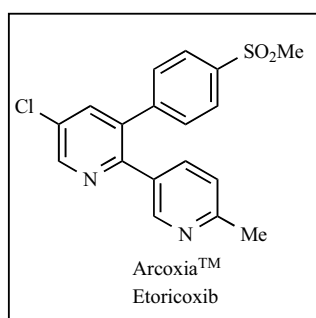


Molecule of the Month

Emerging from the shadow of Vioxx™. Nonsteroidal antiinflammatory drugs (NSAIDs) are a class of medicines prescribed to treat acute and chronic pain [1]. NSAIDs reduce prostaglandin production by inhibition of cyclooxygenase (COX) to afford analgesia. However, while very effective for the treatment of pain and inflammation, this mechanism elicits adverse gastrointestinal (GI) and renal effects. The discovery of COX isoforms (COX-1 and COX-2) and differential functions led to the development of selective COX-2 inhibitors for the treatment of pain that minimized the adverse GI effects [1]. In 1999 Pfizer launched Celebrex™ (30-fold selective COX-2 inhibitor) and Merck launched Vioxx™ (272-fold selective COX-2



inhibitor) [2, 3]. It has been 28 months since Merck & Co. announced the results of the APPROVe trial and withdrew Vioxx™ from the market due to adverse cardiovascular events such as heart attack and stroke; as a result, over 27,000 lawsuits have been filed against the pharmaceutical giant [3]. The cardiovascular risks stems from the selective inhibition of COX-2 which reduces COX-2-mediated vasodilation and inhibition of platelet aggregation. Unlike the nonselective NSAIDs, which balance COX-1-mediated platelet activation with COX-2 vasodilation and platelet inhibition, selective inhibition of COX-2 with drugs like Vioxx may generate an imbalance that predisposes platelet aggregation and ischemia [1]. Despite the potential risks, arthritis patients clamored for the drug, as for many patients, only Vioxx™ relieved their arthritis pain. In November of

2006, Merck announced that it received an approvable letter from the FDA for Arcoxia™, a second generation COX-2 inhibitor with even greater COX-2 selectivity (344-fold) [1, 3]. Also in November of 2006, Merck announced the results of a large outcomes study, coined the MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) program, which demonstrated that Arcoxia™ had similar rates of cardiovascular thrombotic events as Diclofenac™, the most prescribed traditional NSAID in the world [3]. In addition, the MEDAL study showed that Arcoxia™ had a lower rate of confirmed upper GI effects (including ulcers, bleeding and obstructions) than Diclofenac™. However, a recent article in the *Wall Street Journal* raised issues with the MEDAL study [4]. In the article, some doctors were quoted as saying that the study was of limited scope and questioned the comparison of Arcoxia™ to Diclofenac™, which ‘...acts like a COX-2 inhibitor in the first place.’ They advocated comparing Arcoxia™ to a less-similar painkiller such as naproxen. Despite these issues, Arcoxia™ is currently available in 62 countries around the world, but sales in the US are pending an FDA decision that is expected in April of 2007 [3].

REFERENCES

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- [2] For detailed information and press releases describing Celebrex™, see www.pfizer.com
- [3] For detailed information and press releases describing Vioxx™, Arcoxia™, the APPROVe and MEDAL studies see www.merck.com
- [4] Whalen, J. ‘Drug makers try to bring back Cox-2 inhibitors’ in the *Wall Street Journal*, Eastern edition, Jan. 19, 2007, B.1.

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