

Dear FDA Committee Members,

I am a Cancer Rehabilitation Specialist at the Memorial Sloan-Kettering Cancer Center in New York City. A major component of my practice is the evaluation and treatment of musculoskeletal pain disorders in persons with and survivors of cancer. The cox-2 inhibitors are among the most important tools in my arsenal and I have made a strong commitment to becoming intimately familiar with the published data on the safety and efficacy of this class of medicine. As the most prolific prescriber of Celebrex and Bextra at the Memorial Sloan-Kettering Cancer Center, I feel compelled to offer some comments on these medications for your consideration.

Celebrex is not Vioxx. I have been aware of the cardiovascular toxicity from Vioxx since 2000 when the VIGOR trial was published. Despite excluding any patient with a recent history of stroke or heart attack or who required any form of blood thinner to protect against stroke or heart attack, VIGOR demonstrated that patients taking 50 mg per day of Vioxx experienced a 5-fold increase in heart attacks compared to those taking standard doses of naproxen. The similarly designed CLASS trial compared the gastrointestinal toxicity of 800 mg per day of Celebrex to standard doses of ibuprofen and diclofenac. CLASS showed no relative cardiovascular toxicity despite making no attempt to exclude high cardiovascular risk patients and despite having a dose of Celebrex that is equivalent to twice the amount of Vioxx used in the VIGOR trial.

The VIGOR and CLASS trials were quickly followed by a number of prospective studies demonstrating that Vioxx significantly increased blood pressure compared to Celebrex. All NSAIDS can cause hypertension. What is unique to Vioxx is that it causes it more frequently and more severely than other NSAIDS. While much attention has been given to the theoretical possibility that the Cox-2 inhibitors might upset the balance of the body's clotting system and increase the possibility of heart attack and stroke, little attention was given to a more straightforward and well proven theory...hypertension kills!

Several large and very well done epidemiologic studies have consistently demonstrated an increase risk of heart attacks for patients taking Vioxx as compared to Celebrex, other NSAIDS, or no NSAIDS. Simple increases in blood pressure might be enough to explain the increased strokes and heart attacks demonstrated with Vioxx use. Blood pressure is also the likely explanation for the increase risk of cardiovascular events seen with traditional NSAIDS in both the Kaiser Permanente Study and with over-the-counter doses of Naprosyn in the ADAPT trial.

The reported increase in adverse events with Bextra in the high-risk population of patients who have just received cardiac bypass surgery, also, should not be a surprise to anyone with basic knowledge of pathophysiology. All NSAIDS, non-specific and Cox-2 inhibitors, will inhibit prostaglandin in the efferent arteriole of the kidney resulting in fluid retention and hypertension. Fluid retention and hypertension in this population can be expected to directly cause renal dysfunction, heart failure, myocardial infarction, stroke, and poor wound healing. Few populations are as at risk for these complications than the patients included in the cardiac bypass surgery studies. All NSAIDS, at supratherapeutic doses, can be expected to cause these sequelae. No other NSAID or cox-2 inhibitor has ever been tested in supratherapeutic doses in this setting.

So, why are we now finding out that there may be a problem with high doses of Celebrex? Because, for the first time it is possible to give a member of the NSAID group at extremely high doses for long periods of time without increasing the risk of GI bleeding. Traditional NSAIDS such as naproxen were presumed to be safe or even protective of the heart

but were never subjected to long-term trials. I do not think we should be surprised to find out what we already know. NSAIDS can cause or worsen hypertension in at-risk patients. Elevated hypertension causes strokes and heart attacks.

While we do need to further define the risks of these medications we cannot assume that traditional NSAIDS offer improved cardiovascular safety when there is now so much evidence is to the contrary. Nor can we assume that there is an inherent risk in cox-2 inhibition when the epidemiological data does not support this contention. We need to know if the cardiovascular risk now associated with NSAIDS is real, if it is related to hypertension, which patients are most at risk, and if monitoring and controlling hypertension will minimize the cardiovascular risks associated with NSAIDS.

Sincerely,

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