

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

Avastin® Approved for use in Metastatic Breast Cancer – The Controversial FDA Decision

On February 22, 2008 the Food and Drug Administration (FDA) approved Avastin for use in combination with paclitaxel for the treatment of metastatic HER2 negative breast cancer in certain patients.¹ This decision was based in part on data from an open label, randomized controlled trial.² The decision surprised many because it came after an FDA advisory panel had voted 5-4 against approval in December 2007.³ Despite approval of the new indication, the FDA states on its website that “no data are currently available that demonstrate an improvement in disease-related symptoms or increased overall survival with Avastin in breast cancer.”¹

In the phase III trial, 71 percent of women receiving Avastin in combination with paclitaxel suffered a serious side effect, compared with 51 percent of the women who got paclitaxel alone.^{2,3} Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received Avastin plus paclitaxel. The F.D.A. felt that at least five of these were probably or definitely a result of the combination treatment, representing 1.4 percent of the women getting Avastin.³ Causes of death were gastrointestinal perforation (2 patients), myocardial infarction (2 patients), diarrhea/abdominal pain/weakness/hypotension (2 patients). There were no deaths from the treatment itself among women getting only paclitaxel.^{1,2}

A 20% increase in grade 3 to 5 adverse events was observed in the Avastin plus paclitaxel arm compared to paclitaxel alone. Severe and life-threatening adverse events occurring more frequently in patients treated with Avastin included sensory neuropathy, hypertension, fatigue, infection without neutropenia, neutropenia, vomiting, diarrhea, bone pain, headache, proteinuria, and cerebrovascular ischemia.^{1,2}

Trial authors concluded that initial therapy with paclitaxel plus Avastin prolonged progression free survival but not overall survival.² The women who got Avastin and paclitaxel lived a median of 26.5 months, compared with 24.8 months for the women who got paclitaxel alone. This difference was not statistically significant.²

National Comprehensive Cancer Network (NCCN) guidelines for the treatment of recurrent or metastatic breast cancer updated after the FDA approval include the combination of Avastin plus paclitaxel as a preferred chemotherapy regimen citing an evidence level of 2A.⁴ The guidelines note that a variety of chemotherapy regimens are felt to be appropriate and that combination chemotherapy generally provides an objective response and longer time to progression in comparison to single agent chemotherapy. However, combination chemotherapy is generally associated with an increase in toxicity and is of little survival benefit. The Panel concludes that it “finds little compelling evidence that combination chemotherapy is superior to sequential single agents.”⁴

As a breast cancer treatment, Avastin is estimated to cost approximately \$7,700 per month or \$92,000 per year.⁵ The manufacturer has in place an assistance program for Avastin capping patient and insurer payments at \$55,000 per year for patients who qualify.⁶ More information on

this program can be found at:

<https://www.genentechaccesssolutions.com/avastin/professional/assistance/apap.jsp>

At least one patient advocacy group has gone on record against the FDA approval stating that “we believe that they have lowered the bar.” Fran Visco, president of the National Breast Cancer Coalition Fund, told The New York Times “our goal is to get the best treatments out to patients that really will be effective and safe. This particular circumstance will not advance that goal.”⁵

The benefits and risks posed by Avastin in the treatment of metastatic breast cancer are still being determined.¹⁻³ The phase III trial fails to show the drug in combination with paclitaxel offers an overall survival benefit yet does demonstrate that the Avastin combination increases the risk of severe side effects, including death. Under these circumstances, Avastin’s clinical advantage in treating metastatic breast cancer is unclear. The clinical value of Avastin’s use in combination with paclitaxel for this indication remains to be seen.

The ENHANCE Trial – Zetia®, Vytorin® and Plaque Formation

Recently reported results of the “Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia” (ENHANCE) trial have drawn significant attention from providers and patients currently taking Zetia or Vytorin.⁷

ENHANCE compared plaque formation in the carotid arteries of patients with Heterozygous Familial Hypercholesterolemia (HeFH) who were taking either Vytorin (ezetimibe/simvastatin) or simvastatin alone. After two years, even though adding Zetia to simvastatin lowered cholesterol more than the statin alone, no statistically significant difference in plaque formation was observed between the two treatments.⁷ This has left many providers with questions on Zetia’s place in therapy either alone or in combination with a statin.

Considerations in applying ENHANCE to clinical practice include:⁷

- The trial only studied patients who have high cholesterol due to genetic factors. HeFH is a rare disorder that accounts for only a small portion of patients with hypercholesterolemia. ENHANCE results may not apply to individuals with high cholesterol due to other reasons (e.g. diet, lifestyle, medications).
- To date, no ezetimibe/statin combination has been shown to decrease cardiovascular morbidity and mortality more than statin treatment alone.
- The connection between elevated LDL levels and coronary heart disease is well established.⁹
- The ENHANCE trial used a surrogate endpoint, carotid artery plaque formation, whose clinical applicability in general patient populations, is unclear. Large trials, using cardiovascular events as endpoints, are underway and should be completed in 2011.⁸
- Vytorin shows potent LDL lowering beyond that of many statins alone.¹⁰
- Approximately 80% of the patients in this study had been on prior therapy with statins, so the effects of continued therapy may not have been as dramatic as was seen in previous studies where patients were naïve to statin therapy.
- This was only a 2 year trial which may not be an adequate period of time to show a difference between therapies, especially in a heavily pre-treated population.

After the ENHANCE results were released, The American Heart Association urged caution before altering Zetia treatment regimens and stated that it “recommends that major clinical decisions not be made on the basis of the ENHANCE trial.”⁹

Zetia’s place in therapy as a solo agent for the treatment of high cholesterol remains to be determined. Regardless of the markers that are used, generic statins (pravastatin, simvastatin) continue to be the best value because they reduce the risk of heart attack, stroke and death. We do not know if combining ezetimibe (Zetia) with simvastatin is any better than simvastatin alone in decreasing the risk of heart attack, stroke, and death.

Food and Drug Administration (FDA) Alert - Generic Bupropion XL 300 mg

The FDA recently released a detailed report on its re-examination of the bioequivalence data for brand Wellbutrin XL® and Teva's generic bupropion XL.¹¹ Between January 1 and June 30, 2007, the FDA received several post-marketing reports in which patients who switched from Wellbutrin XL 300 mg to Teva’s generic product experienced an undesirable effect. Following a review of the bioequivalence data for both products, the FDA concluded the following:

- The FDA considers the generic form of bupropion XL 300 mg bioequivalent and therapeutically equivalent to the brand product.
- There are small differences in the pharmacokinetic profiles of these two formulations; however, these are not outside the established boundaries for equivalence nor are they different from other bupropion products known to be effective.
- The recurrent nature of Major Depressive Disorder (MDD) offers a scientifically reasonable explanation for the reports of lack of efficacy following a switch to a generic product.
- Adverse effects (e.g., headache, GI disorder, fatigue and anxiety) reported following a switch were relatively few in number and typical of adverse drug events reported in drug and placebo groups in most clinical trials (i.e., including, but not specifically for, bupropion.)

The FDA continues to closely monitor reports of adverse events and therapeutic inequivalence of bupropion products.

To read the full FDA report and other recent FDA Alerts, please see:

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

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

Quick Review: Trial Design

Historically, one of the greatest challenges present in medical trials has been showing that the a cause and effect relationship exists between the treatment and outcome. Proper trial design is the foundation to an evidence based inquiry into the effectiveness of a medication in treating a particular condition. Without this basic foundation, it becomes impossible to determine whether an effect seen is due to the intervention being studied, some unknown confounding factor, or mere chance.

Randomized controlled trials (RCTs) have been determined to be the most rigorous way of determining whether a cause and effect relation exists between treatment and outcome. These trials have certain important aspects:

- **Randomization.** The study sample should be “drawn at random” from a larger population and each study participant is as likely to be selected for one sample group as another. In a study to

determine a medication's efficacy versus a placebo control, this means that each subject is as likely to be selected to receive the medication being studied as to receive the placebo.

- **Control Group.** To reach a meaningful conclusion about the efficacy of the treatment, it must be possible to compare the results seen in individuals receiving the treatment to a control group that is identical in all aspects to the to the treatment group except the treatment. Where a clinical trial fails to include adequate controls, results are likely to be biased in favor of the treatment. In medication trials, the control group often receives a placebo.

In addition to randomization and a control group, RCTs often use blinding to reduce bias. In a single blinded trial, study subjects do not know which study treatment they receive. Where the study is double blinded, the researchers also do not know which treatment is being given to any given subject.

When evaluating a clinical trial for application to your practice, always ask yourself if the trial design is such that a true cause and effect relationship can be shown. Open labeled, unblinded trials are subject to potential result bias, often in favor of the treatment arm. In RCTs, look for basic details on characteristics such as gender, age, and chronic conditions on the subjects in each sample group. Where basic details are not reported, or it appears that the randomization process may have steered certain patients to one treatment arm or the other, be critical of the reported results. Where randomization is not done properly or deeper analysis shows it is not truly present, a cause and effect relationship between the treatment and the result is less likely to exist.

For more information on RegenceRx's commitment to Evidence Based Medicine, please see:
http://www.delfini.org/page_Project_Regence.htm

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

The following medications were added to the Preferred Medication List:

Humira® - a biological agent approved for the treatment of rheumatoid arthritis, moderate-to-severe plaque psoriasis and moderate-to-severe Crohn's disease.

Revisions to Humira Medication Policy - Effective March 2008

Prior treatment with Enbrel® before Humira is covered for rheumatologic conditions is no longer necessary. The medication policy has also been updated to reflect maintenance dosing greater than 40mg every other week is not medically necessary in rheumatologic conditions.

Clinical Rationale

Both Humira and Enbrel (another preferred/formulary option) are similar in efficacy/safety in rheumatologic conditions and psoriasis. Humira also has reliable evidence of inducing remission in patients with moderate-severe Crohn's Disease. For certain conditions, Enbrel or Humira may be more cost-effective depending on how they are dosed. Medication policy has been updated to allow equal choice for either Enbrel or Humira, with the continued recognition of the lack of evidence to support significant benefit with escalating doses or more frequent administration of maintenance dosing with Humira.

For more information, please see the Humira medication policy, available at:
<http://www.regencerox.com/learn/policy/index.html>

Intelence® - a non-nucleoside reverse transcriptase inhibitor (NNRTI) for use in treatment-experienced HIV-infected patients who have continued viral replication with HIV-1 strains resistant to an NNRTI and other ARV agents. Reliable evidence exists that Intelence decreases viral load in patients with resistant strains of HIV-1 when used with other antiretroviral agents.

Isentress® - an HIV-1 integrase strand transfer inhibitor (INSTI) anti-retroviral indicated for use in treatment-experienced HIV-infected patients.

Letairis® - approved for the treatment of pulmonary arterial hypertension (PAH).

Nexavar® - indicated for the treatment of patients with, advanced renal cell carcinoma, gastrointestinal stromal tumor, and advanced hepatocellular carcinoma.

Revlimid® - indicated for use in patients with myelodysplastic syndrome (MDS) who are transfusion-dependent and in patients with multiple myeloma who have failed one prior therapy.

Selzentry® - CCR5 co-receptor antagonists antiretroviral used in treatment-experienced HIV-1 infected adults.

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

Brovana® - indicated for use in chronic obstructive pulmonary disease (COPD).

Divigel® and **EvaMist®** - an estradiol gel and spray form for daily topical use.

Endometrin® a progestin approved for use with assisted reproductive technology.

Exelon Patch® - indicated for the treatment of mild to moderate dementia associated with Alzheimer's Disease and Parkinson's Disease.

Lialda® - approved for the treatment of active mild-to-moderate ulcerative colitis.

OxyContin® - a narcotic analgesic indicated for the treatment of chronic pain.

Perforomist® - indicated for use in chronic obstructive pulmonary disease (COPD).

Sutent® - indicated for the treatment of patients with, advanced renal cell carcinoma, gastrointestinal stromal tumor, and advanced hepatocellular carcinoma.

Symbicort® - approved for the treatment of asthma in patients age 12 years and older.

Tasigna® - a multi-kinase inhibitor indicated for use in adult patients with chronic or accelerated phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML) who were resistant to or intolerant of prior therapy with imatinib (Gleevec).

Veramyst® - indicated for the treatment of the symptoms of SAR and PAR in patients 2 years of age and older.

Zyflo CR® - approved for prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.

For Preferred Medication List/Formulary alternatives for non-preferred products, please see:
<http://www.regencrx.com/learn/covered/therapeutic/index.html>

For our most recently released Therapeutic Class SummariesSM, please see:
<http://www.regencrx.com/learn/physicianRx/index.html>

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

New Generic Medications at the Pharmacy or Coming Soon!¹²

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!

<p><u>Asthma/Allergy</u> Zyrtec OTC® – on shelves – now available without a prescription</p>	<p><u>Mental Health and Sleep</u> paroxetine extended release (Paxil CR®) –late 2008 risperdone (Risperdal®) – early 2008 zaleplon (Sonata®) – on shelves</p>
<p><u>GI</u> balsalazide (Colozal®) – on shelves pantoprazole (Protonix®) – on shelves</p>	<p><u>Other</u> lamotrigine (Lamictal®) – mid 2008 sumatriptan (Imitrex®) – late 2008 topiramate (Topamax®) – late 2008</p>

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

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

1. Food and Drug Administration News Release. New Approval for Bevacizumab(Avastin). March 13, 2008. Available at <http://www.fda.gov/cder/Offices/OODP/whatsnew/bevacizumab200802.htm> (Last accessed April 24, 2008).
2. Miller K. et al. Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer. N Engl J Med. 2007 Dec 27;357(26):2666-76.
3. Food and Drug Administration Advisory Board Dockets. Oncology Drugs Advisory Committee Meeting Transcript. December 5, 2007. Available at <http://www.fda.gov/ohrms/dockets/ac/cder07.htm#OncologicDrugs> (Last accessed April 24, 2008).
4. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Breast Cancer - v.2.2008. Available at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf. (Last accessed April 24, 2008).
5. Pollack A. F.D.A. extends Avastin’s use to breast cancer. The New York Times. 2008 Feb 23. Available online at: <http://www.nytimes.com/2008/02/23/business/23drug.html?scp=2&sq=Avastin+Breast+Cancer+&st=nyt> (Last accessed April 24, 2008).
6. GenentechAccessSolutions.com. Avastin Access Solutions: An Overview. c2008 Available from <http://www.genentechaccesssolutions.com/avastin/professional/index.jsp> (Last accessed April 24, 2008).
7. Merck & Co., Inc. Merck/Schering-Plough Pharmaceuticals Provides Results of the ENHANCE Trial. Merck & Co., INC. Published January 14, 2008. Available from: www.merck.com/newsroom/press_releases/product/2008_0114.html (Last accessed February 15, 2008.)

8. Food and Drug Administration News Release. Early Communication about an Ongoing Data Review for Ezetimibe/Simvastatin (marketed as Vytorin), Ezetimibe (marketed as Zetia), and Simvastatin (marketed as Zocor). January 25, 2008. Available at: www.fda.gov/cder/drug/early_comm/ezetimibe_simvastatin.htm (Last accessed April 24, 2008).
9. American Heart Association. Statement from the American Heart Association on ENHANCE study results. January 15, 2008. Available at: www.americanheart.org/presenter.jhtml?identifier=3053094 (Last accessed April 24, 2008).
10. American College of Cardiology. ACC Statement on ENHANCE Trial. January 15, 2008. Available at: <http://www.acc.org/enhance.htm> (Last accessed April 24, 2008).
11. Food and Drug Administration News Release. Review of Therapeutic Equivalence Generic Bupropion XL 300 mg and Wellbutrin XL 300 mg. April 16, 2008. Available at: http://www.fda.gov/cder/drug/infopage/bupropion/TE_review.htm (Last accessed April 24, 2008).
12. 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.