Reviews/Evaluations

Review of FDA CDER Arthritis Advisory Committee Meeting
Meeting: February 7-8, 2001
Topic: Celebrex and Vioxx

Background

The selective COX2 inhibitors or COX2s, Celebrex (celecoxib) and Vioxx (rofecoxib), were FDA approved for use in osteoarthritis and rheumatoid arthritis and for use in osteoarthritis, acute pain, and primary dysmenorrhea respectively in 1999. Celebrex has since gained additional approval for use in familial adenomatous polyposis (FAP). At the time of the submission of the original NDAs, there existed evidence of comparable efficacy of and a reduction in endoscopic ulcers with the COX2s relative to the comparator NSAIDs studied (ibuprofen, diclofenac, and naproxen). The original NDA databases, however, did not differentiate COX2s from the comparator NSAIDs in terms of GI symptoms or clinically meaningful outcomes such as PUBs. Therefore, the current product labeling for both Celebrex and Vioxx contain standard warnings regarding gastrointestinal toxicity seen in NSAID labeling.

Since initial approval, large, randomized, double-blind, comparator-controlled trials, CLASS and VIGOR (attached), have been conducted to compare GI safety in terms of PUBs. Based on results of these studies the manufacturers of Celebrex and Vioxx petitioned the FDA to remove the GI warning template from their product labeling. The Arthritis Advisory Committee's task was to review the available data and offer guidance to the FDA regarding these petitions.

Important Considerations when evaluating CLASS and VIGOR:

1. There is an inherent difficulty in generalizing data from both CLASS and VIGOR to the general population, since each study used only 1 or 2 NSAID comparators and there exists a large continuum of adverse event rates within the nonselective NSAID class. Findings may not be applicable to other populations or NSAIDs not studied.

2. It is also important to note that the small number of events overall, whether cardiovascular or gastrointestinal, that occurred in either may explain whether or not statistical significance was achieved for various comparisons.

3. Definitions of PUBs and POBs. PUB may not be a clinically relevant endpoint. There are problems inherent with a composite endpoint of symptomatic and complicated ulcers used in both studies. The correlation between symptomatic ulcers and complicated ulcers is too weak to consider in the same endpoint; only a small fraction of symptomatic ulcers result in a serious outcome and many patients with serious outcomes are not symptomatic. The rate of symptomatic ulcers will be higher in a clinical trial because more physicians are likely to work-up these
patients, whereas in practice, they are likely to just discontinue the offending NSAID. Separate analyses allow for more meaningful and accurate understanding of the data. A complicated PUB or POB (perforation, obstruction, or bleed) is the better endpoint and in VIGOR is a secondary endpoint.

**Key CLASS and VIGOR Findings:**

CLASS did not demonstrate a statistically significant advantage in terms of the primary endpoint (complicated event or PUB) at any time for celecoxib compared to NSAIDs (pooled or individual), although trends were evident in favor of celecoxib. Upon post-hoc analysis of patients not taking aspirin, the incidence of combined PUB/symptomatic ulcer event was lower in the celecoxib group compared to pooled NSAIDs and ibuprofen alone (p values < 0.05). With respect to global safety, celecoxib did not demonstrate an advantage over comparator NSAIDs and there existed trends of similar magnitude for increased cardiac toxicity.

VIGOR did demonstrate a statistically significant reduction associated with rofecoxib compared to naproxen for the endpoints of PUBs and POBs. The relative risk was maintained in all important subgroups. Aspirin use was excluded in this study. The rofecoxib re was an increased risk of cardiovascular thrombotic events, particularly MI, in the rofecoxib group.

In BOTH studies during the first 30-90 days, there was no separation between the time-to-event curves. There does not appear to be a clinically meaningful advantage of COX2s when used short-term. Both CLASS and VIGOR and postmarketing data confirm the high risk of complicated ulcers in elderly patients (>/> 65 years) and in patients with a prior history of ulcer disease or using steroids. The absolute event rates were consistent with the range reported in the current GI warning template (e.g. ~ 1% risk with 3-6 months of use and a 2-4% risk with 1 year of use).

**Arthritis Advisory Committee Comments and Recommendations:**

- The committee notes it is unclear as to why differences in results are seen between the studies and most likely do not reflect differences among drugs studied, but study design.
- The committee notes it is dangerous to make general conclusions regarding UGI toxicity based on the post-hoc analyses of subgroups such as aspirin and non-aspirin users and non-prespecified endpoints. A lack of specific information regarding aspirin use limits the interpretation of these analyses.
- Committee members unanimously agreed to retain the current GI warnings in celecoxib and rofecoxib labeling and to revise the labeling to reflect concerns regarding CV safety (at the least, that there is a lack of a cardioprotective effect). Although there appears to be a relative GI benefit for celecoxib and rofecoxib compared to the NSAID comparators, the absolute event rates were consistent with NSAID rates presented in the GI warning templates.
- "The risk of serious GI complications with rofecoxib is still a
concern. Risk factors associated with serious GI bleeding with rofecoxib are the same as for other NSAIDs: age, prior history of ulcer disease, concomitant use of aspirin, warfarin or antiplatelet agents, and corticosteroids (GI Medical Officer Review)."

- It is unclear from VIGOR whether differences in serious CV events are due to a very low rate in the naproxen group (a naproxen benefit) or a very high rate in the rofecoxib group (a rofecoxib detriment). Since there is no placebo group in the VIGOR study, it is difficult to assess whether or not there is a true prothrombotic effect of rofecoxib. Although the sponsor claims that the majority of CV events occurred in patients who should have been on aspirin for cardioprotection, the VIGOR data are consistent even in patients who did not fall into the "aspirin-indicated" subgroup (~ twice the risk). "The sponsor recommends that patients at risk for CV events should receive concomitant low-dose aspirin when taking rofecoxib; however, there may be a loss of the GI safety benefit if this is done".

- A cardiologist member presented compared VIGOR data to The Primary Prevention Project (PPP; aspirin versus placebo in a similar patient population). In this comparison, the event rates with naproxen (VIGOR) and aspirin (PPP) were similar; however, there were significantly greater events rates with rofecoxib (VIGOR) versus placebo (PPP). Therefore, the difference observed may be partly explained by both theories which warrant further study.

- The members unanimously agreed that conclusions cannot be made regarding the concomitant use of aspirin and COX2s and further study is warranted.

- Committee members expressed concern over the fact that the age group most likely to receive these drugs (COX2s) are also the age group with the highest cardiovascular mortality. There is an increasing likelihood that this age group will be on low-dose aspirin for either primary or secondary cardiovascular protection and it is evident from both CLASS and VIGOR that concomitant aspirin use cancels any GI safety benefit of COX2s and may impart increased cardiovascular toxicity, particularly MIs.

- Overall significant adverse events were higher in both celecoxib and rofecoxib groups, although not always reaching statistical significance. In VIGOR, the risk reduction in GI events did not translate into an overall safety benefit of rofecoxib over naproxen. Evaluation of routine safety parameters (deaths, serious AEs, dropouts due to AEs) showed no advantage of rofecoxib over naproxen. "In the VIGOR study the potential advantage of decreasing the risk of complicated PUBs was paralleled by the increased risk of developing cardiovascular thrombotic events."

- These trials underscore an important dilemma when assessing the overall benefit:risk ratio of COX2s versus nonselective NSAIDs. In some patients predisposed to CVdisease, a GI safety advantage of COX2s may be offset by a CV detriment. Therefore, the decision is highly dependent on individual patient characteristics.