Food and Drug Administration
Center for Drug Evaluation and Research

Arthritis Advisory Committee

Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, MD

(Draft) Agenda
February 7, 2001

NDA # 20-998/S009, Celebrex™ (celecoxib, Searle)

8:00 Call to Order and Introductions: E. Nigel Harris, M.D., Acting Chair
Meeting Statement: Kathleen Reedy, Executive Secretary

8:15 Welcome and Introduction: Jonca C. Bull, M.D., Acting Director,
Division of Analgesic, Anti-Inflammatory and Ophthalmologic Drugs

8:25 Regulatory and Scientific Background: James P. Witter, M.D., Ph.D.
Division of Analgesic, Anti-Inflammatory and Ophthalmologic Drugs

8:45 G. D. Searle and Company Presentation

10:15 Break

10:30 FDA Presentation
GI: Lawrence Goldkind, M.D.
Medical: James P. Witter, M.D., Ph.D.

11:30 Open Public Hearing:
Sidney M. Wolfe, M. D., Director, Public Citizen's Health Research Group

12:00 Lunch

1:00 Discussion and Questions:

4:30 Summary and Review

5:00 Adjourn

Food and Drug Administration
Center for Drug Evaluation and Research

Arthritis Advisory Committee

Gaithersburg Holiday Inn, 2 Montgomery Village Avenue, Gaithersburg, MD

(Draft) Questions
February 7, 2001

NDA # 20-998/S009, Celebrex™ (celecoxib, Searle)

1. **Has a clinically meaningful safety advantage been established for Celebrex compared to ibuprofen and/or diclofenac? Please respond specifically for UGI safety and separately for global safety.**

2. **In subjects taking low dose aspirin there was a reverse trend in results for both the complicated ulcer as well as combined complicated and symptomatic ulcer endpoints. Does there appear to be a safety signal in this database regarding concomitant use of COX-2 selective agents and aspirin?**

3. **Are further studies warranted regarding concomitant aspirin and COX-2 selective/ traditional NSAIDs?**

4. **Considering the results of the CLASS trial, do the current NSAID related target organs for toxicity in the current NSAID template remain applicable? (GI, renal/fluid retention, hepatic and skin). See attached template. Please discuss.**

This report contains public information that has not been reviewed by the agency or the Arthritis Advisory Committee. The official summary minutes will be prepared, circulated, and certified as usual. Transcripts will be available in about 10 days. External requests should be submitted to the Freedom of Information office.

The Arthritis Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on February 7, 2001 at the Holiday Inn Gaithersburg, 2 Montgomery Village Avenue, Gaithersburg, MD.

The Committee discussed New Drug Application (NDA) 20-998/S009, Celebrex ® (celecoxib, G. D. Searle & Company) approved for the treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis in adults. The discussion is for modification of the label based on the results of the CLASS Trial, a study of the incidence of significant upper gastrointestinal effects.

The Committee had received a briefing document from both Searle & Company and the FDA Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products. There were approximately 200 persons in the audience.

The meeting was called to order at 8:00 am by E. Nigel Harris, M.D., Acting Chair. The Meeting Statement was read by Kathleen Reedy, Executive Secretary of the Arthritis Advisory Committee. The Committee members, consultants and discussants introduced themselves. A welcome was extended by Jonca C. Bull, M.D., Acting Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products.

The regulatory and scientific background of the cox-2 inhibitor drugs was presented by James P. Witter, M.D., Ph.D., Medical Officer in the Division of Analgesic, Anti-Inflammatory and Ophthalmologic Drugs.

The G. D. Searle and Company Presentation was as follows:

Introduction: Philip Needleman, Ph.D., Senior Executive VP
Chief Scientist and Chairman, Research and Development

UGI Safety Profile of NSAIDS and Celecoxib: Rationale for CLASS Study:
G. Steven Geis, M.D., Ph.D., Vice President, Arthritis, Clinical R & D

Safety Profile of Celecoxib: CLASS, Long Term Safety Trial: James Lefkowith, M.D.
Senior Director, Arthritis, Clinical R & D

Summary: Fred Silverstein, M.D., Chairman, CLASS Executive Committee

The FDA Presentation consisted of:

GI: Lawrence Goldkind, M.D.
Medical: James P. Witter, M.D., Ph.D.
Division of Analgesic, Anti-Inflammatory and Ophthalmologic Drugs

The only speaker for the Open Public Hearing was Sidney M. Wolfe, M. D., Director, Public Citizen's Health Research Group.

The following questions about Celebrex™, celecoxib were addressed by the Committee.

1. **Has a clinically meaningful safety advantage been established for Celebrex compared to ibuprofen and/or diclofenac? Please respond specifically for UGI safety and separately for global safety.**

   There is not a proven clinically important safety advantage in upper gastrointestinal events globally. A minority subgroup without aspirin ingestion showed some advantage, but not comprehensively.

2. **In subjects taking low dose aspirin there was a reverse trend in results for both the complicated ulcer as well as combined complicated and symptomatic ulcer endpoints. Does there appear to be a safety signal in this database regarding concomitant use of COX-2 selective agents and aspirin?**

   The majority opinion was maybe (6), definitely yes (3), firmly between yes and maybe (1), and no (2). After a discussion of statistics, it was agreed the may be a trend of a population at risk.

3. **Are further studies warranted regarding concomitant aspirin and COX-2 selective/ traditional NSAIDs?**

   Yes and several designs were suggested. 2 x 2 factorial; COX-2 vs placebo with and without aspirin longer than 6 months. Aging populations with comorbidities, thrombotic complications. Head to head with multiple NSAIDs. Distinct specific endpoints, duration, dosage, comparator stability were discussed.

4. **Considering the results of the CLASS trial, do the current NSAID related target organs for toxicity in the current NSAID template remain applicable? (GI, renal/fluid retention, hepatic and skin). See attached template. Please discuss.**

   Yes. Suggestions included: adding hypercalemia to ace inhibitor section; broaden range of specific ulcer occurrence at 6-12 months; patient profile of increased coronary heart disease risk; addressing platelet inhibition.

The meeting was adjourned at 3:30 pm.

The Immunex Corporation presentation began at 8:10 am and proceeded as follows.

at

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

*****

ARTHRITIS ADVISORY COMMITTEE

NDA 20-988/S009, Celebrex, (celecoxib, Searle)

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service; the Food and Drug Administration makes no representation as to its accuracy.

Wednesday, February 7, 2001

8:00 a.m.

Holiday Inn Gaithersburg
Two Montgomery Village Avenue
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
735 8th Street, S.E.
Washington, D.C. 20003-2802
(202) 546-6666

PARTICIPANTS

E. Nigel Harris, M.D., Acting Chairperson
Kathleen Reedy, Executive Secretary

MEMBERS
Leigh F. Callahan, Ph.D.
James H. Williams, Jr. M.D.

CONSUMER REPRESENTATIVE
Wendy McBrair

CONSULTANTS AND EXPERTS

ARTHRITIS ADVISORY COMMITTEE CONSULTANTS
Janet D. Elashoff, Ph.D.
David Wofsy, M.D.

CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEMBERS
Steven Nissen, M.D., F.A.C.C.
Ileana Pina, M.D.

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE MEMBER
M. Michael Wolfe, M.D.

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE
MEMBER
Allan R. Sampson, Ph.D.

OFFICE OF BIOSTATISTICS CONSULTANT
Frank E. Harrell, Jr., Ph.D.

GUEST EXPERTS
Byron Cryor, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

HARRIS: I would like to call the session to order. My name is Nigel Harris. I am Dean and Senior Vice President for Academic Affairs at Morehouse School of Medicine and I am also a rheumatologist.

Before we do the introductions, I am going to ask Ms. Reedy to read the statement.

Meeting Statement

MS. REEDY: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions; in accordance with 18 United States Code 208(b), full waivers have been granted to Drs. Frank Harrell, Steven Nissen, Ileana Pina, M. Michael Wolfe and Allan Sampson.

Copies of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office located in Room 12A30 of the Parklawn Building.

We would, however, like to disclose for the record that Dr. Steven Nissen, Ileana Pina, H. James Williams and M. Michael Wolfe have interests which do not constitute a financial interest within the meaning of 18 United States Code 208(a) but which create the appearance of a conflict.

The agency has determined, not withstanding these interests, that the interest of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Drs. Nissen, Pina, Williams and Wolfe may participate in today's discussion of Celebrex.

With respect to FDA's invited guest expert, there are reported interests which we believe should be made public to allow participants to objectively evaluate his comments. Dr. Byron Cryer would like to disclose that, in 1997, he received a research grant from Merck to conduct a small clinical study on rofecoxib. He has received consulting and speaker fees from G.D. Searle, Pfizer and Merck for work on celecoxib and rofecoxib. Additionally, he has previously been a consultant for SmithKline Beecham and Ortho McNeil.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves

from such involvement and their exclusion will be noted for the record.

With respect to all participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

I might add that the waiver criteria can be found at the FDA's site on the Web. I won't quote the law. That is too long.

DR. HARRIS: Thank you.

We can now begin with our introductions. I will start on my left with Dr. Cryer. If you can give your name and where you are associated

DR. CRYER: Byron Cryer, University of Texas, Southwestern Medical School, Dallas, Texas.

DR. WOLFE: Michael Wolfe, Boston University School of Medicine, Boston, Massachusetts.

DR. PINA: Ileana Pina, Case Western Reserve University, Cleveland, Ohio, Cardiology.

DR. NISSEN: Steven Nissen, Cardiologist, Cleveland Clinic, Cleveland, Ohio.

MS. McBRAIR: Wendy McBrair, Southern New Jersey Regional Arthritis Center at Virtua Health in New Jersey.

DR. WOFSY: David Wofsy, University of California, San Francisco, Rheumatology.

DR. CALLAHAN: Lee Callahan, University of North Carolina, Chapel Hill, Department of Orthopedics.

DR. HARRIS: I repeat that I am Nigel Harris, Morehouse School of Medicine, and Dean, Senior Vice President for Academic Affairs. And I should add, a rheumatologist.

MS. REEDY: Kathleen Reedy, Food and Drug Administration, Advisory and Consultants Staff.

DR. WILLIAMS: James Williams, University of Utah, Rheumatology.

DR. SAMPSON: Allan Sampson, Department of Statistics, University of Pittsburgh and currently on sabbatical as a visiting scholar, Department of Family Preventive Medicine, University of California at San Diego.

DR. ELASHOFF: Janet Elashoff, Biostatistics, Cedars-Sinai Medical Center and UCLA.

DR. HARRELL: Frank Harrell, Biostatistics, University of Virginia School of Medicine. I am a Consultant to CDER Biostatistics.

DR. WITTER: Jim Witter from the FDA.

DR. GOLDFIND: Larry Goldfind, FDA.

DR. BULL: Jonca Bull, FDA.

DR. DeLAP: Robert DeLap, FDA.

DR. HARRIS: Thank you.

We will now hear from Dr. Jonca Bull who will give

welcome and introduction.

Welcome and Introduction

DR. BULL: First of all, welcome. Thank you very much to our committee for coming here this morning. Please know how much we appreciate your willingness to share your time and your intellect to assist us in our deliberations on these important topics over the next two days.

Can we ever know enough about the safety of a drug? Can we ever know enough about the safety of drugs that have had widespread acceptance in the marketplace where rare events can become numerically significant numbers.

We are here today as part of a continuum of discussion on the safety profiles of two drugs that were approved in 1999 and that have literally had, I think, one of the most--as, I think, an article in USA Today asserted, some of the most successful launches of drugs in U.S. pharmaceutical history.

We ask that you deliberate carefully, think broadly and, again, welcome.

I would like to introduce Dr. Jim Witter who will be providing for you a regulatory and scientific background in the issues that we will be discussing over the next two days. Thank you.

MS. REEDY: I might comment that our podium is in this position for electronic reasons. We apologize for any

inconvenience.

Regulatory and Scientific Background

DR. WITTER: Good morning.

[Slide.]

I would like to thank, especially the members of the advisory committee, for taking time from their busy schedules to be here.

The discussion for the next two days, then, will focus primarily on the question of whether Cox-2 agents, as currently recognized by the division, are safer than Cox-2 nonselective agents, commonly called nonsteroidal antiinflammatory drugs or NSAIDs. In fact, some discussion will focus on whether these Cox-2 agents were studied at 2X dose and, if so, whether these superphysiologic doses are safer than NSAIDs at their conventional doses.

To help address the various aspects of safety, large and simple trials were conducted by both sponsors. The division is aware that it is not often that meetings to discuss issues of safety postapproval are discussions of improved safety. More often, it is, in fact, the opposite. So this is going to be a welcome discussion for the next two days.

[Slide.]

We thought it would be useful to set this in context. There is a rich history in this area and so we

thought a few minutes to set aside to put that in some kind of--put this meeting in context would be useful.

As we know, acetylsalicylate, also known as aspirin, was first synthesized and sold in 1899. About forty years later, there was the first evidence by endoscopy that this compound could damage the upper GI tract. About 30 years or so later, we started seeing the new safer NSAIDs being developed and approved.

In 1992 was the first widely held idea that Cox-2 was discovered, that, in fact, there was yet another target for these enzymes. Before that time, we thought there was just a single target. In 1998, we had the first advisory committee for the first Cox-2 and it was approved in that year. Today, we are discussing the first large and simple safety trials.

[Slide.]

The FDA has also been involved with the help of the commit

tee, as today, for quite a while. Back in December of 1986, we discussed the databases that went into the formulation of the GI paragraph. In October of 1995, there was a series of two-day meetings where we discussed the revision of the NSAID class label and also had a citizen petition for the removal of peroxicam from the marketplace.

In March of 1998, we had, before the approval of

any of these compounds, a meeting to discuss some of the safety issues that we felt were emerging with these particular compounds. As said before, in December of 1998, we had the advisory committee for Celebrex followed shortly thereafter, in April of 1999, by the advisory committee for the approval of Vioxx and then today and tomorrow, again, the long-term safety studies with these compounds.

[Slide.]

As mentioned, and what I will do is use the previous slide as kind of the focus for the rest of the talk, the GI paragraph, as it exists, points out to us that there are serious GI toxicities associated with these compounds and they can occur both with and without warning to the patients.

Only one in five, or about 20 percent, who develop these serious upper GI events, have any kind of warning symptoms. The GI paragraph notes that patients at risk include those who have a history of prior ulcer or a bleed, are older, are on certain medications or who are in poor health.

It notes that these trends basically continue and that the best way to minimize the risk is to use the lowest dose for the shortest period of time.

[Slide.]

The events that are referred to are often referred

to as clinically relevant events in terms of the upper GI tract and, as stated, again in the GI template and the GI paragraph, it has been demonstrated that upper GI ulcers, gross bleeding or perforation caused by NSAIDs appear in approximately 1 percent of patients treated for three to six months and in about 2 to 4 percent of the patients treated for one year.

In fact, estimates from the ARAMIS database note that NSAID-induced gastropathy may result in 107,000 hospitalizations and 16,500 deaths on an annual basis.

[Slide.]

So NSAIDs have a certain safety toxicity profile which we have become familiar with. As I have indicated, they are both dose and duration dependent and they involve a variety of organ systems and are reported to us as adverse events, either mild, moderate or severe, as serious adverse events or as deaths.

[Slide.]

The NSAID template, then, is a more general structure for how we write these labels for NSAIDs. It describes, among other things, precautions, warnings and adverse reactions involving, as we just discussed, the GI tract, but also the liver, the kidney. It describes anaphylactoid reactions, immunologic effects, effects on skin and others.

[Slide.]

The template, in terms of the liver, notes the metabolic effects of hepatic insufficiency. It notes elevations of the enzymes and sometimes, in 1 percent of the cases, it notes that these can occur up to three times the upper limit of normal. It also points out that there are rare cases of severe reactions involving jaundice, fulminant hepatitis, liver necrosis and hepatic failure and, in fact, some of these can be fatal.

[Slide.]

It notes, in terms of the kidney, that there are certain pharmacodynamic effects of renal failure or dehydration, that these compounds can have effects on blood pressure, particularly with regards to hypertension, that these compounds, NSAIDs, can cause fluid retention and edema in some settings and can be associated, again, with severe reactions such as renal papillary necrosis, interstitial nephritis and renal failure.

[Slide.]

In terms of skin, the template notes that there are reactions such as photosensitivity, urticaria and severe reactions including Stevens-Johnson syndrome, toxic epidermic necrolysis and erythema multiforme which, again, can be fatal.

[Slide.]

For the safety risks, what are the benefits. The efficacy of NSAIDs can be summarized as follows. For OA, they have been indicated for the treatment of osteoarthritis. This is for the signs and symptoms, not for structure or disability as it currently exists in the draft OA guidance document.

NSAIDS are also indicated for the treatment of rheumatoid arthritis, again for the signs and symptoms not for structure or improvement in function or remission claims as exist in the current RA guidance document. They are indicated for acute pain and dysmenorrhea as well as other indications such as ankylosing spondylitis, gout, among others.

[Slide.]

As indicated, there has always been a lot of hope surrounding the Cox-2 field. In fact, in the Wall Street Journal, in '96--this has been shown before at a prior meeting--it was thought that these compounds could not only ease pain but actually slow the disease's debilitating progression. So there has always been a lot of excitement.

As indicated, we had a meeting before approval of any of these compounds back in March of 1998. Primarily, it was to discuss the safety issues and what we were hoping would be the approved safety profile of these types of compounds. And then, as now, we presented to our committee

certain questions.

For example, we asked them to comment about the degree to which endoscopic studies can distinguish between the currently available NSAIDs and the degree of correlation with clinical outcomes. Some of the comments at that time were that endoscopic studies were generally underpowered to answer these questions we had posed, that the measurable--in this case the endoscopic--might drive out the important--in this case, the clinical outcomes.

There was a discussion about the role of endoscopy as a surrogate--how it might turn out to be for the long-term outcomes of interest.

[Slide.]

We, at that meeting, discussed, then, in terms of the GI warning, what kind of changes might be effected with the Cox-2 agents. We discussed, for example, would removal require the concept of equivalence to placebo, which would have to be mutually defined and agreed to, or, if we could be discussing a major revision, what would that include; for example, substantial reproducible evidence of superiority over NSAIDs and that would include, undoubtedly, endoscopic and clinical endpoints.

The discussion was how many NSAIDs would it take. Would it take three? And we would have to obviously agree on which NSAIDs we decided to study.

[Slide.]

At that meeting, we also discussed the importance of words--for example, the idea of being equivalent to placebo. We had a rather lengthy discussion about saying that two treatments are similar does not necessarily mean that they are the same. From a statistical standpoint, failing to show a difference is not showing equivalence. In fact, equivalence requires that the hypothesis, treatment X and Y are different, be rejected in a trial designed specifically for that purpose. And we talked about that.

[Slide.]

We also talked about whether we could best view the potential safety advantage of Cox-2 agents on a mechanistically based origin. For example, on one extreme where Cox-2 was felt not to be present in the platelets, we would have one result. On the other hand, where Cox-2 was present, such as in kidney, we would have yet an opposite result.

It was clear to us that this field was evolving rapidly and targets were appearing where they initially hadn't been found. So we might then be in a position where Cox-2 may be present in some situations and it may not be present in other situations. The stomach may be an example of that and we might, then, get an intermediate result.

[Slide.]

If then, again at this meeting, discussing if the Cox-2 agents were different, were they, in fact, representatives of a different class. And we discussed how many agents it would take to define that class. We were curious, in terms of how more potent inhibitors, if they were to be developed, how they might fit into this scheme.

We, again, discussed the label, whether we would revise the current NSAIDs template or, in fact, write an entirely new label, depending on the data. There was always the question of, in these trials, whenever we were discussing results, how many of the results were actually testing the drug, the theory of how the drug should be working, or a combination of both.

[Slide.]

We always had an eye to the future, wondering about other indications. For example, as I alluded to earlier, any kind of structural modification, OA or RA. We had been hearing about prophylaxis for colon cancer and we had also been hearing about prophylaxis of Alzheimer's disease.

We were certainly aware, and would not have been surprised, if we would have seen some unique adverse events associated with these particular compounds. Of course, we were very interested in the safety and efficacy in children because NSAIDs had typically not been studied in an

organized fashion.

[Slide.]

In December, then, at the end of 1998, celecoxib, or Celebrex, was submitted and discussed. It was, as I have indicated at the bottom there, a large submission, lots of information. From that information, we were able to glean the following.

[Slide.]

In terms of OA, Celebrex was found to be at doses from 100 to 200 milligrams BID more effective than placebo. However, it did not appear that there was any obvious efficacy advantage of the 200 milligram BID dosing and it appeared that 100 milligrams BID was about the same as 200 milligrams on a daily basis.

The efficacy, in terms of the treatment for OA, was comparable to naproxen at 500 milligrams BID and we noted, in the long-term safety trials that were part of the NDA, that most patients, in this case, about 70 percent, increased their dose in the open-label experience and this has been known in the literature as the dose creep.

[Slide.]

In the NDA, then, for Celebrex, it was also indicated for treatment of RA, at doses from 100 to 400 milligrams BID, found to be more effective than placebo. There was no obvious, again, efficacy advantage of going up

to the higher dose of 400 milligrams BID, though. Once more, comparable to naproxen at 500 milligrams BID and, again, we noted that, in the open-label experience, about 70 percent of patients increased their dose, again an example of the dose-creeping phenomenon.

[Slide.]

The NDA did not allow us to give the indication for treatment of acute pain and dysmenorrhea.

[Slide.]

So we discussed, at that time, the Cox-2 hypothesis and wondered how Celecoxib would fare against that. It was really a representative of that, particularly as we discussed efficacy because, as indicated, the analgesic efficacy appeared to be less than NSAIDs for acute pain. So we wondered if the problem was really with the models that were selected in the particular NDA.

We wondered if it was due to the nature of acute versus chronic pain and did this have something to do with the induction of Cox-2, or we wondered whether this was related to the potency or selectivity of celecoxib, among other reasons.

We also discussed that, in these studies, there didn't any obvious efficacy advantage compared to NSAIDs for OA and RA, but we wondered what would happen in long-term trials.

[Slide.]

Then, as indicated later on, the NDA for Vioxx was submitted and, in there, was sufficient information for labeling for OA and it was found that, at doses of 12.5 and 25 milligrams on a daily basis were better than placebo.

Once more, there didn't appear to be any obvious efficacy advantage of the higher dose at 25 milligrams daily. The efficacy was found to be comparable to ibuprofen at 800 milligrams TID and diclofenac 50 milligrams TID and there was no information for us to get any idea of what would happen in an open-label experience.

[Slide.]

For RA, there was no data submitted in the NDA.

[Slide.]

For pain, Vioxx was indicated for acute pain and dysmenorrhea at doses of 50 milligrams daily and, in five-day studies, was found to be more effective than placebo.

[Slide.]

So, at this point in time, it appears that, in terms of efficacy for COX-2 agents like NSAIDS, they are indicated for the treatment of signs and symptoms of osteoarthritis. This is both, again, for Celebrex and Vioxx. They are indicated for the treatment of rheumatoid arthritis, and this is only for Celebrex, at what is now called the 'x' dose.

They are indicated for the treatment of acute pain and dysmenorrhea. This is only for Vioxx. They are indicated also for the treatment of a rare form of cancer known as familial adenometous polyposis, or FAP. This is only for Celebrex and this is now at what we call the 2X dose as adjunctive therapy in this particular condition.

[Slide.]

So, despite their long history of usage, no NSAID has been tested in a large and simple long-term safety trial at doses exceeding the upper limit of the approved labeling in arthritis, particularly at the 2X dose. So we are really going into uncharted waters here. Again, we are always looking to the future.

Thank you.

DR. HARRIS: Thank you very much, Dr. Witter. We will have a discussion this afternoon. We are going to limit any questions the committee might have to just clarification, or whether or not there is any clarification required with respect to Dr. Witter's presentation.

Seeing none, we will move to the next item on the agenda and that will the presentation by G.D. Searle and Company. Dr. Philip Needleman will introduce.

G.D. Searle and Company Presentation

Introduction

DR. NEEDLEMAN: Thank you very much. Good

morning.

[Slide.]

We have been asked by the agency to continue to extend the tutorial points about some aspects of the history and discovery of COX-2 inhibitors and set a context for today's review.

[Slide.]

This will be the agenda that we will proceed under. I will start with the introductory remarks. I am the chief scientist of Pharmacia and the Chairman of Research and Development.

[Slide.]

In 1990, based on our discoveries, we discovered the existence of a novel isoform of cyclooxygenase, the enzyme that produces prostaglandin. We discovered that the newly produced enzyme was intimately associated with inflammation and pain and swelling.

So we set forth this hypothesis that said that there were two enzymes. One was a housekeeping enzyme, a constituent of one, which maintained a physiological function, and those functions were especially prominent in gastrointestinal tissue where the prostaglandin was involved in the synthesis of mucus which protects the stomach and intestine from acid and enzymes. it was also especially present as an enzyme in platelets, and that was COX-1.

We further hypothesized that all existing NSAIDs, aspirin-like drugs, were nonselective and inhibited both enzymes, and indeed these are potent agents and their mechanism of action was the treatment of prostaglandins produced at the site of inflammation.

Their problem and limitation was they also produced mechanism-based side effects by blocking prostaglandins especially in the gastrointestinal tract and in platelets.

This hypothesis was the primary drive of our enormous effort to seek out, and what eventually led to, the discovery of celecoxib Celebrex to achieve the efficacy of NSAIDs, but with a far superior GI profile.

[Slide.]

Now, in the 1998 NDA, we established that here a dose response curve in rheumatoid arthritis patients was fully equivalent in efficacy to the widely used naproxen without evidence of endoscopic damage here being similar through 400 mg BID to placebo, but statistically well less than the 25 percent incidence of endoscopic ulcers induced with naproxen and all the other NSAIDs.

[Slide.]

So, for a perspective, as you just heard, it was reviewed in December of '98 and approved by the end of December 1998, and it was based on its demonstrated

endoscopic upper GI safety compared to conventional NSAIDs.

For the context which you just heard, endoscopy was regarded as a surrogate, so indeed the warning labels for Celebrex reflected that NSAID template. So, this large, well-designed trial was designed to achieve really greatly expanded and clinically meaningful GI safety with the design intended to go for differentiation of that warning label based on the superior safety of Celebrex versus NSAID.

[Slide.]

Now, the class trial's primary objective was the GI safety, but inherently we will able to comment on the systems you saw reviewed - the renal, the cardiovascular, and so on.

This proved to be a quite complicated and rigorous trial. We chose and worked actively at all stages of this to frequently interact and collaborate with the agency, and we designed a trial that really followed the practice of medicine, so we enrolled both OA patients and RA patients, we used multiple NSAIDs, and we allowed cardiovascular use of low-dose aspirin because this age population in practice was using these for cardioprotection.

We used two NSAIDs, agreeing with the agency that we should include ibuprofen because it was regarded as a safer NSAID, and so we wanted two NSAIDs and really to compare to the one that had the higher safety.

Furthermore, as you heard, kind of in an unprecedented way, we used a dose that was 2X the maximum dose in rheumatoid arthritis and was actually 4 times the dose, the maximally achieved dose used for Celebrex in arthritis, but we compared that with the commonly used doses, not even the maximum doses, of the ibuprofen and the diclofenac. So, it was an exaggerated trial to really see the scope of the GI safety and have a long term sense of their utility and their improved potential.

[Slide.]

So, in the context that we were asked by the agency to then say, okay, what do you know in 2001 about the COX-2 hypothesis that you didn't know in 1990 and really started the large program.

Well, the bulk of the information is fundamentally the same. Indeed, there are two enzymes. It is clear in COX-1 that it is restricted to the stomach, the intestine. In the kidney it maintains renal blood flow. The platelets are only COX-1, and platelets are cells that don't have a nucleus, so if you use an aspirin-like drug, you will irreversibly block that COX-1. NSAIDs, all NSAIDs hit COX-1, as well as COX-2, but those are transient inhibition.

It also became clear, and we were asked to talk about this role of COX's in platelets and endothelium. The endothelial cells and the blood vessels, smooth muscle cells

are all normally constituents of COX-1. Their product is PGI2.

Now, on the COX-2 side, indeed, inflammation of all sorts is associated with COX-2 expression, and it is an enzyme that is induced and it is not normally there. We now know that nearly every epithelial tumor expressed COX-2, in precancerous steps, at cancerous, and in metastatic stages, and as Jim Witter showed you, we achieved approval of the pretreatment of a regression of precancerous polyps, the familial adenoma polyposis, and large trials are underway in colon cancer and other cancers.

It is now clear in the next three that COX-2 also exists in the physiological maintenance especially in some species of kidney function. It is present constituitively in the central nervous system, and it plays a large role in female reproduction.

Finally, endothelium has inducible enzymes and in certain kinds of treatments, there can be some induction of COX-2. So, then this is the setting for the CLASS trial where you have that large database to look back to see did you unmask unique side effects.

[Slide.]

The CLASS trial then definitely will allow us to shed light on the roles of COX-1 and COX-2 on the GI events and actually on the blood loss which we think also reflects

GI events.

We have data to really possibly comment about the implications of low dose aspirin, because in the end now we have a large prospective trial with a large database about low dose aspirin, and could at least comment about the possible issues about cardiovascular, renal, and thrombotic events.

What this trial won't add to is this is largely an aged population, so there won't be evidence about female reproduction. A CNS trial has completely different parameters and endpoints, and wasn't doable, and again, the cancer trials are completely different trials, and the long term trials are three years in treatment. So, we can comment in these two areas.

[Slide.]

We were asked to talk about--and it is an important point--about then the use of low dose aspirin, so we are talking about 325 milligrams or less. Aspirin, because it is capable of acetylating a serine in the active side of cyclooxygenase, irreversibly inhibits that enzyme and platelets lacking the nucleus can never reconstitute new enzyme, so one dose of aspirin permanently wipes out platelets. That is by blocking the cyclooxygenase which makes thromboxin, which is the aggregator constrictor substance. Similarly, that is the mechanism basis of the

increase in bleeding potential.

So, in '98 when this was approved, I think there were 18 or 20 NSAIDs proved to be nonspecific, very potent on COX-2, very potent on COX-1. All NSAIDs transiently inhibit platelet COX-1 and the thromboxane production, and there is no difference if it's ibuprofen, diclofenac, or naproxen.

Now, aspirin also has the property of being a direct irritant and damaging the GI mucosa. Importantly, in a recent New England Journal of Medicine paper--and there is a number of important papers--low dose aspirin, this 325 milligrams or less, shows the increased risk of GI ulcer complications on its own.

So, with this context, we could take a look and see what the CLASS data says about the GI side effects of aspirin.

[Slide.]

Now, in the renal system, it is clear now because you have the cDNA probes and the antibodies that both isoforms are expressed constituitively, that is, it is normally there and is turned on inactive.

The confusion starts to occur when you look at the anatomical distribution of the enzyme. The most studies were in rat especially and in dog where there was high expression in the kidney at the sites of renin production,

and indeed you can see COX-2 effects. On the other hand, primates and humans don't have expression in the same site, so that is not so clear.

The database did not distinguish between Celebrex and NSAIDs, so in terms of increased edema, both Celebrex and NSAID had a response, but Celebrex did not exhibit a dose-dependent increase in that response.

[Slide.]

Importantly, we were asked about the cardiovascular and thrombosis. As you know, low dose aspirin is especially used in the treatment, in the secondary prevention of myocardial infarction, and this mechanism-based response is due to the irreversible inhibition of the platelet COX-1 to block thromboxin.

So, there is clear and substantial evidence that low dose aspirin is a benefit during an acute myocardial infarction, during unstable angina, and clearly a benefit in the secondary prevention of myocardial infarction.

In terms of primary prevention, it is a marginal case and there is no clear demonstration anywhere near as clear as the secondary prevention.

Now, in that context, we will remind you that blood vessel smooth muscle and endothelium produces prostacycline PGI2 predominantly from COX-1. That is the opposite of thromboxane in the platelet which causes

aggregation. PGI2 is anti-aggregatory and vasodilate.

Now, it is normally only COX-1, but part of the issue with that could be turned on there, so you are thinking about the site of interaction in blood vessels of platelet and endothelium.

What you have to remember, though, is the endothelium makes continuously prodigious amounts of nitric oxide which in its own right is a very potent antithrombotic and is a potent vasodilator, and nitric oxide sensates in blood vessel is not inhibited by NSAIDs or COX-2. So, the aspirin story or NSAID story doesn't affect the endothelial nitric oxide.

[Slide.]

Now, to illustrate the doses in patients that were COX-2 selective, from the NDA I could show you data on platelet aggregation, so this is platelets removed from patients and treated with arachidonic or other stimuli to measure aggregation.

You see placebo in the white bar. Here, we went to 600 mg twice a day, well above even the exaggerated dose we used in this CLASS study, and you see no inhibition of platelet aggregation. Here, you see inhibition by diclofenac, and you can show full-range dose response curves through the 1,200 mg, and it is COX-2 selective dose without inhibition of COX-1.

[Slide.]

Now, that is pertinent and the reason this is a question at all is this data was published by McAdams, it is from the Garrett Fitzgerald data in which they looked at human urinary PGI2 metabolites, PGIM, and looked at placebo, does of Celebrex that were COX-2 selective and didn't affect COX-1, and looked at doses of ibuprofen.

What you see is a suppression of these PGI metabolites. Since that was a dose that was COX-2 selective, that suggested that there was some COX-2 generated PGI2. Now, we don't know if that is from the epithelium because it is urine, but then this is the basis of the hypothetical consideration.

[Slide.]

So, the question is, is that PGI2 inhibiting platelet aggregation, and this work suggests if it was endothelial, which we couldn't tell, that you would be affecting that PGI2 and endothelium.

[Slide.]

So, here is a cartoon of their hypothesis. If thrombosis is on this balance beam, it is the platelet COX-1 that is causing aggregation, and it could theoretically be the prostacycline, PGI2, made in the endothelial cell.

Since NSAIDs would block both, the beam would stay balanced and there would be no effect on thrombosis,

however, if COX-2 inhibitors were around, you would suppress this, thromboxane could be dominant, and you would have the potential for the risk of a thrombotic event.

So, if the hypothesis is correct--and remember by and large endothelial cells still are predominantly COX-1, if it is correct, then, the expected effect of COX-2 inhibitors would be similar to patients not taking the low dose aspirin in an at-risk population.

[Slide.]

So, what about the CLASS data? What can we say about the potential for assessing the risk? The cardiovascular benefit of aspirin--and now here we are even talking about the secondary prevention because there is no case for primary prevention--the question was the ability of aspirin to reduce the primary event or, similarly, what is the ability of a COX-2 inhibitor to cause a cardiovascular event.

If you look at something like Physicians Health Study, the sample size required would be greater than 20,000 patients for five years to find the event. So, therefore, the CLASS trial, we had 8,000 patients, but only 4,000 patients on Celebrex, was never large enough to detect such a small cardiovascular event due to COX-2 inhibition of endothelial cells.

In other words, with this sample size, you can't

show a mechanism-based event, a cardiovascular event. However, the CLASS trial was large enough for general cardiovascular safety and renal safety, or in other words, if you would see a thrombotic event with this small of a trial, it can't be mechanism based, it would have to be molecule based because the trial is inadequate in size.

[Slide.]

So, in summary, and what we will review with you today, is we feel that there a preponderance of clinical data which exhibits the safety of COX-2 inhibition and Celebrex compared to NSAIDs which would warrant the change of the NSAID platelet.

That is built on now this continuum of data, started with the endoscopy of nearly 5,000 patients in the NDA, it's this 8,000 patient trial with evaluation of ulcers and complications in the CLASS trial, and it's this very large postmarketing surveillance.

We looked at the exaggerated doses, the 2 to 4X of the RA and OA dose, and in that trial, as you heard asked before, there was no new safety signal even in this long-term trial with the exaggerated dose, and we think that Celebrex did not increase the thromboembolic events compared to NSAID, and that was true both in the absence and the presence of aspirin.

[Slide.]

So, with this as a setting, we will lay out the context of the clinical trial and the data, and we will start with Dr. Steven Geis.

UGI Safety Profile of NSAIDs and Celecoxib: Rationale for CLASS Study

DR. GEIS: Good morning.

[Slide.]

In my presentation, I will review the history of our understanding of NSAID-associated upper GI toxicity and review the prospective trials that were used to evaluate the upper GI toxicity of NSAIDs, and then finally discuss the upper GI safety data on celecoxib that we had at the time of the submission of the NDA.

[Slide.]

In reviewing the NSAID-associated upper GI toxicity, I first want to review the various types of toxicity that have been appreciate over the years, incidence of this type of damage, and then to define who are the patients at risk.

[Slide.]

Now, in the 1970s and 1980s when NSAIDs became widely used to treat the approximately 44 million arthritis patients in the U.S., physicians began to be aware that patients were, in fact, developing side effects associated with NSAIDs, and these were predominantly upper GI in

nature.

These included symptoms, but the symptoms also evolved into symptomatic ulcers. These ulcers, in turn, could become complications, that is, the ulcers could bleed, they could perforate, or, in fact, form outlet obstruction in the stomach.

[Slide.]

Now, this slide shows the type of endoscopic appearance of an ulcer that a patient might have had during that time. That is, the patient would have a symptom, the clinician would perform an endoscopy and observe this type of an ulcer which, in that terminology, is called a symptomatic ulcer.

[Slide.]

In some cases, the ulcer was proximal to a blood vessel and if the lesion progressed, the blood vessel could be eroded and we would have a bleeding ulcer or an ulcer complication.

[Slide.]

Also, the ulcers could erode completely through the wall of the stomach or the intestine forming a perforation, and as everyone can see from this type of typical x-ray from a patient who has had a perforation, we have free air under the diaphragm.

[Slide.]

So, as time progressed, clinicians became aware that there was a spectrum of NSAID-related upper GI injury which ranged from symptomatic ulcers and easily could form an ulcer complication, the bleed or the perforation.

[Slide.]

Now as our understanding progressed, certain acronyms and definitions began to evolve and develop and are seen in the literature. Over time, symptomatic ulcers, perforations, and bleeds became referred to as PUBs, whereas, perforations, outlet obstructions, and bleeds became referred to as POBs.

In my presentation and those of my colleagues today, we won't be using this terminology, we will be referring to NSAID toxicity as symptomatic ulcers or ulcer complications.

[Slide.]

To determine an understanding or to establish an understanding of the magnitude of the problem, over the years observational cohort and retrospective cohort or case controlled studies were performed, and in these studies, the investigators examined hospital records for diagnoses of patients who had symptomatic ulcers or ulcer complications, and then looked to see if there was an association with NSAID use. In this manner, they were able to establish what is really the rate of these types of toxicities with NSAIDs.

[Slide.]

They found--and this was repeated by several investigations, and as Dr. Witter pointed out--that it was established that the overall incidence of the symptomatic ulcers and the ulcer complications was on the order of 2 to 4 percent per year. These retrospective analyses also gave us evidence that some of the ulcer complications were symptomatic, but also some of them were not symptomatic, that is, there was no heralding symptom prior to the actual bleeding or the perforation taking place.

It really depends upon what study you read what is the percentage of these types of toxicities that are actually asymptomatic complications, and it can range anywhere as low as 10 percent up to 60 percent depending upon the study.

The retrospective studies also allowed us to look at what is the background rate of this type of toxicity in patients not using NSAIDs.

[Slide.]

As we see here from the work of Dr. Singh and Dr. Perez-Gutthan, that in NSAID users indeed the incidence of ulcer complications by their studies was on the order of about 1.3 to 1.7 percent per year, but in non-NSAID users the rate was about 6-fold lower, on the order of about .03 percent per year, so we knew there was a background rate,

and in NSAID users, these very serious complications occurred about 7 times more frequently.

[Slide.]

Also, investigators were able to estimate what was the mortality due to the GI toxicity of NSAIDs, and here we show the Aramis database, as well as the Tennessee Medicaid database. The Aramis database predicted that the number of deaths in the U.S. due to NSAID GI toxicity was about 1.3 per 1,000 patient years, and then estimating that based on 13 million patient years of exposure in the U.S., this would equate to approximately 16,500 deaths per year in the U.S. alone due to NSAID GI toxicity.

In the Tennessee Medicaid database, they estimated that in the elderly, defined as 65 years of age or older, that the rate of death due to NSAID GI toxicity was about 1.4 per 1,000 patient years. Estimating the patient years of exposure in the elderly of about 2 million, they estimated that there is about 3,300 deaths in the U.S. in the elderly due to NSAID toxicity.

[Slide.]

The retrospective studies also gave us an idea of who are the patients at risk of such problems. Although there were many risk factors identified, those which consistently were the most correlated with the complications were increasing age, a history of an ulcer or GI bleeding,

the dose of the NSAID, and the duration of the NSAID use, as well as the use of low dose aspirin.

[Slide.]

This slide shows the work of Perez-Gutthan, which shows the odds ratios for ulcer complications as a function of age. What we see is in females and in males, that with increasing age, in patients not taking NSAIDs, there is an increased rate of developing or an increased risk of developing an ulcer complication. However, in the NSAID users, that rate is about 5 times higher in all age groups. So, although there is a correlation between age and the likelihood of developing a complication, even the young patients are on NSAIDs are at risk of developing a complication.

[Slide.]

Here, we show the work of Dr. Weil which looked at the risk of upper GI bleeding related to prophylactic aspirin use. The odds ratio ranged from 2 to 4 at doses of 75 mg to 300 mg, all of which are considered prophylactic doses of aspirin.

[Slide.]

The work of Henry looked at the risk of upper GI bleeding of various types of NSAIDs. In this work, they used ibuprofen as the reference NSAID, so if you will, they considered ibuprofen to be the safest although we know that,

in fact, is not the case.

Nevertheless, using that as the reference, they found that the risk of upper GI bleeding with all the NSAIDs was high and was certainly statistically higher than that seen with ibuprofen based on this study.

[Slide.]

So, in conclusion, based on the retrospective studies that were conducted and the observations made by investigators, it was found that symptomatic ulcers and ulcer complications really are on a continuum of GI toxicity, all NSAIDs are associated with this type of toxicity, and approximately 16,500 deaths occur per year in the U.S. due to NSAID toxicity.

[Slide.]

Now, I would like to look at the prospective trials that evaluated NSAID upper GI safety, looking at the endpoints of endoscopic ulcers and the one study that used ulcer complications as an endpoint.

[Slide.]

Now, if we can refer back to the definitions once more, so we now have symptomatic ulcers and endoscopic ulcers. Symptomatic ulcers are a form of upper GI toxicity encountered in clinical practice, and these are identified by a "for cause" endoscopy.

On the other hand, endoscopic ulcers are measures

of GI toxicity in clinical investigations, and these are identified by a scheduled endoscopy in the course of a clinical trial.

[Slide.]

The endoscopic ulcer studies really confirmed what we observed in our retrospective assessments, so here we show the prevalence of endoscopic upper GI ulcers for various NSAIDs, and what is seen is that all NSAIDs were associated with upper GI ulceration at a rate of about 20 to 30 percent.

This work was confirmed by a variety of investigators who did similar types of endoscopic studies and found that NSAIDs produce a point prevalence of ulcers in the stomach and the duodenum ranging anywhere from 5 percent up to as high as about 30 percent.

[Slide.]

The endoscopic studies also confirm the relationship of GI toxicity with NSAIDs and age. Here, we show the work of Cheatum showing that the point prevalence of ulcers as a function of age increases, but importantly, even the younger patients in the range of 30 to 39 years old did have a high incidence or a high point prevalence of NSAIDs ulceration.

[Slide.]

As Dr. Witter pointed out, the question became: