

# PHARMACY NEWSLETTER

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## Darbepoetin (Aranesp®) Update

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Recently darbepoetin (Aranesp®), an erythropoietic agent, has received some negative press. On January 27<sup>th</sup> 2007, a letter was issued by Amgen to health care professionals regarding the results of a study that evaluated the use of darbepoetin (Aranesp®) in patients not receiving or expected to receive chemotherapy or radiotherapy. This study was a phase III, multi-center, randomized, placebo-controlled trial which showed that Aranesp® was ineffective at reducing the number of blood transfusions.<sup>1</sup> In addition, an increased risk of death was demonstrated in patients randomized to receive Aranesp® as opposed to placebo.<sup>1</sup>

On March 9<sup>th</sup>, the Food and Drug Administration issued a Public Health Advisory warning of the risks associated with erythropoietic agents. Three trials, in addition to the previously described, demonstrated a trend toward serious and life-threatening side effects. The first trial demonstrated that patients with chronic renal failure had an increased number of deaths and of non-fatal heart attacks, strokes, heart failure, and blood clots when erythropoietic stimulating agents (ESAs) were adjusted to maintain higher red blood cell levels (hemoglobin more than 12 grams per deciliter).<sup>2</sup> In another trial, patients with head and neck cancer receiving radiation therapy had faster tumor growth when ESAs were adjusted to produce target hemoglobin levels greater than 12 grams per deciliter.<sup>2</sup> A final study revealed that patients scheduled for orthopedic surgery, who received ESAs to reduce blood transfusions during and after surgery, had more blood clots than those not given an ESA.<sup>2</sup>

Currently, Aranesp® is only approved for use in the treatment of anemia associated with chronic renal failure, including patients on dialysis, and for the treatment of chemotherapy induced anemia.<sup>3</sup> Aranesp® is an erythropoi-

esis-stimulating protein with a unique amino acid sequence, longer half-life and greater biologic activity than recombinant human erythropoietin. Various initial dosing strategies with different frequencies and flat doses or weight-based doses have been used for erythropoietic agents. However, the package insert recommends a starting dose of 2.25 micrograms per kilogram administered as a subcutaneous injection or 500 milligrams administered once every three weeks for chemotherapy induced anemia.<sup>3</sup> The dose should be titrated to maintain the lowest hemoglobin level that avoids the need for a transfusion and does not exceed 12 grams per deciliter.<sup>3</sup>

Sufficient time should be allowed before an evaluation of response is made. The National Comprehensive Cancer Network (NCCN) guidelines recommend six weeks for darbepoetin and four weeks for epoetin alfa. The reason for this wait is due to the time required for red blood cell formation, a process also referred to as erythropoiesis. Erythropoietin is a glycoprotein hormone with a molecular weight of 34 kDa and is produced in response to reduced oxygen levels, otherwise known as hypoxia.<sup>4</sup> This hormone stimulates erythroid precursor cells in the bone marrow to proliferate and mature, resulting in a release of erythrocytes. Once hypoxia ceases, erythropoietin production decreases.

In order to achieve the most optimal response, iron supplementation prior to treatment with an ESA is recommended. Intravenous iron dextran followed by iron sucrose is the primary supplement administered at our outpatient chemotherapy clinic. Studies have demonstrated that intravenous iron results in a greater hematopoietic response compared to oral iron and no iron.<sup>5</sup> In addition, oral iron therapy produces a number of gastrointestinal side effects such as

constipation, stomach cramping, nausea, and vomiting.<sup>6</sup> Non-adherence and a sub-optimal hemoglobin response may result as a consequence of these side-effects.

The Centers for Medicare and Medicaid Services have recently changed their guidelines in response to the new clinical findings. Treatment with darbepoetin for anemia due to malignancy will no longer be covered effective March 5<sup>th</sup>, 2007. Patients with chemotherapy induced anemia will still be covered provided that chemotherapy was received within the previous three months and pre-treatment hematocrit level is 33 percent or less. Once treatment is initiated, Medicare will continue coverage as long as the target hematocrit does not exceed 39 percent. The criteria differ depending on the indication and the particular ESA used. For updated information on coverage for renal failure, myelodysplastic syndrome and other chronic conditions, please visit [www.cms.hhs.gov](http://www.cms.hhs.gov).

On May 14<sup>th</sup>, 2007 a coverage decision memorandum for the use of ESAs in cancer and related neoplastic conditions was proposed. New stipulations were recommended on the types of candidates for therapy, length of treatment, and qualifications. In summary, patients with specified cancers would be eligible for treatment if their hemoglobin level was less than nine grams per deciliter in patients without known cardiovascular disease and less than 10 grams per deciliter in patients with documented symptomatic ischemic disease. The maximum coverage period suggested is 12 weeks per year and the maximum four week treatment dose for darbepoetin in 630 micrograms. No clarification is made as to patients who continue to have anemia. Currently, CMS is accepting response from the public regarding this proposal. Amgen has already released their statement which can be viewed on their website ([www.amgen.com](http://www.amgen.com)).

Recently, updated safety information has been added to the package inserts of darbepoetin and erythropoietin. The new label warns of the increased risk of mortality, serious cardiovascular events, thromboembolic events, and tumor progressions when used in off-label dose regimens. Physicians are advised to monitor hemoglobin levels to ensure they do not exceed 12 grams per deciliter. It is also noted that ESAs have not been shown to improve the outcomes of chemotherapy treatment. Patients should be made aware of these risks and urged to speak with their health care providers with any questions.

In conclusion, ESAs are recommended to decrease the chances of blood transfusion. Close monitoring, and careful dose adjustment can be helpful in preventing hemoglobin levels greater than 12 grams per deciliter. In the mean time, it may be prudent to follow package insert recommendations as we wait for more information to become available. Visit [www.cms.hhs.gov](http://www.cms.hhs.gov) for more details.

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# Rosiglitazone

## What is all the buzz about?

zation or death from cardiovascular causes.

By Quynh-Anh Nguyen, Pharm.D.

Rosiglitazone, also known by its brand name Avandia® (GlaxoSmithKlein), was FDA approved in 1999 for the treatment of type 2 diabetes. Since then, there have been case reports and pooled analysis of controlled clinical trials showing a significant increase in the risk of heart attack and heart-related deaths related to its use. This article will provide a review of the latest medical literature as well as recommendations published regarding this topic.

In May 2007, Nissen and Wolski<sup>1</sup> published a controversial article titled “Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes” in the *New England Journal of Medicine*. This article was a meta-analysis of 42 published and unpublished trials comparing rosiglitazone with placebo or other diabetes medications. Results from this analysis showed the odds ratio for myocardial infarction was 1.43 (95% CI, 1.03 to 1.98; P=0.06) and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06) in the rosiglitazone group as compared with the control group. The authors concluded that patients treated with rosiglitazone, compared with placebo or with other antidiabetic regimens, had an increase in the risk of myocardial infarction and risk of death from cardiovascular causes that was of borderline significance.

The “borderline” significant findings from this meta-analysis caused a stir in the medical community as well as concerns of patient safety. The meta-analysis had a number of strengths such as the inclusion of unpublished data and the use of major cardiac events as the primary outcome. However, it was the weaknesses of the study that left clinicians uncertain as to whether rosiglitazone should still be considered for the treatment of type 2 diabetes. This meta-analysis included findings based on limited access to trial results from publicly available sources, not on patient level source data. Also, the majority of the studies included were of short duration (24-52 weeks) and the results were based a relatively small number of events.

In response to Nissen’s and Wolski’s meta-analysis, Home and colleagues<sup>2</sup> published an unplanned interim report on the results from the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes, or RECORD study. This study is a 6-year, randomized, multi-centered, open-label, non-inferiority trial involving 4447 patients with type 2 diabetes who had inadequate glycemic control while receiving metformin or sulfonylurea. Half of patients were assigned to receive add-on rosiglitazone and the other half were assigned to receive a combination of metformin plus sulfonylurea (control group). The primary end point was hospitali-

zation or death from cardiovascular causes. Because the mean follow-up of this study was only 3.75 years, the interim analysis had limited statistical power to detect treatment differences. The authors concluded that the interim findings from this ongoing study were inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes. There was no evidence of any increase in death from either cardiovascular causes or all causes. The rosiglitazone group, however, had more deaths associated with heart failure than in the control group (hazard ratio, 2.15; 95% CI, 1.30 to 3.57).

In May 2007, the FDA published *New Safety Information on Diabetes Drug Rosiglitazone*<sup>3,4</sup> on its website to help guide clinicians as well as patients taking rosiglitazone.

The FDA has not confirmed the clinical significances of the reported increased risk of ischemic cardiovascular events in the context of other studies. However, myocardial ischemic events are currently described in the WARNINGS section of the rosiglitazone label as well as warnings regarding the risk of edema and heart failure.

Discontinuation of rosiglitazone therapy is not advised at this time until the FDA has reached a conclusion about whether new published data warrant any regulatory action. The FDA is conducting its own analysis and considering the results along with other diabetes drugs to determine the risk of cardiac events. There will be an advisory committee meeting open to the public scheduled for July 30, 2007 to discuss the cardiovascular ischemic and thrombotic risk of thiazolidinediones, focusing on rosiglitazone.

At this time there are no data published linking pioglitazone (Actos®, Takeda Chemical Industries) with an increased risk of cardiovascular ischemic events.

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## Varicella-Zoster Vaccine for the Prevention of Herpes Zoster

Kimberlin D. W., Whitely R. J.  
Varicella-zoster vaccine for the prevention of herpes zoster  
*N Eng. J. Med.* 2007;356:1338-1343

Abstract by Irene Yang, RPh

## BACKGROUND:

Varicella-Zoster Virus (VZV) is a herpes virus that causes two distinct clinical syndromes: the primary infection, varicella (chickenpox) and a secondary reactivation of the dormant virus called herpes zoster (shingles). Prior to the universal varicella vaccination program of 1995 in the United States, 95.5% (age 20 to 29 years), 98.9% (age 30 to 39 years), and 99.6% (age greater than 40 years) of the population have shown previous VZV infection. This vaccination program has substantially reduced varicella-related morbidity and mortality. However, outbreaks of varicella continue to occur and studies suggest there is waning immunity over time. Therefore, as of June, 2006, the Advisory Committee on Immunization recommended a second dose of varicella vaccine for all children and for all adolescents and adults who have previously received one dose to cover for primary vaccine failure and waning vaccine-induced immunity. Currently, there are no long-term data available to predict the duration of protection the varicella vaccine will provide.

Herpes zoster (shingles) is the second clinical syndrome caused by reactivation of the dormant varicella zoster virus (VZV). Those greater than 60 years of age are 8 to 10 times more likely to develop shingles than younger people with complications ranging from myelitis, cranial nerve palsies, encephalitis, to the most debilitating complication, postherpetic neuralgia pain, which may persist for years. Anti-viral therapy decreases severity or duration of pain, but does not prevent the development of postherpetic neuralgia. And other treatments such as the use of opioids, tricyclic antidepressants, and gabapentin are limited in their effectiveness in reducing the symptoms of herpes zoster (shingles).

The original VZV vaccine for children is a live attenuated vaccine licensed to prevent primary varicella infection, chickenpox. However, studies have shown that it requires a higher titer of live attenuated virus to induce a significant and durable increase in cell-mediated immunity in older adults. Consequently, a new VZV vaccine (Zostavax) was developed especially to target herpes zoster. It is not indicated for treatment of herpes zoster or postherpetic neuralgia.

So the following questions arise: Who is a candidate for varicella zoster vaccine (Zostavax)? Will the varicella vaccine program protect the population as it ages? Is zoster immunization cost effective? Should the zoster vaccine be used in immunocompromised people?

### **CLINICAL EVIDENCE:**

The Shingles Prevention Study Group provided evidence in a large efficacy study of high titer, live attenuated zoster vaccine. 38,546 subjects 60 years of age or older were enrolled and followed for mean period of 3 years. The subjects were stratified according to age to group of 60 to 69 years old, or  $\geq 70$  years old. At the completion of study, the incidence of herpes zoster was 51% lower in immunized subjects compared to those who received placebo (5.4 cases per 1000 person-years vs. 1.1 cases per 1000 person-years,  $P < 0.001$ ). The incidence of postherpetic neuralgia was 67% lower in immunized subjects compared to those who received placebo (0.5 case per 1000 person-years vs. 1.4 case per 1000 person-years,  $P < 0.001$ ). The duration of pain was shorter in the immunized group compared to the placebo group (21 days vs. 24 days,  $P = 0.03$ ). The vaccine was more efficacious in preventing herpes zoster among persons age of 60 to 69 years old compared to persons greater than 70. However, it provide more protection for postherpetic neuralgia among persons of 70 years or older than those of 60 to 69 years old.

### **GUIDELINES:**

In October, 2006, the Advisory Committee in Immunization Practices (ACIP) voted to recommend a single dose of zoster vaccine for adults 60 years of age or older, whether or not they have had a episode of herpes zoster previously. Person with chronic medical conditions may be vaccinated unless contraindicated. Zoster vaccine is contraindicated to people with a history of anaphylactic or anaphylactoid reaction to gelatin, neomycin, or any other vaccine component. The vaccine should not to be given to people with history of primary or acquired immunodeficiency conditions or those receiving immunosuppressive therapy, including corticosteroids. It is also contraindicated to people with active untreated tuberculosis and pregnant women.

### **RECOMMENDATIONS:**

The vaccine is recommended for all immunocompetent persons over age of 60 years old, provided there are no contraindications. The vaccine is not recommended routinely for people under age of 60 years old because of the lack of efficacy data and cost-effectiveness information for this population.

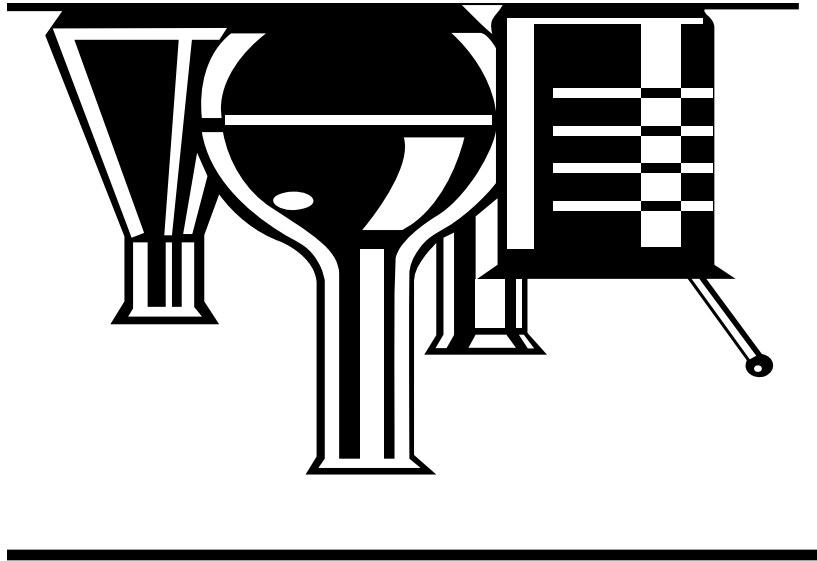
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The Pharmacy Department would like to  
Congratulate  
**Quynh-Anh Nguyen**  
and  
**Christina Sadler**  
for completing our residency program.

We would also like to welcome  
on July 2<sup>nd</sup>  
our two residents for 2007-2008:  
**Tracy Chen and Yvonne Hewett.**

We would also like to welcome our new  
Clinical Coordinator/Residency Director,  
**Cathie Jamieson.**

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Gary Nicholas, Editor

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