Well, we've covered a wide range of topics. My task is try to see if I can pull any of these together in some coherent way. What I will try to do is to summarize different areas. A number of these are going to segue nicely into the specific questions that the Committee has been asked by the FDA to address.

After I summarize, maybe we will have a five-minute stretch break, not a break-break. Don't leave the room, but maybe get up and stretch after I finish and then we will start right back up.

What I've tried to do is hearing the different comments is to see if there are some general themes. That may be helpful for us to think about. If for some reason I have left out your comment or if I've misunderstood, by all means I'm willing to be corrected.

One of the topics that we heard discussed was the representativeness of the sample that is included in these particular trials. In fact, will they generalize beyond the sample of who is being included? Related to that in one way is also, how

are we looking at the aggregate trials?

When we talk about meta-analysis versus when we look at, as Dr. Stine said, the slides that had three different comparisons but were on the same slide we naturally want to go from one to the other when in fact these are different studies with different durations and different populations to some extent.

A second area we mentioned in passing was about the comparator drug, diclofenac, versus the alternatives, was this the best alternative? Did this alternative set them up to have a certain result occur? What are the other issues related to that particular choice? What were the implications for the results that they received?

A third area that we talked about was cardiac risk particularly for naproxen and GI effects and the balance of, let's use NNT or NN save, if you want to use that concept.

If we want to truly try to balance the safety, efficacy, and effectiveness with all of these drugs having some potential negative effects but also some positive effects, how do they balance out? Can

 

looking at absolute risk be one way of trying to help us get a better handle on that? Whether we convert it to dollars or not may not be the issue for this particular Committee; although, that could be looked at.

A fourth topic was the lingering concern about the 30 milligrams. We really didn't see head-to-head studies that allowed us to know much about what can we say about 30 milligrams other than on the efficacy it appeared that 30 milligrams was as good, if you want to use that term, as what we saw for 60, but there is no direct head-to-head comments.

In light of the last comment by Dr. Day, how will a physician know when it's time to move somebody up? If the efficacy for 30 is equivalent to the efficacy of 60, then when would you ever decide to move up the potential dose response negative effects that we saw?

Last, next to the last point, and I'm trying to collapse these in different ways. Who really gets helped? The whole issue of those individuals that don't respond well to Treatment X, do we have any data

to support the fact that they might do well with Treatment Y? It is very possible they might do well with any of the alternatives that are available. There were no, until I heard otherwise, direct head-to-head comparisons looking at that, no crossover studies.

However, Study 960 -- I think that was the number that I heard on there, I got the numbers slightly off -- at least was the kind of study we might have wanted to see if it had been appropriately designed. I wanted to say the absence of evidence is not evidence of absence.

Had we not heard about that study, we were just going to say, "Well, we don't know." That preliminary study raises the issue that we do have to consider.

Do we need to see more studies that, in fact, take those individuals who have not succeeded in Treatment X, whatever that treatment happens to be, and cross them over to the other treatment to see if, in fact, they have a beneficial effect, or else we won't really know are we really helping those people

 

who weren't getting a benefit from those treatments.

I guess the last point I heard was the concept of enriched trials, that is, we're using flare designs, which means you're taking people who are doing "well" to some extent on whatever treatment they are receiving; if they stop that treatment, they get worse; and then they go on to another treatment.

You are taking people who are, in fact, demonstrating some beneficial effect with whatever the alternative that they were taking were, and now we're taking out the people who didn't get a benefit. We are only using that subgroup. Does that in a sense stack the deck in the direction of finding people who are likely to have a beneficial effect?

I did that very quicky. I tried to collapse a bunch of different areas. I didn't mention the risk management program because we're going to get to that in the next questions.

Did I miss other important points that should have been included in that general sense? Because I think it's going to transition us into what the FDA has specifically asked us to talk about.

Anything that I missed? Did I, unfortunately, misrepresent anybody?

(No verbal response.)

CHAIRMAN TURK: Let's take I mean five minutes. Do not leave the room. Stand up and stretch and then we're going to address the questions the FDA has asked us.

(A recess was taken.)

QUESTIONS TO THE AAC AND AAC DISCUSSION

CHAIRMAN TURK: Please take your seats.

We are going to be moving into a different section now in which we actually have a set of questions that the FDA specifically asked the Committee to comment on and eventually we are going to actually do some voting on some of these issues.

When we do the voting, I'm going to ask you, and I'll remind you of this again, when I do ask you to vote we will go around the room. Please state your name for the record as well as what your vote is when we get to those particular topics.

Before we get to any type of voting, there are a couple of discussions questions, many of which

we circled around and sort of start hitting upon, but I think we can see if there any additional discussions of these as we move through it.

The first question that we were asked to address was, has the safety profile of etoricoxib been sufficiently characterized; and if not, what other studies would we want to see or recommend that they should provide? I will open that up.

Yes, Dr. Gardner?

DR. GARDNER: I would like to ask the members of the Committee and specifically the clinicians in thinking about what other studies we might recommend, can you conceive of a way, any way, that the risks that we're seeing can be managed?

When we think about a risk management program, that assumes that we believe that management is possible. I would like to hear from the clinicians whether you think that it is possible; otherwise, I don't what other studies we can recommend.

CHAIRMAN TURK: Dr. Ginzler.

DR. GINZLER: Well, I have great fears about being able to have an effective risk management

program. You know, it's very simple in our hospital. When we go to the P&T Committee with a recommendation for something new, it's restricted to that group of physicians who treat that entity. Only I can prescribe certain things and only cardiologists can prescribe other things.

But we're not talking about restricted prescribing here. We're talking about every physician in the United States being able to prescribe for the approved indications and a myriad of off-label indications.

I really don't think that the education program, in the sort of sketchy details that we've heard, is going to reach and have an effect on the people that need to hear it.

CHAIRMAN TURK: Anyone else I haven't seen?

Dr. Fries.

DR. FRIES: Well, I would answer that I don't think it's been well enough characterized, because of the comparator choice mainly. One would really like to see a comparison outcome study that had Naprosyn plus PPI as the ideal comparator.

That is one area that I would personally like to see additional information on, so we can answer the question of whether there really is a difference, whether diclofenac is or isn't the same.

The second thing that I think would flow from here, and we did this a long time ago, with NSAIDs is a six-way crossover design in which we compared six NSAIDs and RA in the same six in ankylosing spondylitis. That design is quite feasible and quite inexpensive.

The question of what happens after trying a six- or eight-drug crossover design to the drug that comes into last place, including this drug, you could get an answer.

Because a lot of the argument seems to depend on the fact that there is this great unmet need, which means that there are people that are not responding to any present NSAID who would respond to this, and that's a testable fact.

CHAIRMAN TURK: May I ask you, how large a trial was that?

DR. FRIES: The study that we did was a

small trial that had 36 patients with each disease. Each one in a Latin design got the same number of followings of every other one and the same number of positional slots as every other drug.

The design was a six-week trial on a given drug doing a crossover within a crossover without a washout and the patient able to drop out of any given drug, but not the study, at any time from week one on, so someone didn't get stuck in a miserable drug for a long period of time.

We showed, it's not directly attributable here, variability. We weren't specifically answering the question. We showed some superiority but also a lot of variability in that group.

You could expand that study and expand it a little bit in number of diseases. It's a very practical design to answer some of the questions that seem pivotal here.

CHAIRMAN TURK: Duration of that trial would be how long?

DR. FRIES: We assumed that we were likely to see an effect in six weeks or not at all from a

 

given drug.

CHAIRMAN TURK: Thank you.

Dr. Stine.

DR. STINE: Regarding the safety, we talked about this before, but just to reiterate the issue about the 30-milligram dose and the safety of the 30-milligram dose seemed to be less completely characterized than some of the other doses.

CHAIRMAN TURK: Other comments about safety and how well it's been characterized?

Dr. Pasricha.

DR. PASRICHA: I think the safety has been reasonably well characterized. We know it's just as bad as diclofenac and perhaps worse than Naprosyn. You know, I'm not sure how much more data we need to come to those conclusions.

I mean, we can keep asking for more comaparators, but the data as it exists compared to two other nonsteroidals on the market today, the safety has been well characterized.

It's up to us to decide what to do with that data, but I'm not sure getting additional data is

 

necessarily going to help us come to any more conclusions than we already can.

CHAIRMAN TURK: Other comments? We also ask to specifically focus on the cardiovascular safety findings based on the data presented, in particular: from the large outcome trial, the MEDAL trial, specifically about cardiothrombotic effects, edema, congestive heart failure, and hypertensive effects. We're just specifically now looking at the safety from the cardiac side.

Dr. Cannon.

DR. R. CANNON: Well, I think everything we've seen is consistent with the class effect of coxibs on thrombotic risk: myocraidal infractions, cerebrovascular infarction, fluid retention, provocation of congestive heart failure.

Of course, we can't compare this drug with the other coxibs, but from what I see it's consistent with the class effect. I think it's real. I think it's probably greater than what would have been seen with Naprosyn had that been the comparator. In my mind, there is an increased cardiovascular risk with

 

this agent in my view.

I think it comes down to determining whether there is a need, a clinical need, for this drug based on what we've heard about the heterogeneity of responses to older or more traditional NSAIDs. I think that is what we're struggling with, because we don't really have strong data that there is a need for this drug in addition to what is already available.

I think from a safety standpoint, from what I've seen, I don't believe there is any difference or major difference between this drug and the other coxibs. I think they all increase cardiovascular risk.

CHAIRMAN TURK: That's a statement we heard from our cardiology colleague. Is there anyone who is not a cardiologist, a rheumatologist who would like to comment about the cardiac risks that they've heard?

(No verbal response.)

CHAIRMAN TURK: Is that agreement or just inertia?

(No verbal response.)

CHAIRMAN TURK: Okay. We're also asked to

look at specific hypertensive effects, which we saw significant increases from etoricoxib. Any comments that people want to make about safety regarding hypertension in particular?

(No verbal response.)

CHAIRMAN TURK: Are you all tired out?

Yes, Dr. Hennessy?

DR. HENNESSY: If I could choose between a drug that caused hypertension and one that didn't, I would choose one that didn't.

CHAIRMAN TURK: Of course, you're going to balance that with the potential beneficial GI.

DR. HENNESSY: All other things being equal.

CHAIRMAN TURK: Any other comments about safety, about what you've heard, what you would like to see, what other data we need to be collected that would convince you otherwise?

I did get a feeling that if there was a study done with Naprosyn possibly plus a PPI that might be something you would want to see. Is there anything else that you might want to see, or you're satisfied right now?

Yes, Dr. Davis?

DR. DAVIS: I think because of the dose effect that we see with the renovascular, I would want to see longer-term data with the 30-milligram dose that we are supposed to be considering now, in particular how long the patients were able to stay on the 30-milligram dose before there is a dose escalation.

That is one of my biggest concerns about this drug right now is it being prescribed starting at 60 milligrams and it's being used even in higher doses for other indications, albeit it short-term, we can't assure that when it's prescribed.

CHAIRMAN TURK: I believe they are suggesting you start at thirty and then you increase to sixty. What is not clear is at what point you make that decision to switch.

Other comments about safety?

Dr. Rappaport, since you're sitting there, this is a question that you're particularly interested in, are there questions that you would like us to focus on more specifically, or anybody from the FDA,

about the safety issue?

DR. RAPPAPORT: No. I think if that's all the comments there, that's all the comments there are, that's fine.

CHAIRMAN TURK: The last shot. We can come back to it.

Yes, Dr. O'Neil. Thank you.

DR. O'NEIL: I just want to say that when we're looking for a relatively low incidence problem like a half of a percent or a one percent cardiovascular thrombotic risk, studying a thousand patients for nine months on average is not adequate to make me feel like I have any clue whether the 30-milligram dose is as risky as the 60, or it might even me higher for all we know because the confidence intervals were so huge on something with a relatively low incidence rate. We do need more data there.

CHAIRMAN TURK: Okay. We were also asked to look at the efficacy of etoricoxib appropriate dosing. We have talked about that issue. I think we've covered the discussions points partially, because I think in our earlier discussion we covered a lot of

 

the issues that were being directed to us. Now there is actually a request for us to take on a Committee vote.

At this point we will actually ask specific questions on which you're going to be asked to vote yes or no or abstain, I presume you're allowed to do that.

As I said before, I will ask you, those who are voting members, to state your name and then what your vote is and we will go around the table. We will start the first time from left to right. We will start with Dr. Morris. Then, the next time, assuming there is a next time -- the question that we've been asked to vote on, and this is a specific one that it's really going to take you to think through -- yes, Dr. Day? Sorry.

DR. DAY: I just have a brief comment. The way this is laid out is logical, but it is unsettling because we are asked to vote yes or no; and if yes, then there are other things that we would comment on. Some of us might like to have had those things to comment on first that would then drive whether the

 

vote was yes or not. That is just an observation.

DR. RAPPAPORT: Well, you should certainly feel free to comment on those things during this discussion.

DR. DAY: But we're asked to vote now.

CHAIRMAN TURK: Well, if you would like, if you look at those, there is no reason why we can't talk about the things that are there. Would you like to specifically like to raise some that you would like to have discussion about? Dr. Day, have you got anything specific on that list?

DR. DAY: Well, it would be good to. That was why I think three of us were speaking up about the risk management program during the previous discussion because we were worried that it wasn't going to come up before a vote.

The only people we've spoken to are the people from the drug safety and risk management committee background. I think one of the physician members commented also. Does anyone else want to comment on any of these questions before a vote? Because it's an if-then, else. It's a little if you

vote one way, then we'll discuss these things. Does anyone?

CHAIRMAN TURK: We have some people, so we do have some comments.

Dr. Levine.

DR. LEVINE: Just a few thoughts. I can't comment on the cardiovascular, but I think the cardiovascular is more important than the gastrointestinal. I think when you weigh this the GI complications are important, particularly the ones that are complicated.

You can just, as the sponsor knows and everything else, it's pretty easy to look down the endoscope and find anything from a little petechial hemorrhage or something minor to a small ulcer very frequently in all NSAID and less so in the coxibs by a little bit.

I think the important thing is, how serious is the complication? With a trend, with a dose response going up, I think it's probably very real. There is no difference between these two drugs.

I would put it in context. When I vote I

have to balance it with the more serious cardiovascular effects, so that the advantage of a coxib, and it's true, is that a coxib has less potential to cause GI problems, serious problems or less problems. I think the serious problems are really what we have to vote on and not the overall findings that people would find about that.

The second thing is if one is concerned about the use of a drug like this, will coxibs really have an advantage because they are better pretty much than most of the NSAIDs if they were given to somebody who didn't need a PPI, who didn't have a peptic ulcer or a high-risk patient?

When you get into arthritis, you have so many high-risk patients in general that for me voting, it makes it difficult. I think that's an important point. I just think you have to think of the type of patient you have and try to balance the risk.

As someone who is thinking about this, I put cardiovascular first and GI second even with the complications, but I'm concerned about the failure to show a difference with complicated side-effects.

 

CHAIRMAN TURK: Ms. Aronson.

MS. ARONSON: As far as the labeling, I get stuck about who is excluded from the trial, particularly when it comes to obesity, morbid obesity, recognizing that population lives in this country, then recognizing that the study was 75 percent outside of the United States.

I don't know about whether clinicians could comment about the risk within that population of morbid obesity. I know there are some generalities that include the CV and thrombotic events, but also it would include a lot younger population that I don't think we have data on. With labeling, do you announce the populations that are not studied, that may be at risk?

CHAIRMAN TURK: Can someone answer that or take on that question?

Dr. Felson.

DR. FELSON: I'm happy to try to answer it. I do a lot of clinical studies on osteoarthritis, including large cohort studies of OA, so I have a reasonable sense of who gets it and who is in studies.

 

We didn't get the MI data, but the average EMI of people with NEOA at least is in the low thirties in the United States. These are obese and, occasionally, morbidly obese people. In Framingham and in other studies, people with OA have a higher than expected risk of cardiovascular mortality compared to people of age and gender.

People with rheumatoid arthritis who might also get this are also known to be at high risk, increased risk, of cardiovascular morbidity and mortality. I don't have any data as to whether they are at high risk of GI events or complicated GI events.

I think that any data we've seen about increased cardiovascular risk needs to probably be weighed and weighted, so to speak, in terms of that risk probably being magnified or likely to occur at an even greater number of events in people with OA and RA.

Because of a variety of reasons, they are more at risk than other people. They are more overweight. They are more often diabetic. They are

more often sedentary. All of those things increase their risk.

DR. FRIES: I just thought, sort of on the same line, that it was a little curious that there were all of these exclusions from the study and yet they didn't appear in the label.

It seemed to me you should have some kind of consistency. If you don't study them, why then you ought to say they are not indicated in. There was a big mix. That's sort of what you were getting at I think.

CHAIRMAN TURK: Ms. Aronson.

MS. ARONSON: Yes, that's what I was getting at.

CHAIRMAN TURK: I want to ask Dr. Cannon a question. Over the break, I heard you talking about or the issue was raised is it possible to think about are there options to approving or not approving. Can you approve with certain stipulations? I want you to elaborate on that.

DR. R. CANNON: Right. I thought it would be helpful to me and perhaps others that don't have a

 

long experience in serving on Committee's like this to hear from the FDA or to get some instructions from the FDA, just much like a jury would get instructions from the judge before coming to a decision, as to what our options might be regarding our response.

Obviously, we may recommend not approving this drug, but we could recommend approval with a variety of constraints, all the way from what is currently available for celecoxib to even more restrictive constraints to its prescription administration.

I thought it would be helpful, if others agree, to have some instruction from the FDA as to what our options are regarding the range of constraints that might be applied to an approval.

DR. SAAG: Let me just add to that quickly, because I think the timing is interesting with the recent IOM Report on the future of drug safety. The mandate to the Agency, which is not yet a funded mandate but a mandate notwithstanding, to work in this Phase IV area. What are the implications? This is a great example of, well, what is the Agency going to do

in response to these types of circumstances now and in the future?

DR. MEYER: That's a larger question. Let me approach the first question first. Because I know there was some early discussions about restricted distribution or targeting the marketing of this drug. I would not like to see a vote contingent on a recommendation of a restricted distribution, and I'll give you a couple of reasons why.

Number one, I don't think it's clear to me, and we asked questions of the sponsor to try to clarify some of these points, whether a specific patient population that would uniquely benefit from this drug could be identified.

It probably is true that one could identify patients who might be at special risk in relation to the risk of this drug, but that's probably true of other NSAIDs and coxibs as well.

The other matter, though, is that having a restricted distribution plan is a very difficult thing, from a regulatory standpoint and a from a practical standpoint, for the sponsor to impart on a

drug.

I would say that, from a philosophical point of view from the Agency's standpoint, it really should be restricted to those drugs where that drug has a unique role in therapy, a clearly unique role in therapy.

Thalidomide, for instance, is available with a restricted distribution. It has a very restricted role for an important treatment, which is leprosy. One can also look at other drugs that have some restrictions on their marketing and see that they have a unique role in therapy.

Whatever else I think we heard about etoricoxib today, I don't think one can say that a unique role for this drug has been defined. Therefore, I would not want your voting to be contingent on you then saying, "Yes, with a restricted distribution plan." Because I don't think it's something we would consider, and I'm not sure to whom we would restrict.

As far as the Phase IV issue, I'm not sure there is a short answer to that. To the degree that

 

we have a drug before us that has some important questions about its risk/benefit, I would say that if those questions have not been sufficiently answered to vote yes or no, then, in my mind, it should be to a no vote.

Because if you need more data to make your mind up about whether you could recommend this drug to be approved, then those data should be available beforehand, not afterwards.

In other words, if the missing piece is so important that it causes you to not be able to say whether you think this drug should be marketed, then, from a regulatory standpoint when we're in that situation, we're not talking about a Phase IV commitment, we're talking about we need those data prior to approving the drug for marketing.

Because when a Phase IV study is done, particularly if it's going to be a multiyear study looking at outcomes, by the time that study is designed, conducted, analyzed, and reported to the Agency, you may be four or five years down the road.

A lot of patients will be exposed in those

four or five years. I think that if the data needs are so great, then we need to have those data before we make the regulatory decision.

CHAIRMAN TURK: Thank you.

Dr. Cannon, did you want to respond at all, or did that satisfy you?

DR. R. CANNON: (Nodding head.)

CHAIRMAN TURK: Dr. Pasricha?

DR. PASRICHA: I want to go back to the question of unmet need. I'm not a rheumatologist; I'm a gastroenterologist. One can argue that if 50 percent of patients on a traditional nonsteroidal have dyspepsia, then that represents a group of patients that may not be able to take that drug because of tolerability.

We are not talking about the serious complications of upper-GI events. We are talking about patients with dyspepsia, for instance. A lot of my patients say if we put them on even an ibuprofen, that it's tearing them up, and isn't there something else that they can use.

There is actually an unmet need for that

 

group of patients who may respond to a COX inhibitor, whether it is traditional or a coxib, but without the dyspepsia.

Because there is I think a significant group of patients that are taken out of the treatment because of tolerability issues, not so much safety issues but I think tolerability. That is slightly different than there were on safety.

I think we should talk about that because that may represent the unmet need that we are all trying to struggle with. I would just like to open that up for comments from my rheumatology colleagues.

CHAIRMAN TURK: Actually, let me raise it to Dr. O'Neil. You are also a GI doc, so maybe you could comment?

DR. CLIFFORD: She's not.

CHAIRMAN TURK: Oh, you're not. I'm sorry.

DR. O'NEIL: I'm a pediatric rheumatologist.

CHAIRMAN TURK: Oh, I'm sorry.

Let me move over one. Dr. Levine.

DR. LEVINE: It's very true that just the other day coming down here I had a patient on a new

coxib, that's not to be mentioned, but out for one year beginning with an "L."

She had terrific troubles one to the other for dyspepsia and she was fairly young. She would be a good risk patient. I would have no problem considering complicated versus dyspepsia if it was a young person who is healthy, et cetera.

Once they have dyspepsia and everything else, I think they are less liable perhaps a little bit to tolerate a coxib. The problem is I'm afraid that the GI-complicated events is so serious relative to the less serious cardiovascular, and this study here didn't show it.

I feel as I keep going back and forth, and I alluded to, questions exist not on dyspepsia about the heterogenous population, the glucocorticoids, and we don't have information on that, the fact is that it's hard to tease out in my mind big differences in PPIs and aspirin patients on that.

When you put it all together, you look for sort of either a blockbuster or something that is giving us a little advantage. I don't know the

rheumatology end. But I think this end, we're still arguing in gastroenterology whether coxibs are really better than NSAIDs or not.

I think at this point until we could tease out something that was unique with this drug, I think just dyspepsia is not a problem, they are all going to have it, I have to keep thinking in my mind this may be a coxib very much like an NSAID that's traditional. That's the problem, we go back and forth here. I haven't seen data to convince me otherwise.

DR. PASRICHA: I would hate to start an argument with another gastroenterologist, but I just want to emphasize that I'm not talking about complicated events. I think complicated events data is very clear, there is no difference.

But there is a lot of literature from randomized-controlled trials that shows that coxibs reduce the incidence of dyspepsia significantly, and uncomplicated ulcers significantly.

I'm just trying to point out that there is actually potentially a segment of patients, whether it's large or small we can argue, but there is a

 

segment of patients who might be on an alternative to traditional nonsteroidals because of tolerability.

Now, you can argue, as Dr. Graham has argued, that you can just simply add a PPI to the nonsteroidal, that's another option. We are not here to discuss that option.

We are just talking about whether there is an unmet need for a drug like this.

I would like to say there perhaps might be. I would like other members of the Committee to comment on that.

CHAIRMAN TURK: Dr. Fries?

DR. FRIES: I don't think there is an argument about whether there is an unmet need in osteoarthritis. We don't have good drugs. We would all like a disease-modifying drug without any toxicity, and then we would be in good shape.

With regard to the specific point on the table, if I remember the slide right, this drug, the dyspepsia and all the individual symptoms kind of balanced right out to each other. There weren't any striking reasons to think that this drug would cause

less dyspepsia than alternatives.

I agree with your general feeling that there has been a decrease of maybe about a third with prior coxibs that have been looked at over a long time in terms of the minor symptoms. I'm concerned only really about the symptoms that can't be cured by stopping the drug, the ones that put you in the hospital or have you die.

DR. PASRICHA: Well, I think the data does show that there is a reduction, that's one of the questions specifically asked, that there is a significant reduction in dyspepsia. Perhaps, we can ask the sponsor to clarify that?

CHAIRMAN TURK: Dr. Sandborg.

Oh, sorry. It's a specific question? I'm sorry, I missed the question.

DR. CURTIS: Let me just pull up the slide number, please. We looked at a range of endpoints that looked at the tolerability from a GI perspective, because clearly that is another realm of sort of safety and tolerability.

Can we go to the "GI Tolerability Summary"

from the core talk please on Slide 46?

(Staff complies.)

DR. CURTIS: From the MEDAL Program, we prespecified. These are patient discontinuations due to a range of gastrointestinal adverse events and this included any GI symptoms -- abdominal pain, dyspepsia, reflux all grouped together -- and showed a clear about 30 percent risk reduction.

We showed also in the development program that, again, to get to this issue of GI tolerability, these are actually patient discontinuations. This was something that was significant enough that resulted in a patient feeling they could not continue on with study therapy. Again, for etoricoxib relative to the NSAID comparators, about a 40 percent risk reduction. This is a consistent observation with etoricoxib.

Slide 317, please?

(Staff complies.)

DR. CURTIS: Again, looking at the actual rates, large amounts of data, clear differences in rates of patients discontinuing. In addition, we published this in the "Lancet" publication. We looked

 

at and we prespecified a dyspepsia endpoint. It showed a 25 percent decrease, as I articulated earlier, in discontinuations for dyspepsia. There is a clear and consistent GI tolerability benefit separate from the serious GI event. That's just to clarify.

We do see that as an advantage of a COX-2 inhibitor versus a traditional NSAID that, again, may not have the same clinical significance, granted, admittedly, of these serious GI complications, but it is a profile that will result in some patients actually discontinuing an otherwise effective therapy.

I did just want to make one quick point. We firmly believe that naproxen is different from a cardiovascular perspective. There is absolutely no argument with that.

We feel that, just in terms of the data, the data for the rest of the NSAID does not support that this drug is qualitatively different from the rest of the non-naproxen NSAIDs.

When you look at the entire thrombotic and renovascular profile at the doses of thirty and sixty,

this drug fits clearly in the spectrum of the risks and benefits of NSAIDs other than naproxen.

I just ask you to be very clear. We would look forward to working with the Agency to see if there is a way to communicate that kind of information.

Clearly, there are patients for whom naproxen should be the initial choice. But, again, not everyone is going to tolerate naproxen. The GI tolerability of adding the PPI is a function of its adherence and its compliance, and, therefore, there need to be choices other than naproxen.

As I said, the data we feel support that this drug is qualitatively similar to non-naproxen NSAIDs, and that should be viewed in the context of that way.

CHAIRMAN TURK: Thank you. I think we have heard the sponsor's presentation.

Before I go to any new names, there are some names still on the list.

Dr. Sandborg.

DR. SANDBORG: I just wanted to followup on

the issue of the post-approval trends. Over years, I think that it's a slippery slope that people start pushing, assuming that it's safe. Dyspepsia becomes more of a problem and you push it to more obese people with cardiovascular risk, people who are hypertensive because you want to help them.

I'm concerned that the safety profile will decay over time, that any education we do will decay over time, and over time there will be an increased exposure of patients that you would like not to be exposed because of cardiovascular risk.

CHAIRMAN TURK: Dr. O'Neil.

DR. O'NEIL: Well, I think my question was largely answered by Dr. Meyer's comments, but certainly it would not be unprecedented, for example, etanercept, has an indication for juvenile polyarticular arthritis.

It's indication, however, is qualified. It's the only indication for which it is qualified that the patient must have failed prior treatment with a DMARD or been intolerant of a DMARD. It just raises the question whether it would be appropriate to give

an indication for osteoarthritis for patients who are intolerant of the GI side-effects and have low cardiovascular risk.

CHAIRMAN TURK: Dr. Meyer, do you want to comment?

DR. MEYER: Yeah. I did not want to suggest that you couldn't give comments that modify your vote. I specifically wanted to steer people away from restrictive distribution ideas, though.

I think it's perfectly reasonable to say "Yes, but I think it should carry such labeling." In fact, that's to some degree the intent of having those questions follow, "If, yes, what kind of labeling would you want?"

DR. O'ONEIL: The one point is that this is not going to be a cheap drug. They've studied a million patients for a million years. This is not going to be a cheap drug for a long time.

The third-party payers will not pay if you don't meet the indication restrictions and so that is indeed an effective way, not optimally effective perhaps but a somewhat effective way of restricting or

controlling distribution.

DR. MEYER: Yes. Just to be clear, what I would like, and I think I'm speaking for my colleagues here, as much as possible we sort of want a clean up-and-down vote.

Again, if your vote were to be yes and you had in your mind you wanted the indication to be a specific way, then I would think we would come back to that afterwards and with the opportunity to say so.

DR. JENKINS: Yes. If I could add to that, I think what Dr. Meyer has been trying to point out is we heard comments about restricted distribution or restricted access.

That's very different from a regulatory context than second-line status in the labeling for monitoring requirements or whatever. When we look at risk management programs, labeling is kind of the first tier of activities that you can take.

You can have box warnings. You can have second-line indications. You can have recommendations not to use it on certain groups of patients. Those are all designed to try to maximize the safe and

 

effective use, but they are also very difficult for the Agency to actually enforce.

It's when you get into further tiers of restriction where you actually say you have to have certain training to prescribe the drug or the patient has to be registered in a program like, for example, the Lotronex® to get access to the drug. That's what we're talking about when we talk about restricted distribution.

We normally limit consideration of those types of restrictions to situations where the drug really provides a demonstrated benefit that warrants having such a program but also to warrant the other risks that that drug may have leading to those restrictions.

I think what Dr. Meyer is trying to say is we have trouble understanding why we would want to go to a restrictive distribution, a restricted access program to an NSAID, unless it has really demonstrated a considerable benefit over available therapy.

That doesn't mean that the Committee couldn't recommend. You know, you could make a box

drug, or you could contraindicate it. You could make it second- or third-line therapy. Those are all labeling comments that could come after your recommendation of yes or no for approval.

CHAIRMAN TURK: Dr. Day, did you have a question?

DR. DAY: No.

CHAIRMAN TURK: Dr. Ginzler.

DR. GINZLER: No.

CHAIRMAN TURK: Ms. Solanche.

MS. SOLANCHE: Dr. Fries was so right in mentioning that there is an unmet need for good arthritis drugs. However, we have to ask ourselves, the idea should not be that we need new drugs. The idea should be that we need better drugs.

I think we have learned through the work in other areas as, for instance, AIDS drugs and cancer drugs that although it may seem that, well, we need this drug because there might be one person out there who will have a favorable reaction, we can't approve every drug. That's part one.

Part two is the idea of restrictive use, the

 

idea of Stage IV requirements does not work. We've seen it in other drugs. Once the FDA imprimatur is on there, the drug can be prescribed for a myriad of things. It could be prescribed totally out of its area.

Since we have questions about the risk/benefit, I think we are just opening it up for more possible misuse. As a person who has taken every coxib there is and had no good reactions to them -- I was going somewhere with that.

(General laughter.)

MS. SOLANCHE: I feel that the whole class of coxibs have problems in basically these same areas, the CHF problems and gastrointestinal problems, all those things. I don't see how we can think of approving a drug that basically is same old, same old. I was going somewhere, but I'll wait for the next bus.

Thank you.

CHAIRMAN TURK: I think your point was well stated.

Dr. Gardner.

DR. GARDNER: (Shaking head.)

CHAIRMAN TURK: He passed.

Dr. Levin.

DR. LEVIN: Just a reminder to everybody that one can overinvest in the effect of labeling on rational prescribing. I think we have a lot of evidence that says that prescribers don't necessarily and very often, in fact do not follow the advice on the label.

I would just caution that while it's important to have labeling be scientifically accurate, we have evidence that that simply isn't enough to change prescriber behavior in the ways we think it should be changed. I think it is important to keep that in mind.

I think actually the payer issue may be more of a control, that in this environment payers are often met with resistance to their unwillingness to include new drugs in a formulary and in time actually do include those drugs in a three-tier system. People will pay more, but those drugs will get out there.

CHAIRMAN TURK: Dr. Boulware.

DR. BOULWARE: I wanted to ask the FDA to

help me a bit with this decision and provide me some guideline on this. I think I have a good position on where I think it's risk and where it's merit is. It may be a benefit, maybe.

It looks like an awful lot like a drug that already is approved and exists. Can I use, should I use the same standard to vote on this that was used on a drug that does exist, or is it fair for me to say now that, well, there is one like that, so I don't think we need another one like that? It's a matter of timing? I'm torn with that.

DR. MEYER: Well, first of all, you're supposed to be here to help us make our decisions, not the other way around.

(General laughter.)

DR. MEYER: I think that's a fair discussions point, and one that we would welcome input, quite seriously, input from you and other committee members on. Whether diclofenac was an ideal comparator or not, it is a marketed drug. While it is not used to the same degree as some other NSAID in the United States, it does not have insubstantial use.

I think it is a fair sort of philosophical question whether the data for a new NSAID or COX-2 agent needs to show that it has some advantage to what's already on there or whether it needs to show that it's like the other drugs on the market. I don't think we can give you an answer to say that "This is the clear answer."

From a strict reading of the Food, Drug and Cosmetic Act, the drug has to be shown to be safe and effective and there is not really sort of strict mention of relative place in the armamentarium in the Food, Drug and Cosmetic Act. It's not sort of a firm legal answer to what you're saying, but there is sort of a fair, philosophical debate that could be had.

CHAIRMAN TURK: Go ahead.

DR. JENKINS: I would just add to that we find ourselves in places like this frequently as science advances and we learn more about drugs. You know, something that you would have done in years past, as you obtain more information, you have to apply that new information.

I think we are really asking you in 2007,

given what we know, do you recommend that this be approved with all the data that has been presented before you. That is the struggle we are facing and trying to decide, you know, has there been a bright line drawn that changed the standard.

We didn't know about these cardiovascular risks when we were approving diclofenac and a lot of the other drugs in the eighties and nineties. They are out there. I guess some could question, based on some of the presentations today, should all of them still be out there.

That's obviously a question that could be considered, but that's not the question we're here to consider today. We face this often. Science has changed. What should our regulatory position be today in 2007, given what we know about cardiovascular risk, about GI benefit, about tolerability, about benefit as far as efficacy compared to other therapies? That's really what we're asking you to answer from your perspective. I don't think we can give you much more guidance than that. Because we are really looking forward to your answer.

 

DR. BOULWARE: I guess one way I'm going to look at this is, as a person who is a practicing rheumatologist, we do have a paucity of things that are effective that we know one is just certainly better than another. I do have to run through drugs with patients.

As I look at this drug now, and I think I have a fair understanding of its risk and its benefit, I am convinced that there is a class effect, that there is a greater cardiovascular risk.

I'm looking at this now, that if we introduce one more drug like this with this risk, the likelihood that we will have a greater market share of all the patients who have osteoarthritis exposed to this risk becomes a real concern to me, without really any measurable significant benefit, although there might be some less dyspepsia. Nobody is going to die from that, dyspepsia, just dyspepsia.

DR. PASRICHA: Well, nobody is going to die of dyspepsia, but if the patient can't take the drug because of dyspepsia, they are not going to have any benefit for any antiinflammatory for osteoarthritis.

 

It's not a question of the dyspepsia being bad. It's a question of the dyspepsia being a barrier for the patient to come on the drug.

CHAIRMAN TURK: Let me see if I can summarize where we have been and then to bring us to a vote. If for some reason there is something I've left out, by all means you can add it to the list.

We have been asked to balance off the potential beneficial effects on the GI side, tolerability against the potential for cardiac effects, negative cardiac effects. We have heard that the GI effects at least for uncomplicated peptic ulcers appear to be quite favorable for this particular drug. We have heard that the tolerability seems to be favorable for this drug.

On the other hand, we have heard that from the cardiac side, that this seems to be a class effect. There do seem to be significant cardiac effects that are there.

We are being asked to balance, if you will, which is why I was pushing so heavily on the NNT and the harm is the balance of the GI positive side

 

against the cardiac negative side; how do we come down on that; then put that in the context of the population in need and the available treatments that are present for us; and is the data available allowing us to make this decision.

That is sort of where we are. It is, in some sense, where we started. When I read through this, I constantly was going back and forth. I'm sure each one of you did the same thing.

I think we really have to come to the point of saying in our expertise, in our specialty areas, given the information that has been presented in the background documents, given the information that has been presented by the sponsors, and by the FDA is to see if we can come and make a decision.

There is not going to be a perfect answer. Every one of us, we're going to have to balance this, but it's going to be an answer. What we're doing is giving advice to the FDA. The FDA can choose to weigh our decisions in different ways, go through our discussions.

It's not as if we're dictating or saying

"This is what you will do," but rather "The expertise of this particular group of individuals having gone through and read through the materials and listened to the discussions, this is our best recommendation to you."

Dr. Fries, you had a comment?

DR. FRIES: Well, I just think that even when you were talking about the GI advantages you mentioned the point, which to me was a very strong one, that when you had complicated disease, there was no favorable tilt.

CHAIRMAN TURK: Before we take the vote, does the FDA have any other questions or issues they would like us to address as a Committee before we do move on to voting?

(No verbal response.)

CHAIRMAN TURK: Hearing no comments from the FDA, are there any other final comments from anyone on the Committee? If not, we're going to move on to the vote. As I said earlier, I'm going to ask you to say your name and vote for the first question.

Do you recommend approval of etoricoxib for

relief of the signs and symptoms of osteoarthritis?

We will start with Dr. Morris.

DR. MORRIS: Usually, I vote with my stomach, but I'm going to vote with my heart and say no.

DR. GARDNER: Jacqueline Gardner, no.

DR. HENNESSY: Sean Hennessy, no.

DR. CRAWFORD: Stephanie Crawford, no.

DR. R. CANNON: Richard Cannon, no. You were asked about additional studies, it might lead to a yes approval sometime down the future.

The study that I would want to see is a study showing a unique role for this coxib and perhaps other coxibs that would encourage its use in a hierarchical manner, in other words, to balance the increased risk, which I think is a class effect of all coxibs, to show that this drug works when potentially less toxic, more traditional NSAID fail.

CHAIRMAN TURK: In the absence of those data, you're voting no?

DR. R. CANNON: I vote no.

DR. LEVIN: Arthur Levin, no.

 

DR. BOULWARE: Dennis Boulware, no.

DR. STINE: Bob Stine, no.

CHAIRMAN TURK: Dennis Turk, no.

DR. SAAG: Ken Saag, no.

DR. DAVIS: John Davis, no.

DR. SANDBORG: Christy, Sandborg, no.

DR. FRIES: James Fries, no.

MS. ARONSON: Diane Aronson, no.

DR. FRIES: I think you got me, no, Jim Fries.

DR. DAY: Ruth Day, no.

MS. SOLANCHE: Martha Solanche, no.

DR. FELSON: David Felson, no.

DR. GINZLER: Ellen Ginzler, no.

DR. LEVINE: Bob Levine, no.

DR. PASRICHA: Jay Pasricha. Yes, with the additional labeling that Dr. O'Neil mentioned, that it be used for patients who cannot tolerate existing traditional nonsteroidals and who are at lower risk for cardiovascular events.

DR. O'NEIL: Kathleen O'Neil. At this time no.

 

CHAIRMAN TURK: The vote was twenty to one no in response to that particular question.

I want to thank the Committee for all of the time they put in.

DR. MEYER: There was a second part if no, and we heard one discussion point of that. The second part was, what other additional studies might provide support for approval? We have heard one comment on that. I would like to hear other comments, if there are other comments.

CHAIRMAN TURK: Let me just finish thanking the Committee for putting the time in and looking through the wealth of data they were given, listening intently and importantly to the information.

Now we can address the question that would be asked by the FDA. In addition to the study that Dr. Cannon mentioned, are there other studies that we would like to have that might help us help them in the future make a decision?

Dr. O'Neil first and then we will move around.

DR. O'NEIL: If extended numbers of subjects

 

treated with a 30-milligram dose demonstrated lower cardiovascular risk than is seen at 60 milligrams, we might be more comfortable with that, at least I might.

CHAIRMAN TURK: Dr. Morris.

DR. MORRIS: Yes. One of the things I think, to Dr. Meyer's point about having no clearly identifiable population for which a benefit is demonstrated, I think that this drug has some potential in the ulcer area for benefit. There may be, indeed, a subpopulation where there is a benefit, where the benefits would outweigh the risk.

I think if they could do a study on the 30 milligrams showing efficacy for that subpopulation, especially in ulcer healing, that would I think give them a new indication and may indeed the benefit/risk ratio may be positive if they could find a specific population.

CHAIRMAN TURK: Related to that, I would like to see a study that basically took individuals who were not helped or not getting the benefits off of an existing drug and were then crossed over or moved over to this particular drug to see if, in fact, there

 

is a population for who can benefit from this. I think the 960 Study or a variant better done of that would be very helpful.

Dr. Felson.

DR. FELSON: Yeah. I very much deferred to Ms. Solanche earlier when she said what we need is a new type of, and better treatment for osteoarthritis. To the gastroenterologist and the cardiologists here, I have a clinic full of osteoarthritis patients, and none of these drugs work well.

This one doesn't. None of them do. They are better than placebo. There is nothing special about this drug that would warrant giving it to patients and putting them at risk of cardiovascular death, period.

Are there any additional studies that need to be done on this drug or any others of this class for osteoarthritis? No. These drugs are not indicated for osteoarthritis, unless we determine that their cardiovascular risk is less than what it seems, because these are people at high risk of cardiovascular death.

 

That doesn't mean that osteoarthritis doesn't need treatment. It desperately needs treatment, more than rheumatoid arthritis now. It is not a very pleasant disease to have that's successfully treated. This class and conventional nonsteroidals just don't work all that well in many patients.

This is not like many of the other chronic medical disorders that you guys are thinking, "That's the model here, where we have something curative and we can't give it to patients. We ought to try to figure out which patients might benefit from it."

That's not what's going on here. These drugs are modestly effective at best. I don't see any reason to test this or any others in its class further, unless we see that cardiovascular risk is really not increased.

CHAIRMAN TURK: Other help for the FDA on studies they would like to see?

Dr. Day.

DR. DAY: I just have a comment. Listening to the studies people would like to have, no one has

recommended a study where it's naproxen and a PPI. There was a lot of discussion of it before, but it has not risen to the surface now.

CHAIRMAN TURK: Dr. Ginzler.

DR. GINZLER: I would love to see someone be able to distinguish the antiinflammatory from the analgesic effects of nonsteroidal antiinflammatory drugs, not specifically coxibs versus standard nonsteroidals, but of any.

CHAIRMAN TURK: Ms. Solanche.

MS. SOLANCHE: On a completely different note, I would like people from the FDA, the people from Merck, everyone in this partnership patients do not fail drugs, drugs fail patients.

CHAIRMAN TURK: Any other comments?

Dr. Fries.

DR. FRIES: Yes. I did recommend if you were going to do something else, that it should be naproxen versus PPI. I think if you took what we've been talking about all day, you could probably see how that study would likely come out.

Since it would be such a huge study, I kind

of doubt if Merck would want to undertake that particular study. It would be of similar size to MEDAL. It would have a likelihood probably that there would be no GI advantage, so it would be a cardiovascular disadvantage. I don't think that would be likely to help them.

CHAIRMAN TURK: Last comments? Does FDA have any comments?

DR. MEYER: Well, since it seems like we are about to dismiss ourselves, I just wanted to on behalf of the Agency thank Dr. Turk and the rest of the members and temporary members of the Advisory Committee for a very thoughtful discussion.

You obviously did a lot of preparation. I think the advice was tremendously helpful to us. Again, on behalf of the Agency, I thank you all for your hard work and for your attendance and discussion today.

CHAIRMAN TURK: Thank you all very much.

DR. LEVIN: I would just like to take an opportunity to thank the Chair for his articulate leadership of this meeting.

(Applause.)

CHAIRMAN TURK: Thank you all very much. It's been a pleasure. Hopefully, we will see you all again sometime at a future meeting.

(WHEREUPON, at 4:05 p.m., the meeting was adjourned.)

 