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Before the FDA's Arthritis Drugs Advisory Committee on the
Nonsteroidal Anti-Inflammatory Drug (NSAID) Celecoxib (Celebrex)**

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Town Center Hotel,
The Maryland Ballroom, 8727 Colesville Rd., Silver Spring, MD.

Celecoxib is a drug inexplicably granted expedited review by the FDA and if approved, would be the twentieth nonsteroidal anti-inflammatory drug (NSAID) to be marketed in the U.S. It may be considered the fifth different chemical class of these drugs that inhibit the two known forms of the enzyme cyclooxygenase (COX), COX-1 and COX-2 . At paramount issue to the public's safety is whether NSAIDs that are promoted as preferential, selective, or specific inhibitors of the enzyme COX-2, seeking to differentiate them in a crowded marketplace from other NSAIDs, can be labeled as having less toxicity, particularly gastrointestinal (GI) toxicity, than all of the other drugs in this class.

Not frequently discussed is that COX-2 may have other important physiological functions in addition to its role in inflammation such as GI tract tissue repair, epithelial integrity, renal vascular homeostasis, fetal renal development during pregnancy, ovarian function and fertility, and cartilage repair. Purported new classes of drugs such as celecoxib offer not only new mechanisms of action, but also new mechanisms of potential toxicity and the possibility of a new spectrum of adverse effects.

Several weeks ago (November 12, 1998) , the headline of a PR Newswire story, citing Monsanto as a source, referred to phase III studies on Celebrex (celecoxib):

As Effective as Naproxen and Diclofenac but with a Gastrointestinal Safety Profile Similar to Placebo

The text referred to a paper presented at the American College of Rheumatology meeting and described studies using upper gastrointestinal endoscopic exams which showed that the incidence of gastroduodenal ulcers in patients given celecoxib was "four times lower" than in patients taking diclofenac. This finding is consistent with that of Dr. Lee Simon and his colleagues (*Arthritis and Rheumatism*, September, 1998) who found in a phase II study endoscopy trial two different dosage levels of celecoxib "produced no ulcers and was indistinguishable from placebo." Simon et al. went on to warn, however, that "although this model is sensitive to acute mucosal effects, the results do not necessarily correlate with clinical

events such as bleeding, perforation or obstruction" and that "Only larger trials evaluating long-term outcome and higher dosage levels will fully define the GI effects of selective COX-2 inhibitors."

A quite similar "good news" story detailed early results on another selective COX-2 inhibitor, meloxicam, marketed in the UK since September, 1996. A study of healthy people given meloxicam or a placebo (or piroxicam) for 28 days found that, using endoscopy again, "no significant mucosal damage" occurred in either the placebo or the meloxicam group (Brit J Clin Pharm, 1998;46:133-7). But recently, the British Government required a major increase in the warnings on this drug because of severe gastrointestinal adverse effects. In the August, 1998 *Current Problems in Pharmacovigilance*, the British Medicines Control Agency and the Committee on Safety of Medicines reported on the first one year and nine months of marketing experience of Boehringer-Ingelheim's meloxicam. Of a total of 1339 adverse reactions reported to the government for the drug, 41% or 549 were gastrointestinal adverse effects with 18% of these, or 99 being reports of perforations, ulcers or bleeding, including five deaths.

The *Drug and Therapeutics Bulletin*, the British equivalent of our *Medical Letter*, which is sent to all British physicians, said in its August, 1998 issue that "There is no convincing evidence that the risk of the severest adverse gastrointestinal events, namely peptic ulceration, perforation and bleeding, is lower with meloxicam than with other NSAIDs when given at equi-effective doses...Meloxicam has not been compared with ibuprofen...which comes out best in most safety assessments."

As this committee knows well, despite apparently large differences between the more traditional COX-1 inhibiting NSAIDs as far as the occurrence of perforations, ulcers and gastrointestinal bleeding (see attached chart we presented at a December, 1994 meeting of the advisory committee), the committee and the FDA decided on identical class labeling for all of these older NSAIDs which warns about these serious and not infrequent adverse effects.

There needs to be clear evidence from comparative long-term, higher dose randomized trials in which celecoxib or any other COX-2 type of anti-inflammatory drug is compared to the <u>least</u> dangerous of these older drugs, ibuprofen, that there is a statistically significantly lower amount of serious GI complications such as perforations, ulcers or bleeding with the COX-2 inhibitor drug. Unless this evidence is produced, there is no more reason, according to the logic of this committee, to spare any COX-2 inhibitor from the class label now applied to all of the other NSAIDs than there is to distinguish between the members of this older class. The question, among others, is will this committee and the FDA require that such studies be finished before subjecting millions of American arthritis patients, under the unproven assumption that this and similar drugs are much safer, to treatments which, like meloxicam, turn out to be more dangerous?

Table 1, attached, lists some NSAID COX-2/COX-1 ratios with a corresponding number called a GI Toxicity Index (GI-TI). The GI-TI was developed by the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) from 6,276 courses of treatment with 12 different NSAIDs. The GI-TI is a sum of GI symptoms per patient-year of exposure, weighted by severity and number of hospital days and adjusted for risk factors and other key variables. Salsalate has the lowest GI-TI Index at 0.81 and meclofenamate the highest at 3.91. Take note of the GI-TI Index for diclofenac of 1.81 and a COX-2/COX-1 ratio of 0.7 that indicates that diclofenac is about ten times less selective for COX-2 than meloxicam with a reported value of 0.09.

Table 1 was derived from two sources and relates the GI Toxicity Index to the ratio of the concentrations of the listed NSAIDs needed to inhibit 50 percent the COX-1 and COX-2 enzymes. This is the right hand column. A value of 1 would indicate equal inhibition of the two forms of the COX enzyme. A very large value such as 166 for aspirin in the third row would suggest an NSAID that inhibits primarily COX-1. On the other hand, values less than one would suggest greater inhibition of COX-2, such as those for naprosyn and diclofenac.

The values of the GI Toxicity Index (GI-TI) are from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) at the Stanford University of Medicine. The GI-TI is a sum of GI symptoms per patient-year of exposure to an NSAID, weighted by severity and umber of hospital days and adjusted for risk factors and other key variables. The differences in GI toxicity only become clinically or statistically significant between the NSAIDs at the upper and lower end of the range.

Ibuprofen, from observational studies, is generally recognized as having least GI toxicity in clinical practice and has a low GI-TI of 1.13, but a COX-2/COX-1 ratio of 15 indicating that this NSAID is predominately a COX-1 inhibitor. This is an observation that is in direct contradiction that drugs with the greatest COX-2 selectivity should be the NSAIDs with least GI toxicity.

TABLE 1

NSAID (Brand Name)	GI Toxicity Index (mean ± SE)[1]	Ratio of the Concentrations Needed to Inhibit 50% of COX.[2] COX-2/COX-1
salsalate (Disalcid)	0.81 ± 0.51	na
ibuprofen (Motrin)	1.13 ± 0.29	15
aspirin	1.18 ± 0.18	166
sulindac (Clinoril)	1.68 ± 0.29	na
diclofenac (Voltaren)	1.81 ± 0.35	0.7
naproxen (Naprosyn)	1.91 ± 0.21	0.6
tolmetin (Tolectin)	2.02 ± 0.44	na
piroxicam (Feldene)	2.03 ± 0.24	na
fenoprofen (Nalfon)	2.35 ± 0.55	na
indomethacin (Indocin)	2.39 ± 0.34	60
ketoprofen (Orudis)	2.65 ± 0.43	na
meclofenamate (Meclomen)	3.91 ± 0.54	na

na - data not available

1 - Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *American Journal of Medicine* 1998;105(1B):31S-38S.

2 - Taketo MM. Cyclooxygenase-2 inhibitors in tumorigenesis (Part 1). *Journal of the National Cancer Institute* 1998;90:1529-1536.

As early as April 1996, Searle said that celecoxib is "without the side effects associated with currently available agents." Pfizer, which has invested $140 million in a co-marketing agreement with Searle/Monsanto for this drug seemed quite confident, according to an August ABC News story, referring to statements made by Pfizer at a July, 1998 session with Wall Street financial analysts, that "Celebrex would be able to win FDA permission to claim on its label that its side effects are less than those of NSAIDs."

SmithKline Beecham are the makers of nabumetone (Relafen), an NSAID they call a "preferential" COX-2 inhibitor. SmithKline Beecham maintains that COX-1 and COX-2 have overlapping functions, which is probably the case, and that a high degree of COX-2 selectivity is not necessarily predictive of safety, which also is probably true. This has led SmithKline Beecham to their own revised hypothesis. For an anti-inflammatory effect it may be advantageous to inhibit both COX-1 and COX-2 enzymes. According to this theory, COX-2 plays a role in tissue repair, such as ulcer repair, and in skin integrity and could also contribute to the control of blood flow in the kidneys. In other words, not surprisingly SmithKline Beecham maintains that dual COX inhibition may be preferable. Medical theory often depends on what drug you are selling.

The FDA found SmithKline Beecham in violation of the Food, Drug and Cosmetic Act on two occasions for the false and misleading advertising that because nabumetone is a preferential COX-2 inhibitor it was safer than other NSAIDs. The company was required to send a letter to health professionals saying that it had no valid data to support their claim that nabumetone was less toxic to the GI tract, was safer for the kidneys, and caused less bleeding problems than other NSAIDs.