

## Indiana Medicaid Therapeutics Committee Therapeutic Class Review Summary

### **Therapeutic Class:**

Cyclooxygenase 2 inhibitors

### **Overview:**

Cyclooxygenase 2 (COX-2) inhibitors were first introduced to the clinical setting in 1999. Their mechanism of action is to prevent prostaglandin synthesis by selectively inhibiting cyclooxygenase-2 (COX-2) enzymes. COX-2 enzymes are absent from the gastrointestinal (GI) tract, whereas COX-1 enzymes are in most tissues. By inhibiting only the COX-2 enzyme, COX-2 inhibitors avoid GI complications caused by decreased production of the GI protectant, prostaglandin.

Currently, the only COX-2 inhibitor available in the U.S. is Celebrex<sup>®</sup> and there is not a generic formulation for this product. Celebrex<sup>®</sup> is indicated for osteoarthritis, rheumatoid arthritis, primary dysmenorrhea, ankylosing spondylitis, juvenile rheumatoid arthritis, and acute pain. COX-2 inhibitors are proven to be as effective as traditional NSAIDs with less upper GI complications such as bleeding and ulcerations. However, the risk of upper GI complications cannot be completely eliminated. Also, long-term use of COX-2 inhibitors has resulted in renal injury.

COX-2 inhibitors lack platelet effects and therefore, should not be used as a substitute for aspirin during cardiovascular prophylaxis. Furthermore, the concern of COX-2 cardiovascular safety had been raised due to the findings of the Vioxx<sup>®</sup> Gastrointestinal Outcome Research (VIGOR) study. In this study, serious thrombotic cardiovascular events occurred in 45 of the 4047 patients (1.11%) taking rofecoxib compared to 19 of the 4029 patients (0.47%) taking naproxen. In late September 2004, Merck voluntarily withdrew Vioxx<sup>®</sup> from the market based on new, three year data from the Adenomatous Polyp Prevention on Vioxx<sup>®</sup> (APPROVe) trial. This trial showed an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment in patients taking Vioxx<sup>®</sup> compared to those taking placebo. Conversely, the Celecoxib Long-term Arthritis Safety Study (CLASS) did not detect an increased risk in cardiovascular events. However, subsequent analysis yields conflicting results.

Recently, the label for Celebrex<sup>®</sup> has been updated to include a boxed warning indicating potential cardiovascular and gastrointestinal risks that are consistent with warnings of other NSAIDs. Additionally, a medication guide is now required for Celebrex<sup>®</sup>. The boxed warning also includes a new contraindication for Celebrex<sup>®</sup> in the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

| <b>Generic Name</b> | <b>Brand Name</b>                                   | <b>Manufacturer</b> | <b>Generic</b> |
|---------------------|---|---------------------|----------------|
| Celecoxib           | Celebrex <sup>®</sup>                               | Pfizer              | N              |
| Rofecoxib           | Vioxx <sup>®</sup> - WITHDRAWN                      | Merck               | N              |
| Valdecoxib          | Bextra <sup>®</sup> (Sales and marketing suspended) | Pharmacia           | N              |

**Summary:**

Although similar in efficacy and analgesic properties to traditional non-selective NSAIDs, the value of the COX-2 inhibitors lies with their improved safety profile, particularly when gastrointestinal toxicity is of concern. Therefore, these agents should be reserved for use in those patients at increased risk for severe gastrointestinal disturbances.