

# Discussion Cryer Paper – GI Toxicity

## JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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### Highlights

- **TWO-THIRDS REDUCTION IN GI ULCER COMPLICATIONS SINCE 1990:** Dr. Woods (Chairman) pointed out that Dr. Cryer showed a slide illustrating high GI ulcer complication rates through 1990, but that Dr. Fries had published data through the year 2000 showing that ulcer complications have been reduced by two-thirds since 1990, and that this decrease preceded the introduction of COX-2 inhibitors. Dr. Cryer agreed.
- **CLASS STUDY REDUCED GI COMPLICATIONS AT 6 MONTHS BUT NOT 1 YEAR:** Dr. Woods also pointed out the apparent loss of GI protection of celecoxib 400 mg bid v. diclofenac by one year of therapy in the CLASS study. Dr. Cryer agreed. Dr. Cush asked a subsequent question on this issue and Dr. Cryer said that “there does appear to be a plateauing” in event reduction which could be related to early dropout of the most vulnerable patients. Dr. Fleming pointed out that in the CLASS trial celecoxib after 6 months reduced GI complications in non-aspirin patients (by two-thirds) but not in patients on aspirin (aspirin therapy not being randomized but given if clinically indicated); however, at one year this effect in non-aspirin patients had disappeared, suggesting that the GI complications are delayed but not prevented in this subset. Again, Dr. Cryer said that “susceptible people” are removed from the study early. Dr. Cryer was asked about the choice of diclofenac as the celecoxib comparator, as diclofenac appears moderately COX-2 selective. Dr. Cryer said that studies have been completed but not yet published showing that celecoxib and naproxen plus a proton pump inhibitor (PPI) have similar GI effects.
- **PREDICTORS OF HIGH RISK OF GI COMPLICATIONS:** Dr. Cryer said that the most important risk factor was a history of a previous GI bleed, and that PPI therapy did not reduce this risk in NSAID users. Next in importance was anticoagulant therapy such as warfarin. Age was also an important risk factor but the effect was “variable”; risk increases about 2% per age decade so that most patients in their 80s are at increased risk. The more risk factors a patient has, the higher the risk. Dr. Cryer did not

provide definitions for “low”, “medium” and “high” risk but said that about 20-25% of patients are at elevated GI risk and suitable candidates for COX-2 inhibitors.

- **MORBIDITY/MORTALITY ASSOCIATED WITH GI COMPLICATIONS:** Dr. Cryer was asked how dangerous NSAID-induced GI complications were. He replied that a significant GI bleed requires hospitalization and can be fatal. However, most “are reversible”.
- **INITIAL HIGH GI RISK MAY BE REDUCED OVER TIME:** Dr. Cryer was asked if patients considered at high GI risk who show no GI complications by 1 year can be considered no longer at high risk. Dr. Cryer replied that the data were not consistent but that the highest risk occurred in the first 3 months.
- **COXIB GI COMPLICATIONS VS. NON-SELECTIVE NSAIDS WITH LOW-DOSE ASPIRIN:** Dr. Nissen (cardiologist) said that he routinely gives low dose aspirin to patients at elevated cardiac risk and asked if COX-2s were GI protective

in this setting. Dr. Cryer said that the data were not clear but that GI events in this population were too high for us to be “comfortable”.

- **NSAID DYSPEPSIA:** In response to a question, Dr. Cryer said that NSAID dyspepsia was common (10-30%, depending on the definition) and that dyspepsia was not correlated with major GI complications. Although patients could discontinue therapy because of dyspepsia, it was considered more of a “nuisance”. Trials suggested that COX-2s reduced dyspepsia vs. NSAIDs “by a few percentage points” but results were not consistent.
- **LOWER GI COMPLICATIONS:** Dr. Cryer said that a COX-2 (Vioxx vs. naproxen) reduced lower GI endoscopic erosions whereas PPIs did not. These erosions are probably not clinically significant, although chronic reduction in hemoglobin could be an important result of lower GI erosions. In population studies, about 10-20% of clinically relevant GI complications of NSAIDs were in the lower GI tract.

## Discussion Text

DR. WOOD: Thank you very much. Byron, could you just stay there in case there are specific questions for you while the slides are up? I have one. Could you put up slide 4 again? That shows data through 1990.

DR. CRYER: Yes.

DR. WOOD: What surprised me is Jim Freis has updated that data through 2000, and that dramatically changes

what that slide looks like. In fact, he found a 67 percent decline since 1990 in complicated ulcers, the vast majority of which occurred actually before COX-2 specific inhibitors went on the market. So, I am interested, first of all, in why you chose to present 15-year old data when there is new data out there that contradicts that, and whether you would like to comment on his publications from which this data came as well.

DR. CRYER: Sure. It is correct that there are newer data available that have demonstrated a reduction in gastrointestinal bleeds on a population basis. On the other hand, it is also very true that this problem of gastrointestinal bleeding with NSAIDs continues to be a significant problem despite its more recent decline. But, more importantly, he also highlighted a very important observation which is that the declines in gastrointestinal bleeding that have been seen in populations preceded the introduction of COX-2 specific inhibitors, and there are some data sets to suggest, at least in the U.S., that hospitalizations for gastrointestinal bleeding since the introduction of COX-2 specific inhibitors have not markedly declined compared to hospitalizations prior to their introduction.

DR. WOOD: Right. So, most of the 67 percent decline occurred before these drugs went to the market, and that 67 percent occurs from the points on your slide here.

DR. CRYER: Point well taken.

DR. WOOD: And one other point of clarification I guess, the data you showed from CLASS, was that data from the predefined endpoint of the study at 18 months or the 6-month analysis that was published?

DR. CRYER: Just for sake of review, I have pointed out both time-dependent endpoints. The endpoint that was published and shown here, in the JAMA, was the predefined 6-month data and the endpoints that are shown here represent an evaluation of the entire data set. There are clearly differences in the conclusions about the effects of

celecoxib which varied by time and varied by whether one evaluates the data at 6 months or evaluates the entire data set.

DR. WOOD: Just remind us, at 18 months what did the data set show?

DR. CRYER: At 13 months the data, with respect to complications, indicate that there was no statistically significant reduction in upper gastrointestinal complications associated with celecoxib, at a dose of 400 twice daily, when compared to either diclofenac or ibuprofen individually or when compared to both of them together. I will point out for the sake of fair balance that this data does include the 21 percent of individuals who were taking low doses of aspirin.

DR. WOOD: Other questions from the committee? Dr. Nissen?

DR. NISSEN: Yes, this 1-4 percent rate, I am interested in understanding the time-dependent hazard. If a patient is put on a non-selective NSAID and, let's say, for the first year has no GI events, is the risk in the second and third and fourth years the same as it is in the first year? In other words, once you know that a patient is tolerating an NSAID are they no longer at high risk?

DR. CRYER: There are a few answers, sub-answers to that question. It is a complicated discussion. What is clear that risk persists, that even in the individual who did not develop a complication in year one, that individual continues to have risk in subsequent years--two, three, four, etc. There are data sets that suggest that the period of highest susceptibility, highest risk is

within the first three months of administration. Having said that, there are other data sets to the contrary. This incidence of gastrointestinal events that are time-dependent in individuals has been difficult to assess primarily based upon a concept of selection of susceptible individuals. People drop out because of other reasons such as dyspepsia. So, it is difficult to get a firm estimate on that. But it is clear, in summary, that the risk after one year or after any period of time is always persistent as long as the NSAID exposure is present.

DR. NISSEN: Two more quick questions. I didn't see any analysis of COX-2 plus low dose aspirin versus a non-selective NSAID plus low dose aspirin. The reason I am asking that is that, as a cardiologist, in my patients who are taking conventional NSAIDs, if they need aspirin for cardiovascular prophylaxis I give them aspirin. So, the question is: Are there any studies looking at NSAID plus aspirin versus COX-2 specific inhibitor plus aspirin?

DR. CRYER: Well, the CLASS trial addressed that question in a subpopulation of individuals which was under-powered statistically to give a definitive answer to that question. That is an ongoing debate within the medical communities. I will say, however, that while the debate continues what is clear is that with either approach COX-2 specific inhibitor plus aspirin or non-selective inhibitor plus aspirin the ensuing rates of gastrointestinal events are too high for us to feel comfortable that we have risk-reduced those patients sufficiently.

DR. NISSEN: And a final question, symptoms of dyspepsia are obviously one of the issues as well, and I want to make sure I understand what fraction of the population, let's say an osteoarthritis population, simply cannot tolerate NSAIDs because of GI discomfort. Do we have data on that?

DR. CRYER: Sure. A couple of comments about dyspepsia which I didn't mention, NSAID dyspepsia is common. Its prevalence varies depending on how dyspepsia has been defined in trials, and because there have been variable definitions of dyspepsia, its reported rates have varied anywhere from 10-30 percent of NSAID users, but it is clearly more common than complications. In the patient who has dyspepsia, the presence of dyspepsia is not predictive of the patient who might have risk. In most of these studies dyspepsia, in my way of thinking, is considered more of a nuisance issue that can be controlled symptomatically with acid reduction rather than something that presents significant gastrointestinal concern.

DR. WOOD: Dr. Gibofsky?

DR. GIBOFSKY: You commented extensively on the upper GI risk but in your second slide you correctly pointed out that there are problems with traditional medications affecting the structures of the GI tract below the ligament of triads. Could you comment somewhat on the data comparing the effect of COX-2 specific inhibitors versus traditional non-steroidals with or without proton pump inhibitor protection on the lower GI tract?

DR. CRYER: There have been fewer data sets which have assessed the lower gastrointestinal events with NSAIDs. A few comments on the types of studies that have been done, there have been studies using pill endoscopy which have indicated that lesions, endoscopic ulcers and erosions occur in the lower gastrointestinal tract contributed to by non-selective NSAIDs, an effect which can be reduced by a COX-2 specific inhibitor, an effect which is not reduced by the co-therapy approach of adding a PPI to a non-selective NSAID. I am speaking of the lower gastrointestinal effects. Having said that, again similar to the endoscopic ulcer story, these endoscopically detected lesions in the lower gastrointestinal tract probably have very limited clinical relevance. When lower gastrointestinal clinically significant events have been assessed from the prospective trials, the one noted most commonly in the literature is an assessment of the VIGOR trial looking at the effects of rofecoxib compared to naproxen, in which case a 40-50 percent reduction was seen in lower gastrointestinal events with rofecoxib compared to naproxen, again to reiterate, a reduction which would not be expected to be observed with the proton pump inhibitor approach. Having said that, in that assessment of the rofecoxib experience there was an inclusion in the definition of lower GI events of individuals who had had reductions in hemoglobin and hematocrit and who did not otherwise have clinically apparent gastrointestinal bleeding. Probably the best assessment in terms of the risk of lower gastrointestinal events on NSAIDs comes from population-based observational studies. While there is variance in that estimate, it looks like the lower gastrointestinal events probably

contribute 10-20 percent of clinically relevant events when compared to all GI events that might happen on NSAIDs.

DR. GIBOFSKY: One last quick point, would you recognize that there might well be a population of patients whom you would stratify as low GI risk who, nevertheless because of either intolerance, as the last speaker asked, or lack of efficacy to traditional non-steroidals, would be candidates for another class of agents?

DR. CRYER: Sure. Their NSAID dyspepsia is a common phenomenon. I will say that when dyspepsia has been carefully evaluated in the prospective trials of COX-2 specific inhibitors in general there tends to be a reduction in the rates of dyspepsia associated with the COX-2 specific inhibitors. However, when one evaluates the absolute reduction in rates of dyspepsia in the trials it generally tends to be a few percentage points. Finally, some of the other strategies that were mentioned to accomplish risk reduction, for reduction in GI events in patients on NSAIDs, also accomplished reductions in dyspepsia in patients who might experience NSAID-related dyspepsia.

DR. WOOD: Dr. Cush?

DR. CUSH: Byron, two time questions. One, is there a time point at which peptic ulcerations and bleeds plateau over time in NSAID users or COX-2 users? Second, what is the longest data set that we have as far as the use of a COX-2 agent in a clinical trial where observation is carried out? Do we have two-year data; five-year data?

DR. CRYER: Right. There does appear to be some plateauing of the effect. The data sets do suggest that after long-term exposure the rates of events with longer-term exposure are not as great as rates of events with initial exposure to NSAIDs but, again, that may be attributable to the phenomenon of dropping out of susceptibles. The second portion of your question, Jack, was?

DR. CUSH: What is the longest data set we have on COX-2 agents?

DR. CRYER: Well, when one looks at the trials, the prospectively defined outcome trials--we have CLASS, TARGET, VIGOR--there are periods of observation out to 13 months. Having said that, we certainly have longer periods of observations of COX-2 specific inhibitors for trials in which the specific outcome of interest was defined for an endpoint that was other than upper GI bleeding, so specific polyp reduction, Alzheimer's disease, other trials that we certainly will hear about over the course of the next few days, many of which have gone out to periods as much as 3 years.

DR. WOOD: Is there anyone else who has a question that specifically addresses something on a slide that the speaker could show again? If not, we will come back to these questions and ask you, Byron, if you would, to be available this afternoon.

DR. CRYER: Yes.

DR. WOOD: Are there any questions that somebody has specifically? Tom?

DR. FLEMING: Yes, could we go back to the slide that showed the CLASS trial with the time to complicated ulcer?

DR. CRYER: There were two. You can tell me which one you are referring to, this or the next?

DR. FLEMING: Both, this and the next. Basically, here what you are showing us is that in the presence of aspirin there doesn't seem to be a reduction in the complicated ulcers although in those that are not taking aspirin there is this reduction of about two-thirds. If you go to the next slide, that is at 6 months. Hence, we see at 6 months this reduction in the rate in the celecoxib group that is driven by those patients who are not on aspirin. But that effect, as you noted, has disappeared out at a year. I know that is making a lot of a single data set but is this suggestive of the possibility that, in response to Steve Nissen's question, there could be a group that is more susceptible and what you are doing, in the presence of aspirin, is achieving not effect; in the absence of aspirin you are achieving a delayed effect but, in essence, you are going to have the same overall incidence by a year even with the COX-2 specific inhibitor?

DR. CRYER: Sure, your point is that there are likely subgroups of susceptibility for GI risk on NSAIDs or on COX-2 specific inhibitors. But I would say also that underlying that argument, which I think is accurate, is the observation which confounds the whole discussion, which I have mentioned previously, which is that early on in any of these trials you are going to remove the most susceptible of the individuals and those who actually

persist in the trial tend to be the least susceptible subpopulation.

DR. FLEMING: Indeed, but that is the essence of what I am saying, and this would be consistent then with the theory that if there is a particular susceptible group, that group is going to have a higher risk and it is, in fact, going to have complicated ulcers. They just occur somewhat sooner with the non-specific NSAIDs. The COX-2s are not preventing that, they are just delaying the time to the occurrence.

DR. CRYER: I think we are in agreement there.

DR. WOOD: Richard?

DR. PLATT: To extend that, on slide 13 you list some risk factors for NSAID-associated GI toxicity. Can you tell us how well those discriminate low risk individuals from high risk individuals? And, if they do, what fraction of the population falls into low risk, medium risk, high risk? And, quantitatively what are those risks?

DR. CRYER: That is a complicated question but it is an important one. When people like myself have shown these risks we commonly lead to the assumption that these risk are numerically equivalent, which they are not. There are certain risk factors which clearly place one individual at higher risk than others. The highest risk most consistently seen in trials would be that of having had a previous history of a gastrointestinal bleeding ulcer. But not far behind that would be the risk of taking an anticoagulant, such as Coumadin, in association with a non-selective NSAID. Age as a risk factor is

a variable one. Although we suggest in our discussions of this that there may be a threshold of age below which one may be not at risk and above which at risk for having it. In fact, it is a continuum. In fact, the risk contributed by age is about a 2 percent increase in risk per decade of life, such that people who are in their 80s are at very high risk, much higher risk than people who are in their 40s. With respect to your question of quantifying the risk in a population, that is a difficult issue because all of these risk factors do not individually present themselves in any one patient. The more risk factors one has--two risk factors present greater risk than one; three greater than two. I would say, having said that and trying to give you a reasonable estimate, in my opinion the percentage of NSAID users who would likely be candidates for this is probably somewhere on the order of 20-25 percent, depending on how one assesses that. If one looks at an OA or RA population and concludes that age in and of itself is a risk factor, then you are close to 80 or 90 percent of the population that might be at risk based upon that risk factor of age. So, it really depends on which risk factor, and it really depends on the quantitative contribution of the risk factor being described. But, certainly, I would say the one that most clearly and consistently has presented itself as highest risk in the various trials has been the risk factor of having had a previous bleeding ulcer, and it is the one that I would like to underscore which does not appear to be sufficiently risk-reduced by either of the strategies which we have available.

DR. WOOD: Any other questions that are so burning that they have to be asked now and not the discussion? Ralph?

Burning? And let's try and make the answers as brief as we can.

DR. D'AGOSTINO: What are the consequences of complicated ulcers in, say, the CLASS trial where you do see this differential and this catching up? Do they follow to see the consequences of these ulcers? Were they different over the time period?

DR. CRYER: I am sorry, I don't understand.

DR. D'AGOSTINO: What are the consequences? What happened to these subjects after? Were they reversible, the ulcer? Does it lead to mortality?

DR. CRYER: Right, what I assume is driving your question is whether there are differences in mortality—

DR. D'AGOSTINO: Well, morbidity, mortality, what happens.

DR. CRYER: Well, clearly, morbid effects are hospitalization and the complications of them having a massive gastrointestinal bleed, which can be several. The ultimate complication or consequence of these morbid effects is mortality and in these outcome trials there were no differences in the level of mortality. With regard to the various other consequences, most of them are clearly going to be reversible after having suffered a significant hospitalization.

DR. WOOD: Any other smoking questions? Peter?

DR. GROSS: A question on the third to last slide, on recurrent ulcer bleeding in high risk patients, the so-called non-

selective NSAIDs selected diclofenac to compare with celecoxib.

DR. CRYER: Yes.

DR. GROSS: Diclofenac is roughly comparable in COX-2 selectivity. Is that the right drug to test with PPI to show that the PPI plus a non-selective NSAID is comparable to a COX-2 inhibitor like celecoxib? Should they have picked a non-selective NSAID that was less selective for COX-2?

DR. CRYER: Sure. Your point is very well taken and it is one which I tried to underscore throughout the talk, which is that there are clearly differences in the COX-1, i.e., ulcerogenic, effects of non-selective NSAIDs. Diclofenac clearly is an agent which is associated with a lower rate of gastrointestinal ulceration and complications than non-selective NSAIDs. So, in this evaluation of the comparison of diclofenac plus omeprazole compared to celecoxib there is a valid discussion that the results may have been biased in favor of the diclofenac plus omeprazole approach. The reason I showed that is that that was a fully published paper. There are, however, other trials not yet fully peer reviewed, which have been presented in the gastrointestinal community, looking at other NSAIDs, such as naproxen plus a proton pump inhibitor compared to the COX-2 specific inhibitor approach, and the results of those observations again are comparable endpoints between the two strategies.

DR. WOOD: I am going to move us on now and we will come back after the next talk. Dr. Cryer, we would like you to come back up if there are questions at that time as well.