose, pancreatic amylase, serum lipase, fasting cholesterol, fasting triglycerides, and creatinine kinase may be elevated</td>
</tr>
<tr>
<td><strong>Decreased Laboratory Parameters</strong></td>
<td>Serum glucose</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>HIV testing every 3 months in patients taking the medication for PrEP</td>
</tr>
<tr>
<td></td>
<td>Renal function tests prior to therapy and as clinically indicated while taking the medication</td>
</tr>
<tr>
<td></td>
<td>Development of symptoms of acute viral infection, which could indicate HIV</td>
</tr>
</tbody>
</table>

**References:**


Peginesatide (Omontys®): A New Erythropoiesis Stimulating Agent for Anemia of Chronic Kidney Disease
Thomas Pressley PharmD, Deborah Minor PharmD

Introduction
Chronic kidney disease (CKD) is characterized by progressive damage to the kidneys that reduces blood filtration and subsequently waste and fluid elimination from the body. Common complications and associations of CKD include cardiovascular (CV) disease, anemia, vitamin D deficiency, fluid overload, and bone resorption. CKD is staged by markers of kidney damage or glomerular filtration rate (GFR). Stages range from 1 to 5, with stage 5 CKD being the most severe and categorized as kidney failure or end-stage renal disease (ESRD), ultimately requiring renal transplant.²

It is estimated that more than 20 million people in the United States have CKD.³ Based on a review of NHANES data from 1988-1994 and 2003-2006, the prevalence of CKD increased most in patients aged 60 or older, rising from 18.8 to 24.5%. In 2009, almost 400,000 ESRD patients were using some form of dialysis. Patients on dialysis are estimated to have a 5-year survival rate of 35.8%. The cost of care for treating ESRD patients in the United States is over $40 billion a year.⁴ The magnitude of CKD illustrates the need for early identification of risk factors and timely management to prevent and delay kidney disease and its progression.

Anemia of CKD
Anemia is a common complication of CKD. The prevalence of anemia increases with the degree of renal impairment and is almost universal in patients with stage 5 CKD. The World Health Organization defines anemia as hemoglobin (Hb) levels below 13.0 g/dL for men and 12.0 g/dL for women. Factors contributing to anemia in patients with CKD are erythropoietin (EPO) deficiency, shortened red blood cell (RBC) life span, blood loss, iron deficiency, vitamin deficiencies, inflammation, and hyperuricemia.¹ EPO deficiency is the most common cause of anemia in CKD. RBC production occurs as a result of EPO binding to EPO receptors in bone marrow. A deficiency of EPO can occur with direct damage to renal peritubular cells, which produce and release EPO, and a false sense of adequate oxygen supplies. Low oxygen supply is normally a determinant for EPO production and release, but decreased GFR and oxygen consumption in CKD alters these dynamics. Erythropoiesis-stimulating agents (ESAs) mimic the activities of EPO and are used to stimulate RBC production in patients with anemia.¹,⁵
The first available ESA in the United States was epoetin alfa (Procrit®, Epogen®), followed years later by darbepoetin alfa (Aranesp®) in 2001 and methoxy polyethylene glycol/epoetin beta (Mircera®) in 2007. These ESAs are indicated for treatment of anemia in CKD patients receiving dialysis or not. Treatment should be considered when the patient’s Hb level is less than 10 g/dL. Darbepoetin alfa and epoetin beta offer similar outcomes to epoetin alfa but provide longer durations of action and less frequent dosing. Epoetin beta has the longest duration of action allowing up to once monthly dosing, though it is typically used every 2 weeks to improve efficacy. ESAs can be administered intravenously (IV) or subcutaneously (SC) with similar efficacy. All are structurally analogous to endogenous EPO, which increases the risk of inducing an immune response. Pharmacodynamic activity may be reduced and pure red cell aplasia (PRCA), an uncommon, more severe form of anemia, may result from this immune response. Because PRCA is generally unresponsive to therapy with these ESAs, patients must rely on blood transfusions for anemia treatment.

Peginesatide (Omontys®)
Peginesatide (Omontys®) is the newest ESA. This synthetic, dimeric peptide contains a linked polyethylene glycol (PEG) chain and an amino acid sequence that is different from endogenous EPO. Peginesatide acts as an agonist at EPO receptors to stimulate RBC production. Because of its unique structure it provides the potential advantage of a lower risk of immunogenicity compared with other ESAs. This may reduce the occurrence of PRCA associated with ESA use, or it may provide a treatment for PRCA resulting from ESA use. Peginesatide has predictable and dose-dependent pharmacologic effects. It is approved for once monthly use as an IV or SC injection in patients with CKD currently receiving dialysis. The initial dose for ESA treatment naïve patients is 0.04 mg/kg. The dose should be titrated monthly to attain target Hb values of no greater than 11 g/dL. For patients converting from epoetin alfa or darbepoetin alfa, the prescribing information provides dose conversions (see attached Appendix). If Hb rises more than 1 g/dL in 2 weeks or 2 g/dL in 4 weeks, the dose should be decreased by at least 25%. If Hb exceeds 11 g/dL, the dose should be reduced approximately 25% or interrupted until Hb falls below 11 g/dL and resumed at an approximately 25% lower dose. If Hb has not increased by 1 g/dL after 4 weeks, the dose should be increased by approximately 25%. For those that do not respond adequately over a 12 week escalation period, increasing the dose further is unlikely to improve response and may increase the risks associated with ESA use.

Clinical Evidence
Early trials performed with peginesatide showed moderate increases in Hb levels in anemic, CKD patients as well as healthy volunteers. Elevations in Hb values were maintained for a month following a single dose of peginesatide. Higher doses were more likely to result in greater elevations in Hb values compared to lower doses.
Twice monthly dosing resulted in more elevations of Hb beyond 13 g/dL compared to once monthly dosing. Additionally, at equal doses IV and SC, administration of peginesatide resulted in similar responses.\textsuperscript{12}

Other clinical evidence for peginesatide is available at clinicaltrials.gov. Methodology, results, and some statistical analyses are available, but little to no discussion of the results is provided.

In patients with CKD not receiving dialysis, peginesatide was shown to be non-inferior to darbepoetin alfa with respect to elevating and maintaining Hb levels in a range of 11.0-12.0 g/dL after 36 weeks of treatment. The proportion of patients that required blood transfusions and those achieving Hb goal levels were similar between the groups. However, participants receiving peginesatide reported more serious adverse events than those receiving darbepoetin alfa.\textsuperscript{13}

Non-inferiority was shown between epoetin alfa and peginesatide for anemia treatment in dialysis patients naïve to ESA therapy. Patients were allocated to 1 of 3 treatment groups: 2 different peginesatide doses or epoetin alfa. All doses were adjusted to maintain a Hb level of 11.0-12.0 g/dL. The mean change in Hb from baseline to the 28-week endpoint was not significantly different between treatment groups. Also, the percentage of patients that required blood transfusions and those that achieved target Hb values were similar between groups.\textsuperscript{14}

Two phase II drug conversion trials confirmed peginesatide’s ability to maintain Hb levels (10.0-12.0 g/dL) after switching from another ESA (epoetin alfa or darbepoetin alfa) in dialysis and non-dialysis patients. Previous ESA doses were used to determine an equivalent initial dose of peginesatide. Dose adjustments of peginesatide were allowed to maintain Hb values during the 24-week treatment period. Patients receiving dialysis were slightly more likely to remain within the 10.0-12.0 g/dL Hb range and have less than a ±1 g/dL change compared to non-dialysis patients.\textsuperscript{15} Patients on dialysis who were converted from epoetin alfa to peginesatide were just as likely to remain within the target Hb range whether they received a 1-week washout period or not. However, those that did not receive a wash-out period reported more adverse effects.\textsuperscript{16}

Two phase III trials (EMERALD 1 and EMERALD 2) showed that peginesatide was able to maintain Hb levels in dialysis patients after switching from another ESA. EMERALD 1 showed non-inferiority between epoetin alfa and peginesatide at maintaining Hb values during the 36-week treatment period. There was no difference in the number of patients requiring blood transfusions between the treatment groups (RR 1.21, 95% CI: 0.76-1.92). Patients receiving epoetin alfa were more likely to be maintained within the goal Hb range of 10.0-12.0 g/dL (RR 0.88, 95%CI: 0.79-0.97).\textsuperscript{17} EMERALD 2 yielded non-
inferiority between peginesatide and epoetin alfa or epoetin beta for the same primary endpoint as EMERALD 1. Patients maintained within the goal Hb range and those receiving blood transfusions were not significantly different between groups. Adverse effect profiles were similar between the treatment groups for both trials.\textsuperscript{18}

**Adverse Effects**
Peginesatide has a similar adverse effect profile compared to other ESAs. Commonly reported adverse effects during trials included nausea, vomiting, diarrhea, dyspnea, cough, arteriovenous fistula site complications, hypertension, procedural hypotension, muscle spasms, pyrexia, headache, hyperkalemia, and upper respiratory tract infection. Serious CV adverse effects are a risk of therapy with ESAs, including peginesatide. New onset seizures and changes in seizure frequency occurred in clinical trials.\textsuperscript{10}

**Warning/Precautions**
ESA use with target Hb values >11.0 g/dL increases the risk of serious CV effects and has not been shown to provide additional benefit. In clinical trials comparing higher to lower Hb targets (13.0-14.0 g/dL vs 9.0-11.3 g/dL) with ESA use in CKD, an increased risk of death, myocardial infarction, stroke, congestive heart failure, hemodialysis vascular access thrombosis, and other thrombotic events was observed in the higher target groups.\textsuperscript{10,19} Additionally, a rate of Hb rise greater than 1 g/dL over 2 weeks with ESA treatment may increase CV risks.\textsuperscript{10} No trial has identified a target Hb range/value, ESA dose, or dosing strategy that does not increase CV risks. It is important to use the lowest dose sufficient to maintain appropriate Hb levels and attenuate the need for blood transfusions.\textsuperscript{10,19}

In trials including non-dialysis patients with anemia due to CKD, more patients treated with peginesatide (22%) experienced a CV event compared to darbepoetin alfa (17%).\textsuperscript{10} As a result, peginesatide is approved for use only in patients receiving dialysis\textsuperscript{20,21}.

Unlike epoetin alfa and darbepoetin alfa, peginesatide is not approved for patients with cancer whose anemia is not caused by CKD. Use in this population may result in an increased risk of mortality and/or tumor progression or recurrence.\textsuperscript{10}

All ESAs, including peginesatide, are contraindicated in patients with uncontrolled hypertension. Patients with hypertension must have their blood pressure controlled prior to starting peginesatide.\textsuperscript{10}

Immunogenicity is potentially less likely with peginesatide compared to other ESAs. However, detectable anti-peginesatide antibodies were present in 1.2% of clinical trial participants, with a higher incidence associated with SC administration (1.9%) compared to IV (0.7%). About half of those that were antibody-positive required
increased peginesatide doses or blood transfusions to maintain adequate Hb values.\textsuperscript{10} No cases of PRCA were observed in those receiving peginesatide during trials.\textsuperscript{10}

**Therapeutic Monitoring**
Hb levels should be obtained every 2 weeks following the initiation of peginesatide and after each dosage adjustment until stable and monthly thereafter. Serum ferritin and transferrin saturation should be assessed prior to initiation and periodically during treatment with peginesatide. Iron supplements should be used when serum ferritin falls below 100 mcg/L or serum transferrin saturation is below 20\%.\textsuperscript{1,10}

**Conclusion**
Peginesatide has shown to be an effective ESA with a similar adverse effect profile to other ESAs when used in CKD patients on dialysis. One advantage of peginesatide compared to other ESAs is the once monthly administration. Although epoetin beta may be dosed once monthly, it often requires twice monthly use. Although not yet proven, utilizing once monthly dosing with peginesatide may potentially reduce CV risks by decreasing overall ESA exposure, as high ESA doses may be associated with increased risks.\textsuperscript{10,19} Another potential advantage of peginesatide is its structural dissimilarity to endogenous EPO and other ESAs. This may result in a lack of cross-reactivity with other ESAs in patients with anti-ESA antibodies or PRCA, providing an effective alternate therapy. A likely disadvantage to peginesatide is that most CKD patients start ESA therapy before beginning dialysis. Since peginesatide is not approved for non-dialysis patients, therapy would then have to be modified after ESA initiation (Appendix). Without overwhelming benefits over other ESAs, future clinical experience, post-marketing surveillance, and cost will likely determine peginesatide’s role in anemia management.

<table>
<thead>
<tr>
<th>Appendix: Dose Conversion from ESAs to Peginesatide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous Total Weekly Epoetin Dose (U/week)</strong></td>
</tr>
<tr>
<td>Less than 2,500</td>
</tr>
<tr>
<td>2,500 to &lt; 4,300</td>
</tr>
<tr>
<td>4,300 to &lt; 6,500</td>
</tr>
<tr>
<td>6,500 to &lt; 8,900</td>
</tr>
<tr>
<td>8,900 to &lt; 13,000</td>
</tr>
<tr>
<td>13,000 to &lt; 19,000</td>
</tr>
<tr>
<td>19,000 to &lt; 33,000</td>
</tr>
<tr>
<td>33,000 to &lt; 68,000</td>
</tr>
<tr>
<td>≥ 68,000</td>
</tr>
</tbody>
</table>

**return to top**
References

14. “Safety and efficacy of peginesatide injection for the maintenance of anemia in chronic renal failure participants who are on hemodialysis or do not require

Ondansetron 32 mg Withdrawn from U.S. Market

One December 4, 2012, the U.S. Food and Drug Administration (FDA) notified health care professionals that the 32 mg, single intravenous (IV) dose of the anti-nausea drug Zofran (ondansetron hydrochloride) will no longer be marketed because of the potential for serious cardiac risks. The approved labeling is being revised to delete this dose in the package inserts. The FDA is now working with the manufacturers of all 32 mg dose ondansetron injectable products (brand and generic) to voluntarily recall them from the U.S. market.

On June 29, 2012 the FDA released a communication stating that the 32 mg, single IV dose should be avoided due to the risk of a specific type of irregular heart rhythm called QT interval prolongation. QT prolongation can lead to Torsades de Pointes, an abnormal, potentially fatal heart rhythm.

The 32 mg dose had been used as a single dose option when given IV 30 minutes prior to emetogenic chemotherapy. It did not have an indication for prevention of post-operative nausea and vomiting (PONV). The three dose regimen was not affected, nor was the use for PONV. The FDA continues to recommend the intravenous regimen of
0.15 mg/kg administered (up to a maximum of 16 mg per dose) every 4 hours for three doses to prevent chemotherapy-induced nausea and vomiting. In addition, oral dosing of ondansetron remains effective for the prevention of chemotherapy-induced nausea and vomiting. At this time, there is not enough information available for FDA to recommend an alternative single IV dose regimen.
<table>
<thead>
<tr>
<th>IWGDF-IDSA classification</th>
<th>Presentation</th>
<th>Suspected Organism(s) to Cover</th>
<th>Route</th>
<th>Suggested Empiric Medication(s) for Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td>No other factors</td>
<td>Aerobic GPC if no recent antibiotic exposure</td>
<td>Oral; may consider topical if open wound with minimal cellulitis</td>
<td>Dicloxacillin, clindamycin, or cephalexin</td>
</tr>
<tr>
<td></td>
<td>Antibiotic exposure within past 1 month or chronic infection</td>
<td>GPC + gram negative bacilli +/- obligate anaerobes</td>
<td>Oral</td>
<td>Levofloxacin (ciprofloxacin also appropriate at UMMC) or amoxicillin-clavulanate</td>
</tr>
<tr>
<td></td>
<td>Local MRSA &gt;50% or prior history of MRSA infection/colonization within past 1 year</td>
<td>Aerobic GPC + MRSA</td>
<td>Oral</td>
<td>Doxycycline or TMP/SMZ</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>No other factors</td>
<td>Aerobic GPC if no recent antibiotic exposure</td>
<td>Oral or parenteral</td>
<td>Amoxicillin-clavulanate, ampicillin-sulbactam, levofloxacin, ciprofloxacin, or moxifloxacin</td>
</tr>
<tr>
<td></td>
<td>Antibiotic exposure within past 1 month or chronic infection</td>
<td>GPC +/- gram negative bacilli +/- obligate anaerobes</td>
<td>Oral or parenteral, but parenteral may be preferred</td>
<td>Levofloxacin +/- clindamycin, ciprofloxacin + clindamycin, moxifloxacin, cefoxitin, ceftriaxone, ampicillin-sulbactam, ertapenem, tigecycline, or imipenem-cilastatin</td>
</tr>
<tr>
<td></td>
<td>Local MRSA &gt;30% or prior history of MRSA infection/colonization within past 1 year</td>
<td>Aerobic GPC + MRSA</td>
<td>Oral or parenteral</td>
<td>Vancomycin, linezolid, or daptomycin combined with broader spectrum agent (e.g. fluoroquinolone, beta-lactam, or carbapenem as recommended above)</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>No other factors</td>
<td>Broad spectrum: GPC + gram negative bacilli + obligate anaerobes +/- MRSA</td>
<td>Parenteral until systemically stable with culture results</td>
<td>Same agents as used for moderate infection</td>
</tr>
</tbody>
</table>

GPC=gram positive cocci; TMP/SMZ= trimethoprim/sulfamethoxazole