



Rx Focus

COX-2 Inhibitors – A Closer Look

Following the recent withdrawal of Vioxx from the market, the FDA is now requiring a closer look at all COX-2 inhibitors to determine if the increased risk of heart attack and stroke seen with Vioxx is actually a class effect. In other words, do Bextra, Celebrex, and newer COX-2 inhibitors under investigation (etoricoxib and lumiracoxib) increase cardiovascular risk by increasing the likelihood that blood will clot?

In 1999, Celebrex and Vioxx were the first two COX-2 inhibitors introduced to the U.S. prescription drug market. Unlike traditional Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) that inhibit both Cyclo-oxygenase 1 (COX-1) and Cyclo-oxygenase 2 (COX-2), these drugs only inhibit COX-2. COX-2 is an important enzyme involved in the production of prostaglandins at inflammatory sites. By inhibiting COX-2, the inflammatory response is significantly reduced. Conversely, COX-1 is important in maintaining the lining of the stomach. By inhibiting COX-1, traditional NSAID's have the potential for compromising the integrity of the stomach wall. Therefore, the claim to fame of the COX-2 inhibitors was reduced gastrointestinal side effects as compared to other NSAID's.

However, COX-1 is also involved in Thromboxane A2 formation, meaning that it can increase the likelihood of blood clotting. In addition, COX-2 is involved in the production of a vascular protacyclin (PGI2) that inhibits

blood clotting. In other words, by inhibiting COX-2 alone, there is a possibility that there may be an increased risk of blood clotting, and subsequently, an increased risk of both heart attack and stroke. This was found to be the case with Vioxx and resulted in its withdrawal from the market.

Due to aggressive marketing directly to consumers, COX-2 inhibitors have dominated the prescription drug market for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) in the United States in the recent past. With the withdrawal of Vioxx, it is important to determine which patients would benefit from continued treatment with a COX-2 inhibitor and which patients would be better off being switched to a more traditional NSAID. This is dependant on the patient's risk of both gastrointestinal (GI) complications from chronic NSAID use and the patient's risk of heart disease.

Patients with low GI risk should be on a more traditional NSAID, e.g., ibuprofen, indomethacin, meloxicam, naproxen, etc. Patients at high risk for GI complications can be on a traditional NSAID plus a proton pump inhibitor or misoprostol (Cytotec®) or they can take a COX-2 inhibitor provided there is no heart disease.

COX-2 inhibitor therapy should be avoided in all patients with cardiovascular disease. In addition, patients who are allergic to sulfonamides should avoid both Bextra and Celebrex.

Treatment options for patients on low-dose aspirin therapy with low GI risk include a traditional NSAID plus a proton pump inhibitor or misoprostol. (Chronic ibuprofen usage should be avoided in these patients as there is evidence that chronic ibuprofen administration interferes with the antiplatelet effects of aspirin.) Options for patients on low-dose aspirin with previous history of ulcer should not include an NSAID or even a COX-2 inhibitor. These patients should be treated with other analgesics including acetaminophen and/or opioids.

References:

1. "Safety of COX-2 Inhibitors and Their Place in Therapy" by Beth A. Leshner, PharmD, BCPS, Pharmacist's Letter, Detail-Document #201102, November, 2004
2. "Coxibs and Cardiovascular Disease" by Dr. G.A. FitzGerald, New England Journal of Medicine, 2004; 351.1709-11.

December Health Observances

National Drunk and Drugged Driving (3D) Prevention Month

Sponsored by National Commission Against Drunk Driving www.3dmonth.org

Safe Toys and Gifts Month

Sponsored by Prevent Blindness America www.preventblindness.org



Industry Report

Exanta Turned Down by FDA

The March 2004 issue of *RxHints* discussed the likely approval of a promising new anticoagulant, Exanta (ximelagatran), manufactured by AstraZeneca. However, in September 2004, the FDA recommended against its approval due to concerns over liver toxicity. Studies have shown that about 1 in 200 people develop severe liver injury. In addition, higher rates of heart attack and major bleeds were seen during short-term trials when compared to warfarin.

Black Box Warning Added to Depo-Provera Labeling

On November 17, 2004, the FDA announced that Pfizer will add a black box warning to the labeling of Depo-Provera Contraceptive Injection that highlights the potential for bone density loss with prolonged use. The risk of bone density loss is greater the longer the drug is administered, and the loss may not be completely reversible once the medication is stopped. Women should only use Depo-Provera as a long-term birth control method, i.e., for more than two years, if other methods of birth control have proven inadequate.



New Drug Approvals

TARCEVA® 25mg, 100mg and 150mg Tablets

Approved: 11/18/04

Chemical Name: Erlotinib

Manufacturer: OSI Pharmaceuticals and Genentech

Therapeutic Class: Anti-Cancer Agent

Approved Indication: Treatment of locally advanced or metastatic Non-Small Cell Lung Cancer after failure of at least one prior chemotherapy regimen.

Average Wholesale Price:

25mg Tablet: \$27 per unit

100mg Tablet: \$74.29 per unit

150mg Tablet: \$84.42 per unit

Notes: CBCA Rx will require physicians to submit prior authorization information indicating that treatment with Tarceva is Medically Necessary.

TYSABRI® Intravenous Injection

Approved: 11/23/04

Chemical Name: Natalizumab

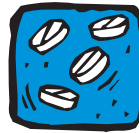
Manufacturer: Biogen Idec and Elan Corporation

Approved Indication: Treatment of relapsing forms of multiple sclerosis.

Average Wholesale Price: not known at this time

Special Notes: First humanized monoclonal antibody approved for the treatment of multiple sclerosis.

Administered by IV injection, therefore, not covered on CBCA Rx plans.



New Generic Approvals

LUTERA™

Levonorgestrel and Ethinyl Estradiol Tablets, USP, 0.1mg / 0.02mg

Approved: 11/22/04

Manufacturer: Watson Pharmaceuticals

Brand Name Equivalent: Alesse®

Approved Indication: Prevention of pregnancy.



2005 Brand Name Patent Expirations

The year 2005 provides clients with a changing pharmaceutical landscape as several noteworthy Brand-Name patents expire. By the end of 2005, it is expected that the following products will have therapeutically equivalent generic medications:

Allegra, Celexa, Biaxin, Duragesic, Oxycontin, Zithromax, and Zofran*.

Each of these products represents a significant portion of high utilization. Frequently the above listed medications rank in the Top 20 prescribed medications. We believe the generic equivalent may significantly lower drug costs.

* Zofran is subject to quantity limits.



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