

-----Rx News-----

***Erythropoietin Stimulating Agents and Chemotherapy Induced Anemia – Emerging Safety Concerns***

Erythropoietin Stimulating Agents (ESA's) are approved to treat anemia in cancer patients receiving chemotherapy and patients with chronic renal failure.<sup>1,2</sup> Examples of ESA's include Epogen®, Procrit® and Aranesp®. Recent safety concerns have emerged surrounding the use of these agents off-label and when providers try to maintain hemoglobin (Hb) levels above the recommended 12g/dL.<sup>3</sup>

**Safety Issues with ESA's - History**

Safety concerns with ESA's began to emerge several years ago. In 2003, a randomized, double-blind, placebo controlled trial showed that patients with advanced head and neck cancer receiving radiation therapy had a higher risk of tumor progression if treated with an ESA to achieve a target goal of Hb>14g/dL in women and >15g/dL in men.<sup>4</sup> In 2005, the BEST trial showed an associated decrease in overall survival when maintenance therapy with an ESA was used to achieve a Hb between 12-14 g/dL in metastatic breast cancer patients undergoing first line chemotherapy.<sup>5</sup> More recent studies and analyses have found a higher incidence of serious adverse effects and or death with the use of ESA's in patients not receiving chemotherapy or when given in unapproved dosage regimens.<sup>6,7</sup>

**Summary of Safety Concerns<sup>1-11</sup>**

Safety concerns associated with off-label ESA use include the following:

- **Thromboembolic Complications**
  - A higher incidence of deep venous thrombosis was documented in patients receiving epoetin alfa who were not receiving prophylactic coagulation.<sup>1, 2, 7, 8, 9</sup>
- **Tumor Progression**
  - A higher incidence of tumor progression was reported in patients with primary breast cancer receiving chemotherapy prior to surgery who were taking an ESA.<sup>7</sup>
  - A higher rate of tumor progression was reported in patients with cervical cancer treated with chemotherapy receiving an ESA.<sup>7</sup>
  - A higher incidence of disease progression was reported in small cell lung cancer patients not receiving chemotherapy but taking an ESA to maintain an Hb level of 12-14 g/dL.<sup>10</sup>
  - A higher incidence of locoregional tumor progression was reported in patients with advanced head and neck cancer receiving radiation therapy and taking an ESA to maintain an Hb level of 14-15.5 g/dL.<sup>11</sup>
- **Increased Risk of Death**
  - ESA's increased mortality in breast cancer patients receiving chemotherapy and cervical cancer patients treated with chemotherapy and radiation.<sup>7</sup>
  - ESA's increased the risk of death when administered to a target hemoglobin of 12 g/dL in patients with active malignant disease receiving neither chemotherapy nor radiation therapy.<sup>1-3,10, 11</sup>
  - ESA's increased overall mortality in patients with cancer related anemia not receiving chemotherapy using an ESA to achieve a target Hb level of 12g/dL. In addition, the need for RBC transfusions in these patients was not decreased.<sup>3</sup>

**Efficacy**

ESA's are effective in increasing Hb levels in patients with anemia. However, ESAs have not been shown to improve or relieve the symptoms of anemia nor to improve quality of life in patients with cancer.<sup>1-3, 6-10</sup>

**Food and Drug Administration Actions**

On January 3, 2008 the FDA released a communication as part of the ongoing safety review of ESAs.<sup>7</sup> New data shows an increase in mortality and shorter time to tumor progression in cancer patients receiving an ESA. The FDA plans to hold another public advisory committee meeting in early 2008 to re-evaluate the risk and benefit balance of ESAs for the treatment of patients with chemotherapy-induced anemia.

On November 8, 2007, the FDA strengthened existing black box warnings for ESA products and approved additional language changes for the labeling of these drugs. These changes include a statement that symptoms of anemia, fatigue and quality of life have not been shown by data from controlled trials to improve in patients with cancer who are treated with an ESA.<sup>6</sup>

### **Centers for Medicare Services Response**

In July 2007, the Centers for Medicare and Medicaid Services (CMS) revised their national coverage guidelines to limit reimbursement of ESAs. The more restrictive guidelines limit coverage for ESAs to cancer patients receiving chemotherapy whose Hb level is <10 g/dL prior to initiation and during maintenance of ESA treatment.<sup>12</sup>

### **RegenceRx Response**

RegenceRx continues to monitor the latest ESA safety and efficacy reports. Currently, Regence requires prior authorization for retail ESA prescriptions. Prior authorization will extend to medical claims beginning March 2008. The medication policies for these agents have been recently updated to reflect:

- Clarification of the definitions of anemia related to kidney failure and cancer.
- Recent Medicare proposals suggesting that anemias related to chemotherapy will be covered; however, anemias related to cancer and not associated with chemotherapy will not be covered.
- A summary of FDA safety data.

*For more information, please see our medication policies and coverage criteria at:*  
[www.regencerox.com/learn/policy/index.html](http://www.regencerox.com/learn/policy/index.html)

### **Avandia® and Cardiovascular Risk – Latest Developments**

#### **FDA News - Avandia Labeling Update**

On November 19, 2007 the FDA updated Avandia labeling to include information on the risk of myocardial ischemia in some patients.<sup>13</sup> The new black box label recommends against co-administration of Avandia and insulin. In addition, the new labeling advises to avoid administration of Avandia in patients with heart disease currently taking nitrates.

*For more information on the FDA's labeling update, please see:*  
<http://www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm>

#### **Recent Glitazone and Cardiovascular Safety Reviews Published in JAMA**

Over the last few months, several new analyses on the glitazones have been published in JAMA.<sup>14,15,16</sup> The analyses were conducted using a variety of methods including: review of individual patient adverse event data, meta-analysis of randomized controlled trials and a case-control analysis of a retrospective cohort study.

Two of the analyses concluded that Avandia (rosiglitazone) was associated with an increased risk of acute myocardial infarction and congestive heart failure.<sup>15,16</sup> One found evidence of a favorable effect of Actos® (pioglitazone) on ischemic events, distinct from its effects on blood glucose control.<sup>14</sup> However, limitations in all of the analyses were recognized by the authors.

### **RegenceRx Response**

Although these analyses add more information to the continuing clinical debate on the thiazolidinedione (TZD) place in therapy, data continues to emerge. This controversy continues to raise awareness about the need to consider the risks and benefits in selecting diabetes medications for patients. RegenceRx will continue to monitor the emerging clinical data and will work to keep our providers informed of new developments as they arise.

The FDA has advised patients taking Avandia to be informed of the possible increased risk of myocardial ischemia. In addition, patients should be screened to determine if they currently take insulin or nitrates and informed that taking Avandia with either of these products may increase the risk of myocardial ischemia.<sup>17</sup> Your patients taking Avandia may have contacted you with questions about this medication. In response to patient questions, the FDA has placed several patient resources on its website.

*For a patient information sheet on Avandia, please see:*

<http://www.fda.gov/cder/drug/InfoSheets/patient/rosiglitazonePIS.htm>

*For the latest patient information on Avandia and cardiovascular risks, go to:*

<http://www.fda.gov/consumer/updates/avandia052507.html>

***FDA Alerts – Safety Concerns with the Smoking Cessation Agent Chantix®***

The FDA has received reports of suicidal thoughts and aggressive and erratic behavior in patients who have taken Chantix, a smoking cessation product. The FDA is working to complete an analysis of materials submitted by the manufacturer of Chantix in an effort to determine whether further action is needed. As soon as this analysis is completed, FDA will communicate its conclusions and recommendations to the public. The FDA urges both healthcare professionals and patients to report side effects from the use of Chantix to the FDA's MedWatch Adverse Event Reporting program.<sup>18</sup>

RegenceRx reviewed Chantix in December 2006 and concluded that there was no useful evidence showing this agent offered improved efficacy or safety over existing formulary agents. Chantix is currently non-preferred /non-formulary on the RegenceRx formulary and is available at that copay only to members with a smoking cessation benefit. It should be noted that drug therapy to assist with smoking cessation is most effective where combined with other non-drug therapies, such as counseling and support, to quit smoking.

*To read the complete RegenceRx Chantix Therapeutic Class Review Summary<sup>SM</sup>, please see:*

<http://www.regencerox.com/docs/physicianRx/chantix1206.pdf>

*To read this and other recent FDA Alerts, please see:*

<http://www.fda.gov/cder>

-----**Evidence Based Medicine**-----

***Quick Review: Risks versus Odds Ratios***<sup>19,20</sup>

Analyses on emerging safety issues of medications often include a statistical tool called the “odds ratio.” A common question for many clinicians is how to translate reported odds ratios into an estimation of risk. Using a reported odds ratio, how does one evaluate the benefits versus risk of a particular medication for a patient?

Odds ratios tell us how much more likely it is that someone exposed to the factor under study will develop the outcome as compared to someone who is not exposed. Where the odds ratio = 1, the condition or event under study is equally likely in both groups. When the odds ratio is greater than 1, the likelihood of seeing the condition or event is greater in the first group than the second group. In many situations, such as when events are rare, one can interpret odds ratios by pretending that they are relative risks.

Another factor to consider when weighing reported risks versus benefits of a particular medication is the type of trial or analysis being reviewed. Case control studies and meta-analyses often report results as odds ratios because it is not possible to calculate relative risk. However, in these types of studies, it should be remembered that odds ratios greater than 1 do not show causation; only an association.

When evaluating a clinical trial for application to your practice, always ask yourself if the results have been reported in clinically significant format. Where adverse event data is reported as an odds ratio in a study other than a randomized controlled trial, be cautious in assuming causation between the factor and the event.<sup>19,20</sup>

*For more information on RegenceRx's commitment to Evidence Based Medicine, please see:*

[http://www.delfini.org/page\\_Project\\_Regence.htm](http://www.delfini.org/page_Project_Regence.htm)

-----**RegenceRx P&T Decisions**-----

**The following medications were added to the Preferred Medication List:**

**Radiogardase™** a new oral therapy approved for the treatment of known or suspected internal contamination with cesium-137 or thallium.

**The following medications will remain Non-Preferred/Non-Formulary at this time:**

**Altabax®** an antibacterial ointment indicated for the topical treatment of impetigo.

**AzaSite®** a macrolide antibiotic indicated for the topical treatment of bacterial conjunctivitis.

**Elestrin®** an estradiol gel formulation indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause.

**Lybrel®** an oral contraceptive indicated for the prevention of pregnancy.

**Lyrica®** an anticonvulsant medication re-reviewed for its added indication for fibromyalgia.

**Neupro®** a dopamine agonist indicated for the management of early Parkinson’s disease.

**Pylera®** a combination product used with omeprazole for treatment of patients with Helicobacter pylori (H. Pylori) infection and duodenal ulcer disease to eradicate H. Pylori.

**Vyvanse®** an oral therapy indicated for the treatment of attention deficit/hyperactivity disorder (ADHD).

**Xyzal®** an antihistamine approved for the treatment of perennial allergic rhinitis (PAR), season allergic rhinitis (SAR), and chronic idiopathic urticaria (CIU) in patients 6 years of age and older.

**H. Pylori Formulary Options**

The RegenceRx formulary includes the option of prescribing a combination of generic products or the brands Helidac® or Prevpac® for the treatment H. Pylori. Current therapy guidelines for H. Pylori treatment indicate:

- The highest eradication rates are achieved with the following regimens:<sup>21</sup>
  - a PPI, clarithromycin, and either amoxicillin or metronidazole for 2 weeks
  - ranitidine, bismuth citrate, clarithromycin, and either amoxicillin, metronidazole, or tetracycline for 2 weeks
  - a PPI, bismuth, metronidazole, and tetracycline for 1 to 2 weeks.
- A one to two weeks course of H. pylori eradication therapy is an effective treatment for H. pylori positive peptic ulcer disease.<sup>22</sup>
- H. pylori eradication therapy has a small benefit over ulcer-healing drug and a larger benefit over no treatment or placebo in the healing of duodenal ulcer.<sup>22</sup>

The cost of H. Pylori treatment differs greatly depending on therapy chosen. As shown in the table below, the pill burden remains similar regardless of whether the individual generic ingredients versus the brand combinations are prescribed. However, the difference in cost between the generics and brands is significant.

<b>Sample Therapy</b>	<b>Length of Treatment</b>	<b>Pill Burden</b>	<b>~ Cost*</b>
<b>Triple Rx</b> amoxicillin 500mg 2 caps BID <i>plus</i> clarithromycin 500mg 1 BID <i>plus</i> omeprazole 20mg BID x 14 days	14 days	8/day 112/course	\$34.64
<b>Quadruple Rx</b> Metronidazole 250mg QID <i>plus</i> Tetracycline 500mg QID <i>plus</i> Bismuth subsalicylate 262mg 2 tabs QID <i>plus</i> Famotidine 20 mg PO bid	14 days	18/day 252/course	\$16.55
<b>Helidac <i>plus</i></b> famotidine 20mg	14 days	18/day 252/course	\$296.44
<b>Prevpac</b>	14 days	8/day	\$355.49

		112/course	
<b>Pylera plus</b> omeprazole 20mg	10 days	14/day 140/course	\$280.61

\* Cost estimate based on AWP (average wholesale price) listed in First Data Bank or MAC (maximum allowable cost) as of September 25, 2007 for 1 package unit.

**For Preferred Medication List/Formulary alternatives for non-preferred products, please see:**

<http://www.regencerx.com/learn/covered/therapeutic/index.html>

**For our most recently released Therapeutic Class Summaries<sup>SM</sup>, please see:**

<http://www.regencerx.com/learn/physicianRx/index.html>

-----**Medication Policy Updates**-----

**The following medications have new or updated Medication Policies:**

**Remicade® (infliximab)** - The medication policy for Remicade has been clarified for initial coverage and reauthorization for Crohn's disease and ulcerative colitis. Remicade is covered for fistulizing or steroid-resistant disease, or when disease modifying agents are inadequate.

**For more information, please see our medication policies and coverage criteria at:**

[www.regencerx.com/learn/policy/index.html](http://www.regencerx.com/learn/policy/index.html)

**A full list of the most recent prior authorization changes can be found at:**

<http://www.regencerx.com/docs/summaryOfRecentPriorAuthChanges.pdf>

-----**Generic Medications**-----

**New Generic Medications at the Pharmacy or Coming Soon!<sup>23</sup>**

Consumers stand to save billions of dollars in prescription drug costs in the next few years as a wave of brand name medications come off of patent. The chart below includes a list of generic medications already at the pharmacy or coming soon to a pharmacy near you!

<b><u>Asthma/Allergy</u></b> cetirizine (Zyrtec®) – January 2008 Zyrtec OTC® – launch January 2008	<b><u>Mental Health and Sleep</u></b> methylphenidate ER (Concerta®) - early 2008 paroxetine extended release (Paxil CR®) –late 2008 risperdone (Risperdal®) – early 2008 zaleplon (Sonata®) – mid 2008
<b><u>Osteoporosis</u></b> alendronate (Fosamax®) – February 2008	<b><u>Other</u></b> granisetron (Kytril®)– on shelves lamotrigine (Lamictal®) – mid 2008 sumatriptan (Imitrex®) – late 2008 topiramate (Topamax®) – mid 2008

**Thank you for helping to keep prescription benefits affordable for our members!**

-----**References**-----

1. Aranesp® (darbepoetin alpha) Product Information. Amgen Inc. Thousand Oaks, CA, March 2007.
2. Epogen® (epoetin alpha) Product Information. Amgen Inc. Thousand Oaks, CA, March 2007.
3. U.S. Food and Drug Administration: 2007 Safety Alert: Aranesp (darbepoetin alfa). Available at: [http://www.fda.gov/medwatch/safety/2007/Aranesp\\_DHCP\\_012707.htm](http://www.fda.gov/medwatch/safety/2007/Aranesp_DHCP_012707.htm) (Last accessed December 3, 2007).
4. Henke M. et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: Randomised, double-blind, placebo-controlled trial. Lancet 2003;362:1225–1260.
5. Leyland-Jones B. et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: A survival study. J Clin Oncol 2005;23:5960–5972.
6. Food and Drug Administration News Release. Information on Erythropoiesis Stimulating Agents (ESA) (marketed as Aranesp (darbepoetin), Epogen (epoetin alfa), and Procrit (epoetin alfa)). November 8, 2007. Available at <http://www.fda.gov/cder/drug/infopage/RHE/default.htm> (Last accessed December 3, 2007).

7. Food and Drug Administration News Release. Communication about an Ongoing Safety Review: Erythropoiesis-Stimulating Agents (ESAs) (epoetin alfa (marketed as Epogen, Procrit) darbepoetin (marketed as Aranesp)). January 3, 2008. Available at [http://www.fda.gov/cder/drug/early\\_comm/ESA.htm](http://www.fda.gov/cder/drug/early_comm/ESA.htm) (Last accessed January 7, 2008).
8. Bohlius J. et al. Recombinant human erythropoietins and cancer patients: Updated meta-analysis of 57 studies including 9353 patients. *J Natl Cancer Inst* 2006;98(10):708–714.
9. Bohlius J. et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD003407. DOI: 10.1002/14651858.CD003407.pub4.)
10. Wright JR. et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer and disease-related anemia. *J Clin Oncol* 2007;25:1027–1032.
11. Danish Head and Neck Cancer Group. Interim analysis of DAHANCA 10, 12:1 2006. Available at [http://www.dahanca.dk/get\\_media\\_file.php?mediaid=125](http://www.dahanca.dk/get_media_file.php?mediaid=125) (Last accessed December 3, 2007).
12. Centers for Medicare and Medicaid Services (CMS): Decision Memo for Erythropoiesis Stimulating Agents (ESAs) for non-renal disease indications (CAG-00383N). Available at: <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=203> (Last accessed December 3, 2007).
13. Food and Drug Administration News Release. Information for Healthcare Professionals: Rosiglitazone maleate. 2007 November. Available from: [http://www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm#2007\\_5](http://www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm#2007_5) (Last accessed December 3, 2007).
14. Lincoff, AM et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. *JAMA*. 2007 Sep 12;298(10):1180-88.
15. Singh, S et al. Long-term risk of cardiovascular events with rosiglitazone: A meta-analysis. *JAMA*. 2007 Dec 12; 298(10)1189-95.
16. Lipscombe, LL. et al. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA*. 2007 Dec 12;298(22)2634-43.
17. Food and Drug Administration News Release. Rosiglitazone maleate: Information for Patients. 2007 November (Last accessed December 3, 2007). Available from: [http://www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm#2007\\_5](http://www.fda.gov/cder/drug/InfoSheets/HCP/rosiglitazone200707HCP.htm#2007_5)
18. FDA News Release. Early Communication About an Ongoing Safety Review Varenicline (marketed as Chantix). November 20, 2007. Available at: [http://www.fda.gov/cder/drug/early\\_comm/varenicline.htm](http://www.fda.gov/cder/drug/early_comm/varenicline.htm) (Last accessed December 3, 2007).
19. Bland J.M. & Altman D.G. (2000) The odds ratio. *British Medical Journal* 320, 1468. Available online at: <http://www.bmj.com/cgi/content/full/320/7247/1468> (Last accessed December 3, 2007).
20. Huw Talfryn Oakley Davies, Iain Kinloch Crombie, and Manouche Tavakoli. When can odds ratios mislead? *BMJ*, Mar 1998; 316: 989 – 991. Available online at: <http://www.bmj.com> (Last accessed December 3, 2007).
21. Howden, CW. et al. Guidelines for the Management of Helicobacter pylori Infection. University of South Carolina, Columbia, South Carolina, and McMaster University, Hamilton, Ontario, Canada *AJG* – Vol. 93, No. 12, 1998.
22. Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD003840. DOI: 10.1002/14651858.CD003840.pub4.
23. Predicted market availability is based on either current expiration date of patent, resolution date of patent challenges, or end of 30-month stay blocking FDA from approving generics. When a generic may become available largely depends upon the action by the courts, the FDA, and the manufacturer; therefore, actual availability date may be subject to change.