these studies. You're expressing to the division at least what your concerns are; that we can look at, the agency can address bringing back to you, because that's what you're telling us -- you want us to come back to you -- with a look at what the co-morbidity populations are in the ADH, which is the large off label use population, and these other things.

And we'll have to sit down with these and figure out. We also know you want a followup report on the extrapyramidal type of effects. You want us to look at that more closely over time. We'll have to figure out how to do that in a way that's meaningful. Okay?

CHAIRPERSON RAPPLEY: Okay. So how about if I divide this then into two questions? We'll take a vote on this statement, and then the next will be our consensus about the recommendations we give to the Committee.

So the FDA will continue its standard ongoing safety monitoring for oral risperidone. All those in support of that, please raise their hand.

And all those who oppose that, please raise their hand.

DR. PENA: So just as a procedural point, just to get it on the record, we'll probably just go around and if you can say, you know, yes or no.

MS. CELENTO: Amy Celento, opposed.

DR. CNAAN: Avital Cnaan opposed.

DR. D'ANGIO: Carl D'Angio opposed.

DR. DURE: Leon Dure opposed.

DR. HUDSON: Melissa Hudson opposed.

DR. KOCIS: Keith Kocis opposed.

DR. MOTIL: Kathleen Motil opposed.

DR. NOTTERMAN: Daniel Notterman opposed.

CHAIRPERSON RAPPLEY: Marsha Rappley opposed.

DR. ROSENTHAL: Geoff Rosenthal opposed.

DR. RAKOWSKY: Alex Rakowsky opposed.

DR. VINING: Elaine Vining opposed.

DR. PENA: And, Mark, you're voting, Mark.

DR. HUDAK: Mark Hudak opposed.

DR. MURPHY: And Lisa wanted me to point out that you're rejecting that this be all that we do.

CHAIRPERSON RAPPLEY: Correct.

DR. MURPHY: But clearly if we think it's --

CHAIRPERSON RAPPLEY: It's a minimum.

DR. MURPHY: -- appropriate to bring other information back to you because you heard yesterday about the agency always has a way of looking at all of these products, they're going to continue that.

CHAIRPERSON RAPPLEY: Yes, we

continue the usual practice.

DR. MURPHY: Right.

CHAIRPERSON RAPPLEY: And now in addition to your usual practice, we recommend to you the statement that Carlos just read.

Yes, Keith.

DR. KOCIS: Can I just throw one other thing on top of that list at least potential for discussion? I'm not sure, at least in my mind, I'm not sure I need to wait another year or two to get additional information before we reconsider the current labeling. So I guess that would be the one question.

And then tied into that would also be what risk mitigation program, information one could consider. I could think of lots of things. Again, I don't use this drug. So I don't really want to say. I simply want to offer that up at this time as to whether strengthening the label, and I don't want to dismiss that it's completely inadequate. I

think it just doesn't emphasize some of the concerns that I and the other people on this Committee apparently have.

And then to address secondarily some of those issues proactively is to consider risk mitigation either with information to the patient and the parent and/or other things that we've discussed yesterday that we could consider.

CHAIRPERSON RAPPLEY: So we could ask the agency to also come back to us with some ways that would be compatible with the agency's mission and meet that concern. Does that make sense, Keith?

Melissa?

DR. MURPHY: I don't think, Keith, as we learned yesterday, that it has to be new, that you're not recommending a risk around, right? That's not what you're recommending, or was it?

Because remember you heard yesterday it has to be a new adverse event and

has to have all of those criteria. So I just want to make sure what you're saying here.

CHAIRPERSON RAPPLEY: You know, I think the Committee needs some guidance from the agency about how are ways that within the mission of the agency that these concerns can be addressed, and if the agency itself cannot address these concerns due to limitations on the agency, then we as a group need to think about other ways to other mechanisms that we could address this.

But we, I think, pretty strongly feel that to whatever extent it is compatible and within the limitations of the agency's ability to make statements we would like to do so in the strongest fashion allowable.

DR. MURPHY: Okay. Because he started talking about labeling. So are you talking about just labeling now? Because remember the ways of communicating are not just in the label. So that's why I'm asking for more clarity here.

DR. KOCIS: I don't want to be specific, but I also want to not say no to any of those things that you just posed to me. In fact, I want to consider all options at our disposal either through the FDA and through the specific avenues we have as an option now or in future when new indications are coming up for approval, and then likewise to consider options that extend beyond this Committee and our own circles.

DR. MURPHY: And the message of these, or the concern about the inappropriate use of this product in areas where it has not been studied.

DR. GOLDSTEIN: Not just inappropriate use, but the cumulative and long-term effects --

DR. MURPHY: Right, right.

DR. GOLDSTEIN: -- on patients who are on maintenance for the approved indications.

DR. MURPHY: Okay.

CHAIRPERSON RAPPLEY: Melissa.

DR. HUDSON: In that regard, I mean, I really think this label is pretty clear. These adverse events are listed in warnings and precautions, and within the sections and special populations and pediatric population it clearly states the long-term effects on growth and development, sexual maturation, bone density, you know, have not been established.

I'm not sure what else they can do at this point. We're asking for something beyond a population that they can really legitimately inform the label.

DR. MURPHY: I'm glad you said that because I actually was going to say this is really an enormous amount of safety information, very specific, large text areas for these in a label.

I mean, I think, I don't know if you guys have any other products that have -- maybe you do -- as much safety information in

them as these products do. So irrespective, it's a lot. You're right. So that's why we're struggling with, you know, exactly how the focus message of what you're concerned about because this is an enormous amount of safety information already.

CHAIRPERSON RAPPLEY: Dr. Notterman.

DR. NOTTERMAN: I would say that my principal concern, and I think some of my colleagues over the potential adverse effects has been amplified by an uneasiness that we don't understand the complexities or the scope of the unlabeled usage, and so my suggestion would be to defer any potential change or increment or escalation of notification and communication with practitioners until we've received the report that we just requested, with the understanding that it would be forthcoming in a reasonable amount of time.

And at that point the Committee could discuss with FDA whether, based on what

we've just learned, further action is necessary or recommended, I should say.

CHAIRPERSON RAPPLEY: And I would like to close with that statement this discussion. If there are further new comments to be brought forward?

DR. MURPHY: Okay. So at this point, I'm just going to repeat it, because we've got a number of recommendations from you which requires bringing back additional information to the Committee. In the meantime though, the Committee is concerned about a number of adverse effects, and particularly the large off label use in populations that aren't defined as the benefit.

You're willing to not pursue asking the agency to communicate in any other way until we get that additional information back to you, and then you will consider the data and decision about what need to be communicated. Is that fair?

Lisa, do you have any thoughts on

that? Tom?

Okay. Thank you.

CHAIRPERSON RAPPLEY: Thank you.

DR. MURPHY: You can see why standards come to you sometimes.

CHAIRPERSON RAPPLEY: Right. Now, I would like to say that we could repeat, as Dr. Farrar pointed out, much of this discussion when we consider olanzapine. So if we could give the message now that we have these concerns for this class of medication and then not repeat ourselves around this particular medication so that our comments can be focused in on things that are pertinent to olanzapine and not general to the class, is that acceptable to the committee?

(Off-mic comments.)

CHAIRPERSON RAPPLEY: Okay. Thank you.

DR. COLLINS: Okay. Now, I'm pleased to be able to present to you the one-year post exclusivity adverse event review for

olanzapine.

Oral Zyprexa, or olanzapine, is an atypical antipsychotic for which Eli Lilly is the drug sponsor. Original market approval occurred on September 30th, 1996, and pediatric exclusivity was granted on January 10th, 2007.

Prior to the pediatric exclusivity studies, oral Zyprexa was indicated for acute and maintenance treatment of schizophrenia in adults and acute and maintenance treatment of mixed or manic episodes associated with Bipolar I Disorder in adults.

The next two slides provide information about the use of olanzapine in out-patient settings. Four million oral olanzapine prescriptions were dispensed for all age groups during the 12-month pre and post exclusivity period. 2.5 percent of these prescriptions were for adolescents 13 to 17 years old, and 1.8 percent were for children zero to 12 years old.

There was a five percent decrease in oral olanzapine prescriptions for all age groups between the 12-month pre and post exclusivity periods with an eight percent decrease for the pediatric population.

Psychiatry was the top prescribing specialty during the post exclusivity period. All psychiatrist prescribed 52.6 percent of all oral olanzapine prescriptions, with child psychiatrists prescribing 4.9 percent of all prescriptions. Pediatricians prescribe 0.7 percent of all oral olanzapine prescriptions, and child neurologists prescribe 0.1 percent of all prescriptions.

The top diagnosis codes associated with oral olanzapine use were depressive disorder for patients 13 to 17 years old and anxiety states in early child psychoses for patients zero to 12 years old.

On November 30th, 2001, the FDA issued a written request for studies of oral olanzapine in the acute treatment of

schizophrenia and the acute treatment of mania in Bipolar I Disorder in adolescent patients 13 to 17 years old. The resulting pediatric exclusivity studies included one pharmacokinetic study and two efficacy and safety studies that utilize flexible dosing ranging from 2.5 to 20 milligrams per day.

The pediatric exclusivity studies demonstrated a statistically significant effect of olanzapine for the proposed uses in adolescents. However, the Division of Psychiatry products concluded that additional safety information was needed to adequately describe the relevant risk information for adolescents in the labeling, specifically in the areas of weight gain, hyperglycemia and hyperlipidemia.

To date, olanzapine has not been approved for the studied uses in pediatric patients. However, safety data from the pediatric exclusivity studies have been incorporated into the drug labeling.

Based on the results from the pediatric exclusivity studies, several modifications were made to the warning section of the currently distributed drug labeling. The weight gain section was modified to include a monotherapy in adolescent subsection. This subsection notes that, one, the average adolescent weight gain during a three-week median exposure was 4.6 kilograms for the olanzapine treated group versus negative 0.3 kilograms for the placebo treated group.

And, two, the percentage of adolescent patients gaining at least seven percent of their baseline body weight during a four-week median exposure was 40.6 percent for the olanzapine treated group versus 9.8 percent for the placebo treated group.

The hyperglycemia section also was modified to include a monotherapy in adolescent subsection noting that the mean change in fasting glucose was 2.68 milligrams

per deciliter for the olanzapine treated group versus negative 2.59 milligrams per deciliter for the placebo treated group.

Lastly, the hyperlipidemia section was modified to include a monotherapy in adolescent subsection. This subsection notes that, one, the percentage of patients with fasting triglycerides that increase by greater than or equal to 50 milligrams per deciliter was 37 percent for the olanzapine treated group versus 15.2 percent for the placebo treated group.

Two, the percentage of patients with fasting total cholesterol that increased by greater than or equal to 40 milligrams per deciliter was 14.5 percent for the olanzapine treated group versus 4.5 percent for the placebo treated group.

And, three, the percentage of patients with fasting LDL cholesterol that increased from borderline to high was 48.3 percent for the olanzapine treated group

versus zero percent for the placebo treated group.

Moving now from the exclusivity studies to post marketing reporting, this table describes the adverse event reports sine marketing approval.

For pediatric patients, there were 949 adverse event reports which comprised 4.4 percent of the total reports. Of these reports, there were 60 death reports with 41 being U.S. cases

Of the 60 crude count pediatric death reports identified since marketing approval, 14 reports were duplicated and two were miscoded adult reports. Of the 44 unique pediatric cases, 12 cases involved drug exposure during pregnancy, and eight cases involved an interdeterminate cause of death. The remaining 24 cases includes six suicide, five metabolic, four cardiac, five unusual use of olanzapine, and four other death cases.

After reviewing the 44 unique

pediatric death cases, the safety reviewer did not identify any new safety concerns.

There are multiple sections of the drug labeling that are relevant to the pediatric death cases. The warning section of the drug labeling includes a subsection on hyperglycemia associated with diabetes mellitus, ketoacidosis and/or coma, and the precaution section includes a subsection on suicide.

The adverse reaction section of the drug labeling includes cardiac adverse events, such as bradycardia, atrial fibrillation, and heart arrest.

The next several slides provide more details for the 24 death cases, and you will note that unlabeled events have been underlines. Three of the six suicide cases involved adolescents who ingested unknown amounts of olanzapine and were not known to have an olanzapine prescription.

The other three cases involved

adolescents with depression, agitation and/or anxiety who committed suicide within two months of initiating olanzapine treatment or increasing the dose.

The five metabolic cases involved adolescents who experienced diabetic ketoacidosis and/or coma with known olanzapine doses ranging from five to 15 milligrams.

Three of the four cardiac cases involved males who experienced cardiac arrythmia or rest while on olanzapine. In two of the cases, death occurred four to eight days after increasing the olanzapine dose to ten or 30 milligrams. The fourth cardiac case involved an 11 year old male who experienced myocardial infarction two and a half years after initiating olanzapine therapy.

For the five unusual use of olanzapine cases, the first case involved a two year old female who, according to the medical examiner, died possibly due to a drug interaction between olanzapine and atomoxetine

used to treat hyperactivity and possible bipolar disorder.

The second case involved a 15 year old male who drowned while on olanzapine and dextroamphetamine. These medications had been prescribed for the treatment of Asperger's Syndrome and Attention Deficit Hyperactivity Disorder.

Cases three, four and five involve children who experience fatal injuries inflicted by their parents when they were asphyxiated after being given olanzapine to sleep and morphine or hydromorphone or killed by other means.

As you will recall, there were four other death cases. The first case involved a 14 year old male with a history of asthma who experienced an acute asthma attack while taking olanzapine.

The second case involved a 16 year old who experienced a possible drug interaction and hepatic steatosis and was

found dead after initiating olanzapine treatment.

The third case involved a 15 year old male who died from necrotizing pancreatitis within three months of initiating olanzapine therapy. Of note, the patient was also on carbamazepine, paroxetine, and valproate, and each of these medications has a labeled association for pancreatitis.

And the last case involved as 12 year old female who died from unknown cases within one month of discontinuing olanzapine and initiating quetiapine therapy. She was diagnosed with diabetes and ketoacidosis three months prior to death and had multiple other diagnoses.

Going back to the table describing adverse event reports since marketing approval for pediatric patients, there were 631 serious adverse event reports with 444 being U.S. reports. You will note again that the definition of a serious adverse event that was

used when identifying these cases is noted in the footnote.

Looking at the post exclusivity period for pediatric patients, there were 69 serious adverse event reports with 42 of these being U.S. cases. Of the 69 crude count pediatric serious adverse event reports identified during the post exclusivity period, three of these reports were duplicates. Of the 66 unique reports, seven were excluded because they were miscoded for age or the adverse event occurred prior to the use of olanzapine.

Of the 59 unique pediatric cases, 11 were excluded because they related to drug exposure during pregnancy. For the 48 remaining cases, the safety reviewer did not identify any new safety concerns.

Once again, there are multiple sections of the drug labeling that are relevant to the serious adverse event cases. The warnings and precautions section of the

drug labeling include subsections on hyperglycemia, weight gain, hyperlipidemia, and Neuroleptic Malignant Syndrome.

The precaution section of the drug labeling includes a subsection on seizures and the adverse reaction section mentioned leukopenia. Of the remaining 48 pediatric serious adverse event cases during the post exclusivity period, there were 27 metabolic effect cases, including cases with increased weight, hyperglycemia, diabetes mellitus, diabetic ketoacidosis, diabetic coma, elevated triglycerides and/or metabolic syndrome.

Four nervous system cases, including three seizure cases and one Neuroleptic Malignant Syndrome case, three blood dyscrasia cases, including two cases of leukopenia and one hemolytic anemia case, and 14 other cases that did not fall into any of these categories.

You will note that out of the cases described on this slide, hemolytic anemia is

the only one that is not included in the drug labeling.

This chart describes the various combinations of metabolic serious adverse events reported in pediatric patients. You will note that there are nine groups of reports for diabetes alone or diabetes combined with another metabolic adverse event.

For the 14 other serious adverse event cases, there were eight cases with labeled events, including three pancreatitis cases and five single case reports. Of note, one of the three pancreatitis cases was confounded by concomitant use of quetiapine and risperidone, both of which are labeled for an association with pancreatitis.

For the six cases with unlabeled events, all of the cases involved a single case report. Once again, the safety reviewer did not identify any new safety concerns.

This completes the one-year post exclusivity adverse event reporting. At

present olanzapine is not approved for use in any patient under 18 years of age, and safety data from the pediatric exclusivity trials have been incorporated into the drug labeling.

In view of the potential metabolic effects with the use of olanzapine, especially in pediatric patients, FDA will continue to evaluate the safety of olanzapine and will decide if any additional risk management regulatory action is needed.

Does the Advisory Committee concur is the question for the group.

And in closing, again, I'd like to acknowledge the assistance of numerous folks throughout the FDA in the Office of Surveillance and Epidemiology, the Division of Psychiatry Products, the Office of Clinical Pharmacology, the Office of Pediatric Therapeutics, and the Pediatric and Maternal Health Staff.

Thank you.

CHAIRPERSON RAPPLEY: Discussion?

Dr. Goldstein.

DR. GOLDSTEIN: Given that this same issue seems to occur in this drug as the other one in terms of metabolic syndrome, and I think your statement before was that there wasn't a differentiation between Type 1 or Type 2 diabetes, but you had thought that most of the cases were Type 1. Is there a mechanism and is it possible to differentiate in these adverse event reports whether or not this is onset of Type 1 or a new onset of Type 2?

I think that information would be helpful, particularly given the epidemic we're seeing of Type 2 in children, in elucidating what the safety effects are of these drugs.

DR. LAUGHREN: Someone from OC would have to comment on that. I mean, I think we are limited by what we have in those reports.

DR. McMAHON: I would like to ask Dr. Diak who did the review to comment.

DR. DIAK: Hi. I'm Ida-Lina Diak.

The reports unfortunately, due to the AERS reports, don't have enough information. So I have specified actually in my review, which I believe you have copies of, not all of the reports did state whether it was Type 1 or Type 2 and whether it was new onset or a preexisting condition.

CHAIRPERSON RAPPLEY: But given the information we received yesterday about the new data sets that are now available and right now you're just learning how to use those and learning what information actually is available there, it might be possible to have more specificity than about diagnoses, not from the spontaneous reporting system, but through some of these surveillance data sets.

DR. McMAHON: Yes, I think if we were to get more specificity about Type 1 versus Type 2 time to onset data when it occurred versus when a person started using the drug, all of that information, it would be

very helpful. I think it's pretty safe to say that the AERS database is not going to reliably give that.

So We will have to turn to other sources for that.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: I'm not going to repeat anything I already said. Two comments on this. One, they didn't use the structured label as we had seen previously and the like, and when you look at the label here -- and, again, I find it less than ideal that under pediatric use safety and effectiveness in pediatric patients have not been established, although when you read through and you go through the different subsections integrated into the adult and the specific side effects that we're looking at, there is included that adolescent data.

So I think moving this towards the structured form, it would likely address that concern about it being varied because there is

information and we should use that when we make decisions about using this drug.

The second thing, I didn't get to make this comment to Dianne, and it's similar here in the sense that, you know, throughout the years we are asked to look at these drugs one year after pediatric exclusivity, and when already many of the decisions have been made about risk mitigation and labeling and things, and then we're also told that, well, we can't really do that now or, you know, that opportunity was lost and that was a year ago in the sense that we weren't involved in the initial approval for the indications and stuff.

So it just becomes unsettling to us because I think had we seen this data or at least in some circumstances we might have been able to impact at that time rather than now, a year later, saying now that we review this data, we're looking at this and what can we do about that, and I don't think we should stop

trying to do what we think is in the best interest of the children and the utilization of the drug in the kids.

CHAIRPERSON RAPPLEY: Well, again, I know it's frustrating for you all because you're not involved in the approval process where they are limited to the studies. Okay? And as you know, this one -- you saw the letter -- didn't get the approval. So I don't know if the division wants to make anymore comments about that, but the point as you heard yesterday of why we're doing post marketing follow-up is because, you know, normally after something gets out in the market or you see that there's a new indication for pediatrics, the potential for it being used more and having more problems. That doesn't always work because there's so much off label use, and we understand that.

But the concept that we want to be able to have a post-marketing assessment, so

that's why you end up getting this data that you then have to try and apply. It's not really a retroactive fit. It's just, okay, this is what we knew at the time of approval or in this situation non-approval. Here is what we see in the post-marketing.

Now, is there anything that that post-marketing informs us that we should be doing differently than what was already in the label? That's really what the question is.

DR. KOCIS: And there's two things, and certainly as we talked about, we learned new things in the first year, and that's certainly what we're most interested in, but yet -- and again, I don't want to use a specific to this drug or this morning, but over the meetings of the years I've been here, there has been information in the studies that were done that at least in my mind some of those drugs and some of that information we knew at the time of approval, and we didn't learn anything more during the year. We just

reemphasized -- continued to see what we knew at that time, and again, it's just unsettling at this point to then say, well, we're handcuffed in what we can do because yadda-yadda-yadda.

CHAIRPERSON RAPPLEY: Well, you're not handcuffed. I mean, you can make a recommendation that you think that the information was there, and it still looks like that information is there, and we still need to do additional emphasis or focus on the pediatric part of it.

Now, in this one, I think they really made a point of going in and putting the pediatric safety into the label. So it is there.

Your point about -- and I think what he's saying, Tom -- is that having something more in the pediatric subsection because when it's not approved, the approach now is to try to put that information off, and they refer them back to the clinical trials

part so that it would be helpful to have something there. Okay?

And then, Lisa, I want you to add to your statement. Again, now all of these products before they have an action are coming to an internal review. The pediatric group does have an opportunity to make recommendations before that action is taken. The pediatric group is not always involved in a line-by-line discussion with the labeling. They are frequently, but I think you can speak to that.

But, I mean, it's not always at the same level is what I'm trying to say when it comes to the PeRC as it would be in a lengthy negotiating meeting.

DR. MATHIS: You are right, and I actually think that this labeling change happened prior to the PeRC and prior to a lot of our thoughts about consolidating information in that section of labeling.

But you absolutely are correct, and

I think that that's a really helpful suggestion and something that we'll address in the future PeRCs as well.

CHAIRPERSON RAPPLEY: Dr. Hudak.

DR. MURPHY: So we can fix that.

DR. HUDAK: Yes. I guess I'd just like to ask a general informational question, and from what I understand you had a meeting yesterday that might have spoken to this and you can cut me off at any point if that's the case.

But with respect to all of these reports and so forth, especially when we consider these drugs that are similar classes or similar indications, is there any way you can glean from the database information that would allow you to normalize some of these complications.

In other words, I have no idea looking at these two drugs now whether, you know, these complications which I think are very significant complications from a

metabolic standpoint are more or less frequent in a particular drug. I mean, I don't know if you have information about the number of prescriptions, whether you can break it down by duration of therapy because some of these things, I think the side effects are idiopathic and acute and some may be sort of more likely to occur with a cumulative drug exposure, but I find the numbers fairly unsatisfying in terms of being able to really get my hands around the meat of the risk issue.

If your interest is in getting comparative safety information across drugs in the class, which would be something that we, of course, like to have, I think you'd almost have to have head-to-head comparisons in a controlled setting, for example, to look at metabolic risk.

But, again, it always comes down to who is going to take on a study like that. I mean, it would have to be an agency like NIH.

I don't think you're going to learn that very well from post-marketing reports.

DR. HUDAK: Well, I guess I can't say that I wouldn't learn anything without looking at what the information might be. If you have, you know, a drug that has ten times higher complication of metabolic issues than another drug, I mean, that's pretty powerful.

DR. LAUGHREN: You know, it may be that there are some other databases and maybe some of these newer databases that are becoming available to FDA - Sentinel and so forth - could give us access to large cohorts that might allow you to get at some of those kinds of things.

MS. McMAHON: Ann McMahon, OSE.

I just would agree that it's going to be very difficult using passive surveillance systems to do any kind of comparison that would be very believable as far as rates of adverse events because there are so many different issues that go into

whether someone happens to report a particular adverse event for a particular drug in a particular population. It's going to be very hard to do anything with the passive surround system in that regard, but I would also say that it probably would need to be a head-to-head type comparison. I would agree with that because even in a system, a large database, if it's not a randomized situation, you still could have all kinds of problems with interpreting the data. That would be my guess.

Certainly as far as this passive surround system, it's going to be really hard to make direct comparisons.

CHAIRPERSON RAPPLEY: And that would be something we could include in a recommendation to the BPCA, to let that be part of the thing that they set out as important to look at for NIH funding.

Dr. Rakowsky. Then Dr. Goldstein.

DR. GOLDSTEIN: This is to Dr.

Murphy and Dr. McMahon, and if this was covered yesterday, again, please stop me.

Given that for the approval process, the pediatric age groups between zero and 17 are broken up into four or five different subgroups. I can't remember off the top of my head what they are.

Would it make sense when you're reporting safety data to follow those same age group demarcations?

As this data was being presented, I commented to Dr. Farrar, you know, it's unlikely a newborn is going to be given this particular drug, and of course, the next two slides had a one year old and a two year old.

(Laughter.)

DR. GOLDSTEIN: But that data in and of itself, if you can see to my mind this may be a mechanism to see potentially some age related, at least some safety issues. If there's only an n of one or two in the two year old population with this drug and both of

them had significant safety issues, that may be some relatively low hanging fruit for safety information that could be gleaned from this type of subcategorization.

CHAIRPERSON RAPPLEY: Dr. Dure.

DR. DURE: Yes, I just had a question for Dr. Collins. Those are two nice presentations. The second though is a drug that is not approved in childhood, and so I'm just curious because your bullet here, "decide if any additional risk management regulatory action is needed."

What are you thinking about?

DR. COLLINS: And that I'd have to defer to the division.

DR. LAUGHREN: Well, obviously, we've already included even though the drug is not approved in pediatric use yet, we have included a lot of safety information, in particular the metabolic information in the warning section.

So I guess the question is beyond

that, is there anything that you -- I mean, I just want to point out as context that we obviously do include information and labeling for off label use if we think it's important for prescribers to know about that. That's what we've done here.

So is there anything else that I guess you can recommend that we might do to highlight this?

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: Yes. I wanted to go back to the concept of rates and usage because it struck me, too, when I was looking at these. We cannot calculate rates. We don't have denominators. There's no question about it, and it is passive surveillance.

What has been brought to us typically and at least helped me as I've looked at these over the years are the usage reports because what the usage reports gives us and now yesterday you introduced to us a new database that would also get the mail

order usage reports in which we don't have now. What it gives us is how many were prescribed and at least some context if not of rates at least relative rates between -- they're not absolute rates by any means, but they're relative rates between the various drugs.

And I would suggest that in looking at the few atypical antipsychotics we actually look at those numbers when we come back to this, whenever it is we come back, because it will give us something as long as we remember that we're looking at relative and not absolute.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: You know, I think this drug since it's not approved, we have an opportunity to look at pediatric safety and what we may require upon approval or in the risk mitigation process that follows.

Again, this is not what I do for a living. There's a lot of smarter people

around the table and elsewhere who could give you probably an exhaustive list of things, but certainly the things that pop into my head to require would be things like hemoglobin A1c to look along with weight and glucose to see what is the chronic exposure that we can evaluate, to look at the impact of hyperglycemia over time.

Obviously, I think the sponsor would want to know whether the drugs that are being used will induce or predispose children to developing a chronic, debilitating, life shortening disease. I think that's who would be interested in funding these studies to have that knowledge, and again, at the time of approval, you know, putting in some additional risk management things, the movement disorders, again, from the neurology standpoint to begin to look at that prospectively in that first year, and to be able to gather that data along with the passive surveillance to move this forth since

we have a lot of concern about the class of drugs and as these new drugs are coming out, to begin to refine what we know and learn more as time goes on.

And finally, you know, with the labeling and the negotiation of the labeling, you know, I assume that FDA can say you're saying there's no safety or efficacy data in pediatrics. That section is empty on this label. Well, what can we have?

We have concerns about X, Y and Z. Do you have that data or should you get that data? And, again, incorporating that into what happens after approval. So there's just a few idea.

CHAIRPERSON RAPPLEY: So I'd like to --

DR. LAUGHREN: Just one follow-up on that. This label that you have in front of you is in the old format. This is going to be reformatted into the new format, and a lot of those problems will be fixed.

DR. MURPHY: And just to point to Dr. Kocis that this is your opportunity to tell the division because obviously they're going to be doing some additional labeling what you think needs to go into that because we've obviously heard your concern.

So I think what we're hearing is just what you said, some additional concerns about these areas, and I won't repeat them all that you all have said.

CHAIRPERSON RAPPLEY: Dr. Notterman.

DR. NOTTERMAN: Just a brief comment to follow up on Dr. Kocis. I think that in terms of the various elements of the metabolic burden and the weight gain, it might be appropriate for the division to specify or suggest some mitigating activities. Monitoring of hemoglobin A1c might be appropriate or have to be studied, attention to diet, nutritional counseling. The average weight gain, I think, was over five kilograms,

which is substantial, and it might be possible to mitigate that through appropriate anticipatory guidance and perhaps those elements could be specified.

CHAIRPERSON RAPPLEY: So the Committee needs to vote. The statement is that the FDA should continue to evaluate the safety of olanzapine and decide if any additional risk management regulatory action is needed.

So those who would support this statement, please raise your hand -- oh, a question. Yes.

DR. CNAAN: How does our statement from the previous summary fit into this?

CHAIRPERSON RAPPLEY: Yes, I think we could then make an additional comment that we'd like those recommendations that we made about risperidone to apply to olanzapine because it is in the same class of medication.

DR. GOLDSTEIN: Well, they may have to be addended because this is not approved,

whereas Risperdal is.

CHAIRPERSON RAPPLEY: Right. Good point.

DR. MURPHY: I think if it's acceptable with the Committee what we will do is we're going to take the class issue that you mentioned before, and I'd like us to focus just on this product because it is in a different stage, as Dr. Goldstein pointed out, and have the Committee make sure you articulate what you're telling the division as they go forward.

CHAIRPERSON RAPPLEY: So you would like us to restate recommendations pertinent to olanzapine, in particular.

DR. MURPHY: Yes, pertinent to olanzapine in particular.

CHAIRPERSON RAPPLEY: Okay. So then this --

DR. MURPHY: Because they're telling you that --

CHAIRPERSON RAPPLEY: I understand

why. So I just haven't formulated it as succinctly as I did with the risperidone.

DR. DURE: Well, in this case they want us to say whether they should continue to evaluate the safety, and then does FDA decide any additional risk management regulatory action.

CHAIRPERSON RAPPLEY: Well, that is their -- they do that. That's what they do and they take recommendations for us about that. So I think what we need to recommend to them now is the specific areas we'd like you to attend to as you do this continuing review.

DR. MURPHY: Right. The question in view of the discussion is, again, a little disconnected, if you will, because what it's saying is do you agree that we're going to go ahead and decide if any additional risk management regulatory action, and what in essence as you have already said is that we agree that there needs to be additional risk management, and here are our thoughts about

it.

CHAIRPERSON RAPPLEY: So we will take a vote on this question, but then we will recommend to the agency that as they continue to evaluate the safety of olanzapine, they consider in particular the metabolic syndrome and mitigation of risk in the pediatric population. Is that acceptable to the Committee?

DR. RAKOWSKY: Can we also add that if it gets approved or if it starts being used more in the pediatric population that they also break it out by age groups and more specificity like we asked for.

CHAIRPERSON RAPPLEY: Does the agency have that recommendation? Did you get that, Carlos?

DR. McMAHON: That's a request to break down the drug use data then or the adverse event data or both?

DR. RAKOWSKY: I think at this time the drug use in pediatrics is so low you get

so few granularities there, but if it would increase, to start breaking it down to more specificity.

CHAIRPERSON RAPPLEY: So we could say break down into the use data and the safety data according to age groups as much as feasible with the database.

DR. GOLDSTEIN: "Stratify" might be a better term.

CHAIRPERSON RAPPLEY: I think that's a good point. We've got lots of really capable epidemiologists on the staff. So as we misstate some of these things, you all substitute the appropriate, I think, terms for that.

DR. MURPHY: Yes. I mean, you all indicated clearly it's a futile act that we won't do it. Okay.

CHAIRPERSON RAPPLEY: So then the Committee, given those recommendations to the agency, continue to evaluate the safety of olanzapine and decide if any additional risk

management regulatory action is needed.

Those who support that, please raise your hand.

Any opposed?

So that is a consensus support of that statement.

Are there any other safety issues or ongoing issues with these last two medications that the agency is working with or sponsors are working with the agency on that we should be aware of?

(No response.)

DR. MURPHY: I think that it's clear that the agency is working on this and we'll take your recommendations into consideration as they move forward with this.

CHAIRPERSON RAPPLEY: Thank you.

I would like for us to take our break now, and then when we return we'll start with Levaquin. Because we have spent a lot of time on this, I'd like us to take a ten-minute break if the Committee is okay with that.

Thank you. So reconvene in ten minutes.

(Whereupon, the above-entitled matter went off the record at 10:34 a.m. and resumed at 10:48 a.m.)

CHAIRPERSON RAPPLEY: Okay. We would like to resume.

DR. COPE: Dr. Durmowicz, would you introduce yourself and background to start?

CHAIRPERSON RAPPLEY: Thank you.

DR. COPE: Thank you.

DR. DURMOWICZ: Good morning. I'm Beth Durmowicz. I'm a general pediatrician with an interest in children and youth with special health care needs, and I'm a member of the Pediatric and Maternal Health staff.

I have the pleasure to present the adverse event review for Levaquin or levofloxacin. My presentation will include background drug information, drug use trends, information from the pediatric exclusivity studies, labeling changes secondary to the

pediatric exclusivity studies, and additional relevant safety information and labeling, adverse events, and I'll conclude with a summary.

Levaquin or levofloxacin is an antibacterial in the fluoroquinolone class. The sponsor is Ortho McNeil. The oral table in injectable formulations were approved originally on December 20th, 1996, and the oral solution was approved on October 21st, 2004.

Pediatric exclusivity was granted on March 14th, 2007, and the labeling changes secondary to the exclusivity studies occurred on September 11th, 2007.

Levaquin is approved in adults for multiple bacterial inflections. No pediatric indication was approved related to the pediatric exclusivity studies.

Of note, in May 2008, Levaquin was approved for inhalational anthrax post exposure in pediatric patients greater or

equal to six months of age.

This slide presents the information on the drug use trends for oral levofloxacin in the out-patient setting during the three-year period April 1st, 2005 to March 31st, 2008. This represents the period two years prior and one year after the granting of pediatric exclusivity in March of 2007.

Overall the pediatric use of levofloxacin is decreasing, approximately 17 percent over this three-year period. Patients zero to 18 years of age represented approximately 1.2 percent of the total projected patients who filled a prescription, and this equates to approximately 112,000 patients in the one-year post exclusivity period. And patients zero to 18 years of age represented approximately one percent of the total dispensed prescriptions. This is approximately 130,000 prescriptions per year over the three-year period. Ninety-three percent of these prescriptions were prescribed

for patients 12 to 18 years of age.

General practice, family medicine, doctors of osteopathy was the top prescribing specialty, and the top diagnosis code in patients zero to five years was urinary tract infection; six to 11 years, cellulitis; and in patients 12 to 18 years, chronic sinusitis.

A written request was issued for studies of levofloxacin in June of 2006. The pharmacokinetic studies showed that systemic exposure at ten milligrams per kilogram per day twice a day in patients less than five years and ten milligrams per kilogram daily in patients greater or equal to five years both orally and intravenously were not equal to adult exposure.

The clinical studies were Phase 3 studies in patients six months to 17 years and four studies were submitted. Two of the studies were active controlled, the first a community acquired pneumonia study in patients six months to 16 years, the second a study of

acute otitis media in patients six months to five years.

The third study was a uncontrolled study of acute otitis media, and the fourth study was a long-term, one-year prospective surveillance study of musculoskeletal disorders in patients six months to 16 years.

Tendinopathy, arthritis, arthralgia, and gait abnormality were the adverse events of interest in this study.

Results of the studies showed that efficacy was comparable and not inferior to the comparators. However, no indication for community acquired pneumonia or acute otitis media was sought or approved secondary to the musculoskeletal events.

I will now briefly discuss the safety data from these four studies. The first study was the controlled study of community acquired pneumonia. Seven hundred twelve subjects were available for safety evaluation.

Two deaths occurred in this study, both within the levofloxacin group, but neither were thought to be treatment related. The first death report or death case of the study was a 13 and a half year old with multiple foci pneumonia, with pneumatocele, fever, and respiratory distress. This patient suffered a cardiorespiratory arrest on day three of the study five minutes after bronchoscopy. The patient had been being treated with levofloxacin 250 milligrams twice a day for three days.

The second death case was a 2.2 year old who died after presentation to the emergency department with a febrile illness associated with virulent laryngitis, leukocytosis, airway trapping, and respiratory distress. The patient had completed a ten-day course for pneumonia and had been considered to be clinically cured.

Serious adverse events occurred in 33 or six percent of the levofloxacin treated

group versus eight or four percent of the comparator treated subjects.

Musculoskeletal disorders occurred in two percent of the levafloxisin treated patients versus one percent in comparator treated subjects.

The second controlled study, the acute otitis media study, had 1,607 subjects available for safety evaluation. This study was actually not requested in the written request but provided for safety data.

No deaths occurred in this study. There were ten serious adverse events in the levofloxacin treated group versus 13 in the comparator treatment group. Most of these serious adverse events were considered doubtfully related or not related to the study drug.

The incidence of musculoskeletal events was higher in the levofloxacin treated subjects, and the difference between the treatment groups was significant with a P

value of 0.02.

The uncontrolled acute otitis media study had 204 subjects available for safety evaluation. This study also is not requested in the written request but submitted for safety data.

No deaths occurred. Seven subjects reported eight serious adverse events: a maculopapular rash with dehydration was reported in two subjects with a possible relationship to the study drug, and one subject developed bloody diarrhea, and the relationship of this was felt to be very likely. Musculoskeletal adverse events occurred in six subjects.

The long-term surveillance study results are presented in this slide. Two thousand three subjects were available for safety evaluation after the one-year period or at the one-year period. Musculoskeletal disorders were reported more frequently in the levofloxacin treated subjects over the one-

year period, and the incidence of the musculoskeletal disorders are presented in this table.

And as you can see, levofloxacin had a statistically higher incidence of musculoskeletal disorders than the comparator group at the 60-day period after first dose and the one-year period after first dose. The most frequently occurring musculoskeletal disorder was arthralgia.

Labeling changes secondary to the pediatric exclusivity studies occurred in September 2007 to reflect that levofloxacin is not indicated for pediatric patients, to describe musculoskeletal adverse events and to provide information on the clinical studies in adverse event profile. Changes to the highlight sections were in the use and specific population, pediatrics, and provided the following information.

Pediatrics, musculoskeletal disorders, arthralgia, arthritis, tendinopathy

and gait abnormality seen in more Levaquin treated patients than in comparator, shown to cause arthropathy and osteochondrosis in juvenile animals.

In subsections from the warnings and precautions, use of specific populations and nonclinical toxicology are referenced. Information included in the full prescribing information under Section 5, warnings and precautions, musculoskeletal disorders in pediatric patients and arthropathic effects in animals. Labeling states that levofloxacin is not indicated in patients less than 18 years due to increased musculoskeletal disorders, and the pediatric use section is referenced, and the animal studies are described.

Under Section 6 of labeling, serious otherwise important adverse reactions, the musculoskeletal disorders in pediatric patients are discussed in greater detail, and warnings and precautions is again referenced.

Within the use in specific

populations, pediatric use subsection, labeling states that levofloxacin is not indicated. The clinical trials are described, including a table with a musculoskeletal disorder incidence which I projected earlier.

There have been additional labeling changes since the changes associated with pediatric exclusivity. Of note, in May 2008 a new indication was approved for inhalational anthrax post exposure in pediatric patients greater or equal to six months of age and the dosage is provided for the patients. And this dosing is based on a model to determine the proper kinetics.

In addition, a boxed warning and medication guide were added to provide information on the risk of tendon rupture in tendinopathy in October of 2008.

This is the boxed warning that was added on October 3rd, 2008, to labeling. Additional relevant safety labeling information is included in the warnings and

precaution section and includes tendinopathy and tendon rupture, hypersensitivity reactions, other serious and sometimes fatal reactions, hematologic and renal toxicities, hepatotoxicity, central nervous system effects, including convulsions anxiety, confusion, depression, and insomnia, Clostridium difficile, associated diarrhea or colitis peripheral neuropathy, prolongation of the QT interval and isolated cases of torsade de pointes, musculoskeletal disorders in pediatric patients and arthropathic effects in animals, light glucose disturbances, photosensitivity and phototoxicity, and the development of drug resistent bacteria.

Levofloxacin is a Category C pregnancy medication, and other important adverse events listed include hypotension after rapid of bolus intravenous infusion, crystalluria or cylindruria, and the other adverse events are all discussed in the warnings and precautions sections.

So moving on from the exclusivity studies to the post marketing reporting of adverse events, this table presents the crude counts of adverse events since marketing approval in December 1996 for patients zero to 16 years of age. As you can see, there are a total of 116 reports, 89 from within the United States, 100 serious adverse events, 77 from the United States, and three reports of death.

This slide presents information about the three deaths since marketing approval. The first report was of a 13 year old male with cerebral palsy, mental retardation, and seizures treated for bronchopneumonia who died of an unknown cause while on levofloxacin. Note this patient was on multiple concomitant medications.

The second patient is a 12 year old male with reactive airways disease and allergies who developed dyspnea and anaphylaxis six to ten minutes after taking

levofloxacin, benzydamine hydrochloride, which is an anti-inflammatory agent, and cromoglicate sodium, which is a mast cell stabilizer for acute pharyngitis. This patient became comatose and died eight days after the event.

The third case is a 12 month old, and we did double check the age on this report. This report is a 12 months old with a complex past medical history, including colectomy, ileostomy, ulcerative colitis, and rheumatoid arthritis, who developed a pelvic collection and sepsis. This patient was treated with levofloxacin and metronidazole while on multiple concomitant meds. The patient developed metabolic acidosis, deteriorated and died of a myocardial infarction.

As mentioned in the table there were 100 serious adverse events reported in pediatrics, and we took a particular focus on musculoskeletal events as well as central

nervous system events. As you can see, 39 percent of the serious adverse events were musculoskeletal in nature. The reports include 21 reports of arthralgia or arthropathy, 13 reports of bone or tendon symptoms, five of those being tendon rupture, five reports of myalgia or myopathy.

The top diagnosis for patients who reported a musculoskeletal event was sinusitis, and the most common age was 12 to 16 years from which 82 percent of the reports were received.

There were 19 central nervous system events, and I reported the events, more than one. So five reports of seizure, four reports of abnormal behavior or confusion, three reports of hallucination, and two reports of panic attack. The diagnosis seized where the patients had a central nervous system event or sinusitis and unknown.

So in summary, no new safety signals were identified after completed

pediatric focused safety review on the use of levofloxacin. A boxed warning and medication guide were added to labeling October 3rd, 2008 to strengthen the existing warnings about the increased risk of developing tendinitis and tendon rupture in patients of all ages.

At this time FDA does not recommend any additional labeling changes. FDA recommends to continue routine ongoing post marketing safety monitoring. Does the Committee concur?

CHAIRPERSON RAPPLEY: Thank you.

Before we go on to discussion, would you like to introduce your new member at the table?

Thank you.

DR. BELEN: Dr. Ozlem Belen from Division of Special Pathogens and Transplant Drug Products. I'm a pediatric infectious disease specialist. I've been in FDA for the past seven years and with the division for the past three years.

CHAIRPERSON RAPPLEY: Thank you.

And just to recognize that we have five standard reviews, including this one, to complete before lunch, so if we can keep our questions as focused and comments as focused as possible.

Dr. Goldstein.

DR. GOLDSTEIN: Just very short, very minor. On page 208 under the musculoskeletal adverse event reports, the second paragraph notes that there were twice as many females reported with musculoskeletal symptoms, but the reviewer was unaware of any biologic reason that would make girls more susceptible to these events.

My understanding is that there actually are biomechanical reasons that adolescent females are more susceptible to these types of events and so it's just a clarification that I wanted to bring up.

DR. NOTTERMAN: I noticed that also. I agree, particularly with ACL

injuries.

The other question I was going to ask pertains to the box warning and to some of the other material where it's indicated that the risk of tendon rupture and tendinitis is particularly great over the age of 60, and I just want to make sure I understand that that is a true biological susceptibility and isn't an ascertainment bias that reflects the fact that the drug is not prescribed to a large extent under the age of, say, 12 or 16, according to the data you provided.

DR. BELEN: Before the approval of the black box warning and the medication guide as well, an extensive review other than the OSE review within our division evaluated the populations at risk.

And so although we identified that overall there is an increase relative risk of tendinitis and tendon rupture in all ages, the elderly population as well as concomitant steroid users, as well as transplant patients

were identified specifically having higher relative risk.

This was basically based on mostly literature search, not based on the OSE review that was provided to us, but maybe they can provide more input if they have more information relating to those patients specifically.

DR. NOTTERMAN: My only concern would be making sure that practitioners don't take this age delimiter as indicating that perhaps it's relatively safer to use it in younger patients, particularly older adolescents.

DR. BELEN: I would like to point out specifically we added in all ages. That concern was discussed within the division, with other divisions, as well as the Pediatric Division as well. So when you look at the black box warning, it says this happens in all ages, but the risk is further increased.

So I want to point out that the

risk is actually beyond whatever is there for this age group. So that was important for us to let the geriatric practitioners to know that this risk is there for when they prescribe it to elderly population because this population is at greater risk when they are debilitated.

CHAIRPERSON RAPPLEY: Dr. Rosenthal.

DR. MURPHY: And in our discussions, you know, there is that Section 5.6 which does talk about pediatrics specifically because we were actually concerned when we saw the black box. It did sort of take away. I mean, if you weren't familiar with the field, you could read it, but I think by having that in there and because of the fact that there was an actual increased relative risk in the elderly that the pediatrics is still, I hope, clear that they do have this risk, too, in the labeling.

CHAIRPERSON RAPPLEY: Dr.

Rosenthal.

DR. ROSENTHAL: My comment is actually not necessarily specific to Levaquin, but Levaquin provides a vehicle for making the observation. In the warnings and cautions section of the label under prolongation of the QT interval, there is a sentence which I think is a great sentence, boilerplate sentence. It says Levaquin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia and patients receiving Class 1A and Class 3 anti-arrhythmic agents.

I would just add to that that some additional phrase or wording that would include in that list other agents known to prolong QT because, you know, as this Committee has discovered and as the work of many in the room have shown, there are agents that aren't included in this list that are important prolongers of the QT interval and increased arrhythmic risk, particularly when

taken with other drugs that also prolong QT.

CHAIRPERSON RAPPLEY: Can you bring up the slide again that has the direct question on it for the Committee?

DR. DURMOWICZ: Yes.

CHAIRPERSON RAPPLEY: So no new safety signals, a boxed warning and medication guide have been added as recently as October. At this time the FDA does not recommend any additional labeling changes. FDA recommends to continue routine, ongoing post marketing safety monitoring.

Does the Committee concur? Do you wish -- go ahead.

DR. NOTTERMAN: Just to follow up on that last point, there are drugs for which FDA has placed a black box warning concerning QT interval change, and those black box warnings refer generally to the concomitant use of other drugs such as Levaquin which prolong or may prolong QT intervals.

So it would be good if there was

some harmonization between this Section 5.8 and the black box warning, for example, on drugs such as ziprasidone, which is a very broad warning about the use of any drug that could produce QTc interval lengthening.

DR. BELEN: Simply when you're making decisions regarding the black box warning, we have to look at the benefit-risk profile of the drug as well. So I have to look into all of the drugs which contain fluoroquinolones, for example, and look at that ratio.

So, therefore, you're right. We have to have harmonization, but we have to also look at certain risk for the certain drug as well.

DR. NOTTERMAN: I'm not suggesting a black box warning for QT interval here. I'm just suggesting that 5.8 mentioned the class of drugs that has a black box warning already for use with drugs like Levaquin. It's the same point that we just heard from Dr.

Rosenthal.

DR. BELEN: Yes. Thank you.

CHAIRPERSON RAPPLEY: So with that recommendation then to the agency, how many affirm that the FDA continue routine, ongoing post marketing safety monitoring? Please raise your hand.

Any opposed?

So we support that by consensus.

DR. MURPHY: Okay. So you're supporting this statement with the addition to the bullet that there is an additional labeling change as stated concerning --

CHAIRPERSON RAPPLEY: That we seek harmonization around the caution of prolongation of QT to include other agents that are known to cause QT prolongation.

DR. MURPHY: Right, in 5.8. So I just want to make clear --

CHAIRPERSON RAPPLEY: Five, point, eight.

DR. MURPHY: -- for Carlos and the

minutes that it's adoption of this concurrence with the recommendation.

CHAIRPERSON RAPPLEY: With that recommendation, yes. Thank you. Very good.

Dr. Collins.

DR. COLLINS: Okay. Good morning again, everyone. I'm now pleased to be able to present to you the one-year, post exclusivity adverse event review for lamotrigine.

Lamictal, or lamotrigine, is an anti-epileptic drug, or AED, for which GlaxoSmithKline is the drug sponsor.

Original market approval occurred on December 27th, 1994, and pediatric exclusivity was granted on February 14th, 2007.

Lamotrigine's current indications include adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastuat Syndrome, and primary generalized tonic-clonic seizures in adults and pediatric

patients two years and older, and conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone or valproate as a single anti-epileptic drug.

In addition, lamotrigine also is indicated for bipolar disorder maintenance treatment to delay the time to occurrence of mood episodes in adults treated for acute mood episodes with standard therapy.

The next two slides provide information about the use of lamotrigine in out-patient settings. Since lamotrigine is not approved for pediatric patients younger than two, I have highlighted the use data for that age group in yellow.

7.2 million lamotrigine prescriptions were dispensed for all age groups during the 12-month pre and post exclusivity period. Nine percent of these prescriptions were for pediatric patients zero

to 16 years old, and 0.02 percent of these prescriptions were for pediatric patients less than two years old.

There was a 22 percent increase in the lamotrigine prescriptions for all age groups between the 12-month pre and post exclusivity periods and an 11 percent decrease for pediatric patients younger than two years old.

Psychiatry was the top prescribing specialty during the post exclusivity period. Psychiatrists prescribed 50.4 percent of all lamotrigine prescriptions. Neurologists prescribed 18.3 percent, and pediatricians prescribed 1.1 percent.

The top diagnosis codes associated with lamotrigine use in patients zero to 16 years old were diagnoses related to epilepsy at 51 percent and diagnoses related to bipolar disorder at 34 percent.

Of note, prior to the written request for pediatric exclusivity studies,

lamotrigine already had a box warning for serious, life threatening, and fatal rashes in adult and pediatric patients.

In addition, lamotrigine already had an approved pediatric indication for adjunctive therapy for the generalized seizures of Lennox-Gastuat Syndrome in pediatric patients two years and older.

On December 17th, 1998, the FDA issued a written request for studies of lamotrigine as adjunctive therapy for partial seizures in pediatric patients one month to 16 years old. The resulting pediatric exclusivity studies were broken into two groups. For pediatric patients two years and older there was one efficacy, short-term safety, and pharmacokinetic study.

For pediatric patients of one to 24 months, there was one efficacy, short-term safety, and PK study, and one longer term safety and PK study.

For pediatric patients two years

and older, the pediatric exclusivity study demonstrated efficacy for adjunctive treatment of partial seizures. In the safety analysis serious rashes, including one rash related death, were seen in pediatric patients receiving adjunctive therapy.

For pediatric patients one to 24 months old, the Division of Neurology Products was unable to determine that lamotrigine is safe and effective for adjunctive treatment of partial seizures. Protocol specified analyses fail to detect a statistically significant treatment difference between adjunctive lamotrigine versus adjunctive placebo therapy, and adverse event data needed reanalysis using coding scheme more appropriate for a pediatric population unable to communicate symptoms.

Based on the findings of the pediatric exclusivity studies for patients two years and older, lamotrigine was approved for the studied use, and safety data were incorporated into the drug labeling.

For pediatric patients one to 24 months old, lamotrigine was not approved for the studied use. No labeling change was made as labeling of negative pediatric studies was not required when these studies were reviewed. However, the Division of Neurology Products acknowledges that labeling the study data for one to 24 month olds would be consistent with the 2007 reauthorization of the Best Pharmaceuticals for Children Act.

This slide lists all of the labeling sections that were changed based on the results of the pediatric exclusivity studies. Changes were made to the box warning, clinical pharmacology, clinical studies, indications and usage, warnings, precautions, and adverse reactions sections of the drug labeling.

The next several slides provide details of the safety labeling changes. The box warning section was changed to update the pediatric serious rash data. After the

pediatric exclusivity studies, the incidence of serious rash in pediatric patients receiving adjunctive therapy was 0.8 percent, and one rash related death had been reported out of 1,983 pediatric patients on adjunctive therapy.

The clinical pharmacology section, age in pediatric patients subsection, was changed to note that, one, lamotrigine clearance was influenced predominantly by total body weight and concurrent anti-epileptic drug therapy;

Two, oral clearance was higher on a body weight basis in pediatric patients weighing less than 30 kilograms than in adults;

And three, patients weighing less than 30 kilograms may need an increase of as much as 50 percent in maintenance doses based on clinical response.

The warning section, serious rash in pediatric population subsection, updated

the incidence of serious rash associated with lamotrigine in the prospectively followed pediatric cohort, including the occurrence of the one rash related death.

In addition, the revised labeling included data supporting the increased risk of rash with concomitant use of valproate acid.

The acute multi-organ failure subsection noted the updated number of pediatric fatalities associated with multi-organ failure and various degrees of hepatic failure. This subsection also noted the fact that the majority of these deaths occurred in association with other serious medical events.

The adverse reaction section, adjunctive therapy in pediatric patient subsection, was updated to include the most common adverse events seen in pediatric adjunctive therapy trials.

In addition, the subsection was changed to include information on the rate of discontinuations due to adverse events, and

the most commonly reported adverse events leading to discontinuation in pediatric placebo controlled trials, and in the larger group of pediatric placebo controlled and open label trials.

Lastly, the incidence and controlled adjunctive trials in pediatric patient subsection was changed to include updated treatment emergent adverse event data.

Moving now from the exclusivity studies to post marketing reporting, this table describes the adverse event reports since marketing approval. For pediatric patients, there were 1,787 adverse event reports, which comprised 12.5 percent of the total reports. Of these reports, there were 106 death reports, with 30 being U.S. reports.

Out of the 106 crude count pediatric death reports identified since marketing approval, 23 reports were duplicates, resulting in 83 unique pediatric cases. Of these unique cases, there were 38

cases of expected epilepsy complications, 16 cases of labeled warnings and precautions, 19 cases of adverse events with a high background rate in the general population, but lamotrigine cannot be excluded as a contributing factor, and ten other cases.

After reviewing the 83 unique pediatric death cases, the safety reviewer did not identify any new safety concerns.

There are multiple sections of the current labeling that are relevant to the pediatric death cases. Serious rashes in pediatric patients are discussed in the box warning, and the warning section of the drug labeling.

The precaution section includes sudden unexplained death in epilepsy and status epilepticus, and the adverse reaction section of the drug labeling mentions infection and pancreatitis.

The next several slides provide more details for the 83 unique pediatric death

cases identified since marketing approval, and you will note that unlabeled events have been underlined.

Of these cases, there were 19 cases of seizure, prolonged seizure or status epilepticus, 19 cases of patients found dead, death, or sudden death, and 16 cases of rash, Stevens Johnson Syndrome, or toxic epidermal necrolysis. All of these events are consistent with the current drug labeling.

Again, there were 19 adverse events that have a high background rate in the general population, but lamotrigine cannot be excluded as a contributing factor. Of these cases, nine involved in utero exposures, four involved pulmonary events, such as pneumonia, pulmonary infection, or aspiration pneumonopathy, and there was one case of each of the six events noted at the bottom of this slide.

Of note, pulmonary infection, sepsis and Varicella infection are not

specifically mentioned in the drug labeling, but infection in broad terms is listed as an adverse event.

The ten other death cases are described in greater detail on the next five slides. Overall, an association of these deaths with lamotrigine is unclear, because the cases include concomitant medications, underlying medical conditions and/or insufficient details.

There were four cardiac cases. The first case involved a ten year old male on lamotrigine monotherapy for four and a half years who was found unconscious and could not be revived. Autopsy showed signs of myocarditis.

The second case involved a 13 year old male who experienced increasing seizures over three years of lamotrigine treatment. Topiramate was added. Two months later, he was admitted to the hospital for an unspecified reason, and he died suddenly.

Autopsy found acute myocarditis.

The third case involved a 16 year old who experienced cardiac arrest one month after initiating lamotrigine and oxcarbazepine treatment for unknown indications. He was hospitalized, and died one week later.

And the fourth case involved an eight year old female who was found dead six months after initiating lamotrigine therapy to treat epilepsy. Autopsy found cardiac insufficiency and generalized inflammation of the respiratory tract.

The two pulmonary cases included a three year old male with encephalopathy and on oxygen treatment who developed respiratory and cardiac failure after 18 months of lamotrigine therapy, and a four year old male with global developmental delay, and on lamotrigine for one and a half months to treat seizures, who experienced fever and vomiting, a 30 minute seizure and respiratory arrest, and died.

The first hepatic case involved a

one year old male who developed an unspecified cerebrovascular disorder, hepatic abnormality, and purpura, after one year valproate sodium, and two weeks lamotrigine treatment for epilepsy.

The second hepatic case involved a 15 year old female who experienced rash and discontinued lamotrigine after three weeks of treatment for blackouts. The rash resolved, blackouts continued, occasional vomiting developed, and phenobarbital was started.

Two days later, which was two and a half weeks after lamotrigine was stopped, she was diagnosed with liver failure. A few days later, she had brain edema and death occurred. The occurrence of Reye's Syndrome also was considered.

The last two other cases involved an eight year old female on two years of lamotrigine and two months of topiramate therapy who developed hemorrhagic pancreatitis and died within 20 hours, and a ten year old

male with multiple disabilities on lamotrigine for ten months who developed renal failure and died. Amphotericin and acyclovir, both of which are associated with renal failure, were started two days before the onset of the adverse event.

Going back to the table describing the adverse event reports since marketing approval, for pediatric patients, there were 1,250 pediatric serious adverse event reports, with 635 being U.S. reports. You will note again that the definition of a serious adverse event that was used to identify these reports is provided in the footnote.

Looking at the post exclusivity period for pediatric patients, there were 172 serious adverse event reports, with 105 of these being U.S. reports.

Of the 172 crude count pediatric reports from the post exclusivity period, 398 adverse events were identified in three or more reports. Of these 398 events, 285 were

labeled, 57 were unlabeled, and 56 were events inappropriate for labeling because they can occur with all drugs, for example, the adverse event report of a drug being ineffective.

Once again, the safety reviewer did not identify any new safety concerns during her review of these serious adverse events.

There are multiple sections of the drug labeling that are relevant to the 285 labeled serious adverse events. The box warning section of the drug labeling discusses serious rash, including toxic epidermal necrolysis. The warning section discusses serious rash, including Stevens Johnson Syndrome, angioedema, fever, and lymphadenopathy, hypersensitivity reactions, including generalized hypersensitivity, disseminated intravascular coagulation, and lymphadenopathy, multi-organ failure, including hepatic failure, disseminated intravascular coagulation, and elevated transaminases, and blood dyscrasias, including

thrombocytopenia.

In addition, there are 33 different serious adverse events included in the post marketing reports which are noted in the adverse reaction section of the drug labeling as indicated on this slide.

The 57 unlabeled pediatric serious adverse events identified during the post exclusivity period are characterized on this slide. They included eight abnormal behavior events, six aggression events, four events each for blister, candidiasis, coagulopathy, and septic shock, and three events each for abnormal feces, anuria, blood pressure decrease, coordination abnormal, dysmorphism, hypotension, jaundice, lactose intolerance, and mucosal inflammation.

The safety reviewer did not identify a safety signal in these unlabeled serious adverse events.

Moving from the post marketing adverse event reports to FDA's risk management

activities, on January 31st, 2008, the FDA issued an alert that patients on anti-epileptic drugs should be closely monitored for behavior indicating suicidal thoughts or behavior or depression. This alert was based on FDA analyses of reports of suicidal behavior or ideation from placebo controlled studies of 11 anti-epileptic drugs in which the rate of suicidality was 0.43 percent for patients on anti-epileptic drugs, versus 0.22 percent for patients on placebo. Results were generally consistent among the 11 drugs.

The Division of Neurology Products has given presentations on this topic during prior Pediatric Advisory Committee meetings.

The 11 anti-epileptic drugs included in the analyses are listed on this slide. FDA is working to include information on the risk of suicidality in the labelings of all anti-epileptic drugs used for maintenance therapy.

The FDA's risk management

activities also have included a review of Lamictal medication errors related to name confusion. Lamictal tablets are primarily confused with Lamisil tablets, and this name confusion is well documented, and known to impact both adult and pediatric populations.

However, reported medication errors for Lamictal in pediatric patients have not increased since pediatric exclusivity was granted.

Interventions implemented to minimize medication errors due to name confusion include, one, listing the name pair, Lamictal and Lamisil, on the Institute for Safe Medication Practices Confused Drug Names List;

Two, the current ongoing, extensive educational campaign developed by the Lamictal sponsor to alert patients and health care professionals about the errors involving Lamictal and Lamisil name confusion;

And three, RxSafety Advisor, which

is a software program that alerts pharmacists to potential look alike and sound alike names by displaying a warning message prior to a claim being made, and after the claim is accepted. And overwrite code must be entered to bypass the message, and unlike many pharmacy warning systems, this message cannot be paged through.

The Lamictal sponsor has been working to help pharmacies implement this technology since 2007. In the future, the FDA will continue to monitor medication errors by assessing the communication programs developed by the Lamictal sponsor monitoring the effectiveness of the RxSafety Advisor, and monitoring for name confusion.

This completes the one-year post exclusivity adverse event reporting. At present, lamotrigine is not approved for use in patients under two years of age. Safety data from the pediatric exclusivity trial for two to 16 year olds have been incorporated

into the drug labeling, and the Division of Neurology Products is planning to include inflammation on the one to 24 month old study in labeling.

The safety review did not reveal any new safety concerns for lamotrigine. FDA is working to include suicidality data in the labelings of 11 anti-epileptic drugs, including lamotrigine. FDA also will continue to monitor medication errors related to name confusion, and FDA will continue its standard ongoing safety monitoring for lamotrigine.

And the question to the Committee is does the Committee concur with this approach?

And in closing I just would like to acknowledge the assistance I received from FDA staff in the Office of Surveillance and Epidemiology, the Office of Clinical Pharmacology, the Division of Neurology Products, the Office of Pediatric Therapeutics, and the Pediatric and Maternal

Health staff.

Thank you.

CHAIRPERSON RAPPLEY: Thank you.

Dr. Murphy, would you like to introduce the new people at the table?

DR. MURPHY: I'll ask each of the individuals from the Division to please introduce themselves, and a little bit about your background.

DR. HERSHKOWITZ: Hi. I'm Dr. Norman Hershkowitz. I'm a team leader in the Division of Neurology Products. I have trained as an adult neurologist. I'm also trained as a pharmacologist. I have a Ph.D. in pharmacology.

DR. SHERIDAN: I'm Dr. Phil Sheridan. I'm a medical officer with the Division of Neurology Products. I'm a pediatrician and pediatric neurologist.

CHAIRPERSON RAPPLEY: Thank you.

So open for discussion. Dr. Cnaan.

DR. CNAAN: Since there don't seem

to be questions in lamotrigine itself, I have a generic question for the division. In this --

DR. HERSHKOWITZ: Could I ask you to speak up?

DR. CNAAN: In the suicidality report, it included 11 drugs because they were the only drugs that had good controlled randomized clinical trials, et cetera. There were several drugs that were not included, because they're mostly too old, and didn't have this quality of studies.

Are there any plans to do anything about the labeling of those older drugs that were not included in this suicidality analysis just to inform that this is an issue in the same vein?

DR. HERSHKOWITZ: I'll refer you to the Advisory Committee, and the Advisory Committee voted that the division should include labeling for these other drugs, and I think legally -- I don't think I can tell you

what we're doing now, but I'll refer you to what the Advisory Committee recommended.

CHAIRPERSON RAPPLEY: Other questions or comments?

I would like to make a comment that it seems to me on hearing this presentation that, in this particular medication, the process worked really well, and what was accomplished here was exactly what was set out to be accomplished with the changes that have brought pediatric issues to people's attention.

One, you identified the very unique communication issues of people who are zero to two years of age, and I think that's important to acknowledge, and to create new mechanisms to determine signs and symptoms in that age group.

Two, we got new clearance data, and looked at new dosing requirements for this medication in children, in particular.

And three, some alerts were

generated in response to signals detected during the post exclusivity analysis that led to generalizations relevant to the entire class.

So it seemed to me that the intent of legislation and special act, and all of your extra workload, and our extra workload, resulted at least in this case in exactly the things we wanted to accomplish. So I commend the division for that.

DR. MURPHY: I think a clarification from the division was that you're basically agreeing or anticipating that they are going to put some information in, but you're reading this as saying that they will get that additional information in the label.

So I can tell you that we had a number of discussions about the wording of this. So because the agency cannot talk about, you know, any activities that are ongoing, so I think basically if you have a recommendation, because that's what you were

saying, and if others on the Committee agree with you, that you think that the division should include the information on the one to 24 month old study in the labeling, which of course, I can predict what your response is, but I just think for the record that if that's what you think should happen, then you need to go on the record to say that.

CHAIRPERSON RAPPLEY: So the Committee would need to concur that that information should be included in the labeling.

DR. HERSHKOWITZ: I didn't catch what you said. If it was a question, I'm a little --

DR. SHERIDAN: The answer is yes.

CHAIRPERSON RAPPLEY: So my own personal comments --

MR. HERSHKOWITZ: I have a little Meniere's disease, and my tinnitus is very high today.

CHAIRPERSON RAPPLEY: I can relate