to that.

My own comments were meant to be a compliment, and I think that Dr. Cnaan's comment was to see that this additional information was included before the other medications, and you concurred that that recommendation has already been given to you.

So we would like to also affirm that recommendation coming from this Committee, in addition to wherever else it came from, and so then yet another recommendation this Committee might make is that the information known about the zero to 24-month group also be included in the labeling.

Would this Committee like to make that recommendation?

So yes, we would. And so can you move to the last slide then about the question posed to the Committee?

Yes, Dr. Rosenthal?

DR. ROSENTHAL: I just have one

very nitpicky point. In the label under the adverse events section, under cardiovascular, migraine is listed, and I just wanted to know whether Dr. Dure put you up to that. As far as I'm concerned, migraine is in his system, and if there's a cardiac migraine, we would call that angina. So maybe just a clarification.

CHAIRPERSON RAPPLEY: Okay. So the question is, or the statement is, given the information on Slide 44 and 45, that the FDA will continue to monitor medication errors related to name confusion, will continue standard ongoing safety monitoring for lamotrigine, and will take the recommendations under advisement made by the Committee this morning.

Those in support of that, please raise your hand.

Any opposition?

So there is consensus on that. Thank you.

DR. MURPHY: Do you all have any questions?

Okay.

CHAIRPERSON RAPPLEY: Moving on to Ambien. Given that we are an hour behind at this point in time, if we could, again, keep our questions and comments focused, and ask our presenters to focus on those informations on the slide that are particularly relevant, we will read each slide as it comes up.

DR. MURPHY: And could I have the people from the division also introduce themselves at this point so we won't have to interrupt the flow? So if you would --

DR JILLAPALLI: I am Dr. Devanand Jillapalli with the Division of Neurology Products. I am the acting team leader for sleep products. I have training in adult neurology.

DR. DAVIS: I'm Dr. Carol Davis, and I am a clinical reviewer in the Division of Neurology. My residency was in PM&R.

DR. DURMOWICZ: Great. I'm now going to present the one year adverse event review for Ambien, or zolpidem tartrate. My presentation, again, 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 in labeling.

I'll also present adverse event since approval in one-year post exclusivity. I will conclude with a summary.

Ambien, or zolpidem tartrate, is a sedative hypnotic in the imidazopyridine class. Sanofi Aventis is the sponsor. Zolpidem was originally approved on December 16th, 1992, and pediatric exclusivity was granted on November 20th, 2006. The labeling changes secondary to the pediatric exclusivity study occurred on March 28th, 2007. Ambien is only indicated in adults for the short-term treatment of insomnia characterized by

difficulties with sleep initiation.

This slide provides information about the use of zolpidem in the out-patient setting over the three-year period December 1st, 2004, through November 30th, 2007, reflecting the two years of use before and one year of use after the granting of pediatric exclusivity on November 20th, 2006.

The overall use of zolpidem is increasing in adults, approximately 15 percent since exclusivity. However, the overall use in pediatric patients is decreasing, approximately five percent since exclusivity.

Patients zero to 16 years of age accounted for less than one percent of the total dispensed prescriptions, which is approximately 51,000 prescriptions per year over the three-year period, and patients zero to 16 years accounted for less than one percent of the total projected patients who filled a prescription for Ambien, which is approximately 25,000 patients over the one-

year period post exclusivity.

General practice, family practice, doctors of osteopathy was the top prescribing specialty for Ambien. The top diagnosis code in patients six to 11 years was sleep disturbances, and in patients 12 to 16 years, sleep disturbances and depressive disorder.

A written request was issued in July 2006 to study the safety and efficacy of zolpidem in children with ADHD associated insomnia. A pharmacokinetic study in 64 patients two to 18 years of age was conducted to inform the clinical trial, and use doses of 0.25 milligrams per kilogram per day to a max of ten milligrams per day.

The clinical study was a Phase 3, double blind, randomized placebo controlled parallel group study comparing the efficacy and safety of zolpidem to placebo in 201 pediatric patients with ADHD associated insomnia for eight weeks. The results of the study showed that zolpidem did not

significantly decrease latency to persistent sleep compared to placebo.

The safety data from the clinical trials presented in this slide, there were no deaths. Psychiatric and nervous system disorders comprised the most frequent treatment, emergent adverse events.

As you can see, dizziness occurred in 23.5 percent of the zolpidem treated patients versus 1.5 percent of placebo; headache 12.5 percent in zolpidem treated patients versus 9.2 percent of patients who are treated with placebo; and hallucinations occurred in 7.4 percent of patients treated with zolpidem versus zero percent in the control group.

In the adult trials, the incidence of hallucinations was less than one percent, and dizziness was one to five percent.

Labeling changes secondary to the pediatric exclusivity studies occurred in March 2007 to reflect that zolpidem did not

decrease sleep latency, to describe psychiatric and central nervous system adverse events, and to indicate that safety and effectiveness in pediatric patients have not been established.

Within the highlight section of labeling, changes were made to warnings and precautions and use in specific populations, and within the full prescribing information of labeling, changes were made to warnings and precautions, Section 5, use in specific populations, Section 8, and patient counseling information, Section 17.

Safety information in the current labeling secondary to the pediatric exclusivity studies includes information in the highlights section under use in specific populations. Under pediatric use, the labeling states that safety and effectiveness is not established.

Hallucinations, incidence rate, 7.4 percent, and other psychiatric and/or nervous

system adverse reactions were observed frequently in a study of pediatric patients with attention deficit hyperactivity disorder. Subsections 5.6 and 8.4 of the full prescribing information section of the labeling is referenced.

Within the full prescribing information, information from the pediatric exclusivity study is included in three sections of labeling. Under Section 5, warnings and precautions, two subsections has information. In Subsection 5.3, labeling describes the incidence in the clinical trials of hallucinations in adults and in pediatric patients.

In Subsection 5.6, labeling states that safety and effectiveness have not been established in pediatric patients, and the clinical trial in patients with ADHD is briefly described, specifically stating that zolpidem did not demonstrate decreased sleep latency compared to placebo, and the

hallucinations were reported in 7.4 percent of zolpidem treated patients, compared to zero percent of the patients who received placebo.

Within the pediatric use section, again, labeling states that safety and effectiveness of zolpidem have not been established in pediatric patients. The study is described, and includes the total number of patients in the study, the patients treated with zolpidem versus those treated with placebo. The study results are stated that zolpidem did not significantly decrease latency to persistent sleep, and the psychiatric and nervous system disorder incidence within the treatment group and within the placebo group are reported.

Section 17.4 includes a medication guide which states that Ambien is not for children.

Additional relevant safety information included in labeling is included in the warnings/precaution section, and

includes the need to evaluate for co-morbid diagnoses. So your anaphylactic and anaphylactoid reactions, abnormal thinking and behavior changes, withdrawal effects, central nervous system depressant effects, worsening of depression or suicidal thinking, and cautions used in special populations.

Ambien is a Category C drug in pregnancy, and all of the important adverse events are listed in warnings and precautions.

Of note, Ambien does not have a boxed warning or a contraindication other than a known hypersensitivity to the ingredient.

Moving on from the pediatric exclusivity to the post marketing reporting, this table provides the adverse event reports since marketing approval. As you can see, in pediatric patients zero to 16 years of age, there were 134 total reports, 77 from the United States, 107 serious adverse events, 57 from the United States, and 15 death reports, 11 of those being from the United States.

The adverse events reports of death since marketing approval are summarized in this slide. Of the 15 crude cases of death identified, two are duplicates, and I'd like to refer you to your handout that has an integrated death summary table to describe all of the deaths that were reported.

Six cases were excluded secondary to hearsay, accidental ingestion, inappropriate maternal dosing or overdose. Of the remaining seven reports, two were cases of suicide, both 15 year old and 17 year old males. Both had a history of suicide attempt and/or a mental health disorder. One report was of a cardiomyopathy, and there were four reports of congenital abnormality, or neonatal complication.

Of note, all of these four reports noted that the patient was exposed to multiple medications in utero.

This table actually presents the information of adverse event reports during

the one-year post exclusivity period. Pediatric patients zero to 16 years of age, a total of 20 total reports, eight from the United States, 18 serious adverse event reports, seven from the United States, and four reports of death, one of those being from the United States.

To review the fatal adverse events reported since one year post exclusivity, four reports of death in patients zero to 16 years were included in the crude counts of the adverse event reports. After further evaluation, two of the reported cases were excluded secondary to misuse or abuse or accidental ingestion of zolpidem, and an additional report of a 17 year old was found.

The 17 year old was a male who died of an apparent suicide. His past medical history was significant for anxiety, insomnia, and psychiatric treatment. The patient's diary revealed suicidal thoughts, and a gender identity disorder. Although the patient was

reported to have taken zolpidem on a regular basis, the drug screen was positive for caffeine only.

The second death report was of a pregnancy termination at approximately 23 weeks of gestation secondary to multiple anomalies and malformations. The preliminary autopsy results suggested a neurological cause for the deformities, and this mother was noted to be on multiple medications.

The third report was of a newborn male who was born at home and presented to the emergency department approximately one hour after birth in respiratory arrest. The resuscitation was unsuccessful. This mother was reportedly a chronic substance abuser who used multiple medications.

So here we've got presented information about the serious adverse event reports in the one-year patient, and this includes patients zero to 17 years of age. There were 13 unique reports identified, which

includes the three previous reports of death that we've discussed.

Of these 13 reports, six reports were of neurologic or psychologic events. Five reports were of congenital abnormalities or neonatal complications; one report of a hypersensitivity reaction; and there was one generic complaint.

Of note, there were no new serious unexpected events identified.

So further information about the neurological or psychological serious adverse events. All the reports were in the adolescent population. The first report was the suicide that we discussed previously. There was also a report of a patient with seizures, tetany, extrapyramidal effects, and dystonia; a report of seizure, and a patient was also on a weight control medication; a report of an adult drunk, a report of delirium, and a final report of dizziness, palpitations and hallucinations.

Further analysis of the seizures in patients zero to 17 years was unrevealing.

Looking further at the congenital abnormalities, fetal malformation or neonatal complications, two of these reports were the death reports we described previously. In addition, there's a report of a term neonate who experienced respiratory failure at the time of birth, a term neonate with talipes equinovarus, and a fifth report of a neonate with glandular hypospadias.

Of note, there was exposure in utero to multiple medications for all of these patients, and no pattern of malformation or teratogenicity was noted.

The hypersensitivity reaction was an adolescent who developed a rash after the first dose of Ambien, and after the second dose, the patient developed a rash, vomiting, and throat swelling shut. Of note, anaphylaxis is a labeled event.

The generic report was of an

adolescent who reported a lack of effect when switched to the generic form.

So in summary, due to the pediatric exclusivity studies, labeling has been changed to reflect that, compared to placebo, zolpidem treatment did not significantly improve sleep onset, and was associated with increased risk of neurologic and psychiatric adverse reactions, particularly hallucinations in pediatric patients with ADHD.

No unexpected adverse events were identified during the one-year pediatric exclusivity review. The FDA recommends returning to routine standard safety monitoring for all patients.

Does the Advisory Committee concur?

And I also would like to acknowledge the people who have helped us with the presentation and the background information.

CHAIRPERSON RAPPLEY: Open for discussion. Alex.

DR. RAKOWSKY: Dr. Durmowicz, can you go back one slide, please?

DR. DURMOWICZ: Sure.

DR. RAKOWSKY: So the labeling change is just the first point, or are you also saying that you have to state the known expected adverse events were identified? Is that in the label, the way it's written?

DR. DURMOWICZ: Can you repeat the question? I'm sorry.

DR. RAKOWSKY: In that first major bullet, you have two sub-bullets.

DR. DURMOWICZ: Yes.

DR. RAKOWSKY: Is that second sub-bullet actually in the label now?

DR. DURMOWICZ: No, I don't believe so. I'll defer to the division. I don't believe that statement is in the labeling.

DR. RAKOWSKY: Okay. Because the way it's written, it sounds as though you've added that to the label.

CHAIRPERSON RAPPLEY: No, that's a

comment to us as a Committee; is that correct?

DR. DURMOWICZ: Yes, that's our comment to you.

DR. RAKOWSKY: Okay.

CHAIRPERSON RAPPLEY: Further discussion? Dr. Rosenthal.

DR. ROSENTHAL: You know, in terms of the pediatric use section on the label, a statement is made that safety and effectiveness have not been established. It seems like, not only has the effectiveness not been established, and I realize that, depending on how the studies were powered, this may be too strong of a statement, but it seems like we really didn't see any effectiveness in terms of that, and we really did see some adverse effects.

And so I'm wondering whether the language doesn't need to be stronger about not using this agent, you know, for the indication in which it was studied.

DR. DURMOWICZ: I'll defer the

question to the division.

DR. JILLAPALLI: I'm sorry. We recognize that there are folks, healthcare providers, that might find the use of this drug in certain pediatric patients other than those in ADHD, and so we labeled it to provide the information that we obtained from the study in the ADHD population.

And we at that time felt that perhaps using much stronger language would discourage the use in those pediatric patients where it might be useful.

DR. ROSENTHAL: So is there evidence of efficacy of this agent in the pediatric population in any context?

DR. JILLAPALLI: No, we do not have any evidence of efficacy.

DR. ROSENTHAL: So this is seeming a little bit like the discussion that we had around cough and cold medications, where we really don't have any evidence of efficacy, but we do have some evidence of risk.

DR. JILLAPALLI: That's correct.

CHAIRPERSON RAPPLEY: Dr. Notterman.

DR. NOTTERMAN: Just to round out that discussion, however, the labeling change does indicate that a study was performed, and that it failed to demonstrate efficacy, and in fact -- I'm referring, I'm sorry, to page 319 in the briefing book, which is the label.

So the label now does indicate that a study was performed and it failed to document efficacy, and that, in fact, there were serious adverse events, notably hallucinations and other psychiatric disturbances.

Am I correct that this is a change?

DR. MURPHY: Yes. This was new information put into the label as a result of these studies. Am I saying that incorrectly?

DR. DURMOWICZ: No, I think that's correct.

DR. MURPHY: Yes. It's back to

what Marsha was saying earlier. You know, this is part of the initiative. The studies got done, and they showed they didn't work. So the question that seems to be on the table is, well, we know it's being used off label, should there be any more emphasis on the adverse event part of this?

And I think you're trying to address, well, it's described.

So I'm going to be quiet now, but the answer is, yes.

DR. NOTTERMAN: And if I'm correct, the use has been decreasing. There's a 29 percent decrease, if I remember correctly. Let me see -- a 13 percent decrease in use, zero to 16, from baseline to post exclusivity.

I'm asking these questions because I want to understand if this process is actually working the way that we hope it's working.

DR. MURPHY: We think that this is an example of getting informative negative

labeling. The tension I'm hearing is some people might have wanted more on the adverse events, but we think that this was a very positive step, reflects the legislation of getting this kind of information in the label.

DR. ROSENTHAL: Can you clarify for me how the contraindication section works? I mean, it seems like hypersensitivity to any agent is a contraindication, and there are very select other ones, but you know, it seems to me that there may be something that could be added to that section for agents where there seems to be an imbalance between the effectiveness and the risks.

DR. MATHIS: I'll actually take that one for you.

Good. I'm glad you asked a question. They told me you were supposed to ask -- or I was supposed to ask you a question yesterday. Well, this is reversed.

So the contraindication section is a section where there's databased evidence

that the product should never, ever be used in a given population, where the risks always outweigh the benefit.

So I think, in a situation like this where you have hypersensitivity, I believe that you have to have a documented case of hypersensitivity to include that in labeling under the contraindication section of labeling.

So you'll see some drugs that don't have that in there, although I imagine it's always a possibility with any product. Now, the other extent is, if you're talking about a situation where, in the population where it was studied, you had adverse events, so you don't want the product approved in that population, because there may be some patients within that population for whom the benefits would outweigh the risks, that wouldn't rise to the level of a contraindication.

But that is why it's so important to put that negative information into the

labeling, so that way people who are trying to use this product can understand the amount of adverse events associated with the product balanced against the efficacy.

And I think if you were to ever see this product come in in another formulation, we would have to go through the discussion with PREA, and consider whether or not we would want this product studied again in the pediatric population, in this pediatric population. And I think if we were basing it on the data that we have now, we would probably consider a waiver based on safety, and then that information would be incorporated into labeling, the safety concerns.

CHAIRPERSON RAPPLEY: So in summary, the concerns that were noted in the presentation were incorporated into the label in language as strong as the agency would use under these circumstances.

Ms. Vining.

MS. VINING: Just a question. That line that says, safety and effectiveness has not been established in pediatric patients, has been a common line in labeling for decades, and now we have new information. But I think some confusion is that that line remains even though new information is added.

Is there a way, given the new law that's in place, to change that tag line so that it is not confused with drugs that don't have safety and efficacy?

DR. MATHIS: We have been able to do that. One of the issues that comes up frequently is that the regulations actually call for that language, but it calls for that language or other appropriate language, and I think a lot of times people read that as requiring that language in this section of labeling.

So as we have been moving forward, we have been addressing that and trying to remove it. I think in this case it may be a

situation where there weren't two adequate and well controlled studies. I'm not sure if that's the case or not, but we're addressing that.

DR. MURPHY: I think the other thing, and I don't think it applies here, but just in general to answer your question is that, particularly if there are a number of indications, you don't want to take out the fact that it just hasn't been studied, you know, because you're providing the negative information so they can see it was negative there, but you don't want to always completely remove that statement.

I mean, we've been told it's not a helpful statement, and we understand that. But we can't wordsmith it, if you will. So there needs to be some indication in the label if there are other indications besides the one that you actually got studied, that you still remain with no approved indications for pediatrics, if you will.

MS. VINING: But would there ever be an opportunity to say safety and effectiveness for, whatever, compulsive disorder, has not been established so that you tie it directly to the indication versus more blanket statement?

Because it appears to be more blanketed.

DR. MURPHY: In this case, because you don't have a bunch of other indications, you could have done that.

Sometimes, as Lisa was beginning to allude to, they will not want to say it quite as strongly because there is, particularly in those inconclusives, or the situation which you described previously where we think the study - there may be trends - you think that they just didn't get something right about it, and you don't want to close the door completely. In other words, you want to say, in this study done this way, it didn't show any effect, without coming out and saying, you

know, it's not been shown to be effective for children.

Do you see what I'm saying?

So that's why the divisions really do struggle with how to relay to the public their level of evidence without having to repeat the whole trial. I think your complaint is that we've had this language forever, and it really isn't useful, and why can't we get it out?

I mean, that's sort of it.

CHAIRPERSON RAPPLEY: And I think, further, that language sort of perpetuates the thought that we hardly ever study anything in children anyways, so we can never draw any conclusions about children.

So that language has been with us perhaps too long, and if we have an opportunity to revisit that, I think that would be important, because people do fall back on that as well. What can we ever know about children, so we just have to use it, you

know, in an idiosyncratic way.

DR. GOLDSTEIN: So just to follow up on that, maybe Dr. Mathis could explain the difference between the labor and delivery statement and the pediatric use statement on page 361.

Labor and delivery, it says, Ambien has no established use in labor and delivery, whereas the pediatric statement, the safety and effectiveness have not been established.

Thank you.

DR. MATHIS: It actually goes to the regulatory requirements under labor and delivery. And that section of labeling is specific for drugs that are approved in that process, and Ambien is not approved in the process of labor and delivery.

The pregnancy and lactation section would be, hopefully it would have more information in it than the labor and delivery.

CHAIRPERSON RAPPLEY: And a final comment from Ms. Celento.

MS. CELENTO: I guess I just wanted to ask for clarification on the fact that the med guide specifically says Ambien is not for children, and it does say that actually under what is Ambien. It does not say it under who should not take Ambien, but it's in the med guide that Ambien is not for children, and I understand it may not be in the label because you want to give doctors flexibility, but there just seems to be some inconsistency.

DR. MURPHY: Well, I had the same question, because -- is there even a med guide for this product?

There is. Okay, and that's just telling us what the statement says in the med guide. Okay. So back to her question, that there seems to be an inconsistency between the two.

DR. JILLAPALLI: We recognize that there is some inconsistency. The med guide is more geared to patients and parents of children, and it's more difficult to explain

to them that, in a certain segment, in certain circumstances, that the benefits of the drug may actually outweigh the risk, and that's something that we've left the healthcare provider to make that sort of risk-benefit decision, and discuss that with the parents of the children.

DR. MURPHY: So you weren't here maybe for some earlier discussions where the Committee was looking for a stronger statement, and I think they found it in your med guide. So the issue here is, if the med guide is making statements such as Ambien is not for children, why could we not put it in other places?

I mean, is that sort of what I'm hearing from the Committee?

What Lisa is saying, we have certain regulatory language we're supposed to use, but again, the other part of the label is written in language that's for physicians. This is written for general public, and so

some of it is just, maybe the general public forthrightness language is more informative than the physician language.

DR. MATHIS: I think there may be a nuance here that we're missing, and one is that, first of all, I'm not sure, does anybody know if the indication says specifically what it says on the slide, which is adult only short term-treatment of insomnia?

Is this verbatim from the label?

DR. DURMOWICZ: I'd have to double check that. Do you know?

DR. MATHIS: Somebody double check it, because if it does say --

CHAIRPERSON RAPPLEY: I can read from the label right here, "Ambien is indicated for short-term treatment of insomnia characterized by difficulties with sleep initiation. Ambien has been shown to decrease sleep latency for up to 35 days in controlled clinical studies." No mention of age.

DR. MATHIS: Never mind.

DR. DURMOWICZ: In a previous version of labeling, this is the most -- for the medication guide, this is the most recent version -- there was actually more wording in the parent guide, and the division maybe could be able to comment on that. And I think sometimes we feel that less is more, and so instead of kind of a longer paragraph in the medication guide, it was shortened with the most recent labeling change.

CHAIRPERSON RAPPLEY: So I think I want to clarify this question, and not to prolong the discussion, but the division felt it was important enough to put in the med guide, Ambien is not for children, but they felt that they should not consciously decide to not put that strong a message into the labeling for health professionals. Is that true?

DR. JILLAPALLI: I think in principle that's true.

DR. MURPHY: I think you all have

heard previous discussions about, you know, the more language we put in, the more the physician is restricted, and so if the evidence is such that you want to say, it is not for children, then you are putting any physician who ever wants to or needs to use Ambien in a very difficult position.

So that's the balance here in that it gets back to, we're trying to get products studied, yes, we want them studied, but we also understand the practice of medicine is never going to be able, or is always going to have a need for physicians to have some leeway.

If you put in the statement in the labeling, and it is in the med guide, I understand that, but if you put it in the rest of the physician part of the labeling, it's not for children. It notches it up a little bit. So that's the balance.

You could say that you think it should be notched up. What we're trying to

explain, to Ms. Celento's very observant comment, was that they didn't make that. They decided to leave it one way in the medication guide, and leave it differently in the other.

Do you all have anything to add?

CHAIRPERSON RAPPLEY: Dr. D'Angio.

DR. D'ANGIO: I'd just add one thing. I think that maybe it is appropriate to leave the physician language the same as it is. The discussion that we're having is based on one study, and I think, to make the decision that it never should be used in children, or to get close to that, may be more of a conclusion than anyone could make on the basis of one study.

CHAIRPERSON RAPPLEY: Shall we consider the question then that, given that the labeling was changed to reflect the comments on the Slide 19, that the FDA return to routine standard safety monitoring for all patients.

Those who support this, please

raise your hand.

And those opposed?

So by consensus, we support this. We still have two more to do before lunch, and the reason we're pushing this is because we have a full afternoon.

So I would once again ask our presenters to try to highlight what's important for us to take home from the slide, because we will commit to reading the slide that's presented to us, and then our questions to be very focused.

Thank you.

DR. MURPHY: I'm going to ask our division representative to go ahead and introduce herself.

DR. LINDSTROM: I'm Dr. Jill Lindstrom. I'm a dermatologist, and I serve as a clinical team leader in the Division of Dermatology and Dental Products.

CHAIRPERSON RAPPLEY: Please start.

DR. BROWN: Okay. Hello and now

good afternoon. I am Patricia Brown, a medical officer in the Division of Dermatology and Dental Products and will be presenting the one-year post exclusivity adverse event review for terbinafine. The drug brand name is Lamisil, and the active ingredient is terbinafine hydrochloride. The therapeutic category is antifungal and the sponsor is Novartis Pharmaceuticals Corporation.

The original market approval was 1992 for the prescription topical cream, which was switched to over the counter in 1999. Tablets, topical solution, topical gel were approved 1996, 1997 and 1998, respectively. The oral granules formulation was approved September 28th, 2007.

A pediatric written request was issued December 28th, 2001 to study an age appropriate formulation of oral terbinafine in the treatment of tinea capitis. The pediatric written request was amended several times. The applicant submitted data from a number of

studies, including a PK study and a safety and efficacy study.

Pediatric exclusivity was granted December 4th, 2006. The indications for the various products are as follows: the oral granules is for tinea capitis in patients four years and older; tablets, onychomycosis in adults; topical cream, tinea pedis, tinea cruris, and tinea corporis in patients 12 and older; topical solution, tinea versicolor in adults; topical gel, tinea pedis, tinea cruris, tinea corporis, and tinea versicolor in adults.

Pediatric use accounted for approximately two percent of the total dispensed oral terbinafine prescriptions in the out-patient setting. There were no dispensed prescriptions for Lamisil oral granules in either adult or pediatric populations during the study period. The study period was December 1st, 2004 to November 30th, 2007.

Of note, oral granules was approved September 28th, 2007, and the product launch was delayed.

Exclusivity studies for Lamisil oral granules included a PK study, single and multiple dose in 16 children, aged four to eight years and diagnosed with tinea capitis. There were also two randomized, six week active controlled studies. The active control was griseofulvin.

These studies evaluated safety and efficacy in 1,549 subjects age four to 12 years, diagnosed with tinea capitis. Of these, 1,042 subjects were exposed to terbinafine and 507 were exposed to griseofulvin.

In the pharmacokinetic study, systemic exposure showed high interindividual variability. In general systemic exposure in children was similar to adults.

In the pivotal studies with regard to efficacy, terbinafine achieved superiority

over griseofulvin in one of the two pivotal studies. When subgroup analysis by species of fungal organism was performed, in both studies for T. tonsurans, terbinafine was more efficacious than griseofulvin.

However, in both studies for M. canis, griseofulvin was more efficacious than terbinafine. It should be noted that the U.S. prevalence of T. tonsurans is 90 to 96 percent and M. canis is one to five percent.

With regard to safety, the pivotal studies showed generally similar profiles of adverse events for both terbinafine and griseofulvin.

Regarding the pediatric population, exclusivity studies resulted in approval of a new formulation, Lamisil Oral Granules, approval of a new indication, tinea capitis, and labeling with information on usage, dosing, adverse events, clinical pharmacology, and clinical studies.

This slide summarizes the warnings

and precaution section for the pediatric formulation. Most of the information, however, came from the adult label. The following have been reported: cases of liver failure, some leading to death or liver transplant; severe neutropenia; Stevens Johnson Syndrome and toxic epidermal necrolysis; lupus erythematosus.

This slide summarizes the adverse reaction section. Adverse events greater than one percent in the pediatric pivotal trials included nasopharyngitis, headache, pyrexia, cough, vomiting, upper respiratory tract infection, upper abdominal pain, and diarrhea. This is not an exhaustive list.

Adverse reactions seen during post approval use for all formulations include thrombocytopenia, agranulocytosis, pancytopenia, anemia, myalgia, rhabdomyolysis, acute pancreatitis, and hair loss.

Pediatric exclusivity has not impacted the number of reported medication

errors. However, name confusion has occurred. Lamisil has been confused primarily with Lamictil. This is a well documented error, and interventions have been implemented that a previous speaker has alluded to. The Lamisil-Lamictil name pair has been added to the Institute for Safe Medication Practices and Confused Drug Names list. There has been an extensive educational campaign, and in 2007 the RxSafety Advisor was instituted. This is a software program that alerts the pharmacist to look alike and sound alike names. We will continue to monitor.

This slide shows the pediatric adverse events in the one-year post exclusivity period. So this is one year. It's a smaller time period than we will be talking about in the next slide. These are crude counts for reports of all sources from the data, pediatric exclusivity, December 4th, 2006, through January 4th, 2008. U.S. reports are in parentheses.

Of note, serious adverse drug experiences are defined per CFR 314.80, which include death, life threatening hospitalization, disability, congenital anomaly, and other serious and important medical events.

It should be pointed out that the category of "other" is based on the reporter's judgment of what is serious, and note for the pediatric age group zero to 16 years, there have been a total of seven events of which four were U.S. reports, and all were considered serious.

In contrast to the previous slide, this shows the pediatric adverse event since marketing approval, 1992 to the end of the study period. Crude counts of errors reports for all sources reveal in the pediatric age group a total of 84 adverse events. Forty-eight are U.S. Of these 80 were serious; 45 in the U.S.

One pediatric death has occurred.

This was a case of in utero exposure to terbinafine. The infant died after being diagnoses with Trisomy 13. This event is not likely to be related to terbinafine exposure.

This slide shows the strategy used by OSE to narrow the 47 serious cases since market approval in 1992. Remembering the earlier slide, two slides back, there were 80 crude count cases of which 77 represent non-duplicated reports. Of these 77 cases, 30 were excluded, 29 for various reasons such as drug ineffective, medication errors, no temporal relationship, and one was excluded for miscoded age.

This leaves 47 remaining cases that will be discussed in the following slides, and the next few slides discuss the serious pediatric adverse events since marketing approval in 1992. Skin reactions totaled 16 events. These are in the labeling. These have included the following, some of which required hospitalization: skin rashes,

erythema multi-forming, Stevens Johnson syndrome, toxic epidermal necrolysis, skin striae, hives, pruritus, and alopecia.

Neurologic events totaled five cases. These have included single reports of seizure or shaking spell, headache and neck pain, mental impairment, walking difficulty which might have been related to skin rash, and somnolence. Only headache is labeled.

There were five cases of gastrointestinal events. Of these, abdominal pain, vomiting and diarrhea are labeled. A non-labeled event was hematochezia in a three year old after three weeks of oral terbinafine. This event resolved after discontinuation.

Hematological events totaled three cases and included leukopenia, thrombocytopenia and anemia, and neutropenia, all of which are labeled events.

Musculoskeletal events totaled two cases and included myalgia and rhabdomyolysis,

both of which are labeled.

Continuing, hepatic events totaled two cases, both of which are labeled. One was a case of fatigue and upper abdominal cramps. In this case GPT was elevated and hepatosplenomegaly was noted. The other case was one that included increased bilirubin and alkaline phosphatase levels.

Renal and urinary events totaled two cases, both unlabeled. These consist of single reports of nephrotic syndrome and incontinence.

Psychiatric events totaled three cases, all unlabeled. A 13 year old developed depression, anxiety, insomnia, nausea, forgetfulness, and social withdrawal after three and a half weeks on oral terbinafine. The patient recovered with discontinuation.

The concomitant medication was metoclopramide, and labeling for that medicine includes depression under warnings. A 16 year old with a history if depression on

escotelpram and having a history of lime disease developed worsening depression and suicidal ideation after one month on oral terbinafine.

A 16 year old developed thoughts of self-harm after two months of oral terbinafine. The patient recovered after discontinuation of the terbinafine.

The category of other events totaled nine cases all of which are unlabeled. For oral terbinafine these included a 14 year old diagnoses with ALL 12 days after a three month course of terbinafine, a 13 year old with increased carbamazepine level after one month. The increased level resolved with adjustment of the carbamazepine dose. The patient completed three months of terbinafine.

This event was considered to be unlikely to be related to the terbinafine because the patient was on other medicines that could have inhibited CYP450 3A4 isoenzyme and the terbinafine is an inhibitor of the

CYP450 2D6 isoenzyme.

A 14 year old developed hypoglycemia after four weeks on terbinafine. This resolved without discontinuation of the terbinafine.

A five year old was noted to have chest pain and breast development after the first dose.

A ten year old developed ecchymosis after two days of treatment.

For typical terbinafine, four events were reported and no trend was seen.

In summary, for terbinafine no safety signals unique to the pediatric population have been identified since market approval, 1992. Since 1992, three psychiatric events were found in the pediatric population. However, there was underlying illness or use of concomitant medication that confounded the interpretation of causality.

Exclusivity studies resulted in approval of a new formulation and a new

indication.

This completes the one-year post exclusivity adverse event reporting for terbinafine. The FDA will continue its ongoing safety monitoring for terbinafine.

Does the Advisory Committee have any additional comments?

For providing information and advice for this presentation I'd like to acknowledge the contribution of the following individuals: from the Office of Surveillance and Epidemiology, from my own division, the Division of Dermatology and Dental Products, from the Pediatric and Maternal Health staff, and from the office of Pediatric Therapeutics.

Thank you.

CHAIRPERSON RAPPLEY: Thank you.

Open for discussion. Yes, Dr. Dure.

DR. DURE: It's more a question for information. It seems like your PK data for the oral preparation, the 16 kids, is that

typical? Did you extrapolate from, you know, the big studies that they did? I mean, it just seems like a small number because there was a lot of variation. There was a lot of variation. The coefficients was like 36 to 64 percent in an individual.

DR. LINDSTROM: I agree that there was a fair amount of variation seen. it is a fairly typical number, and it does represent the number agreed upon in the written request.

CHAIRPERSON RAPPLEY: Dr. Cnaan.

DR. CNAAN: Looking at the baseline bullet, 8.4, which is on page 8 of the label, this one is confusing to me. It describes that there were two randomized active control trials and it describes the side effects, but then it leaves us hanging. It doesn't have a statement of it worked; it didn't work. So I guess I'm just a little confused why this label is different from other labels when they have this Section 8.4 tell the reader what to think or what was found.

DR. LINDSTROM: That's a good question because this label is slightly different. A reason for that difference might be explained by the indication which specifies that the product is indicated for the treatment of tinea capitis in patients four years of age and older. So really the entire clinical study section would reflect the two trials that are referred to in Section 8.4.

DR. CNAAN: Except that in the two trials one was positive but the other was not.

DR. LINDSTROM: It depends on what you mean by a positive. I take your point, and yet I think that it's important to look comprehensively at the data presented in the clinical studies section. The outcome of these two trials, I think the outcomes, the data from them were to me, were very interesting, and we did present the primary outcome measure, complete cure from both arms in all subjects.

But on subgroup analysis, very

interesting findings were brought out and for the reasons that Dr. Brown discussed in her presentation, we also included in labeling subgroup analysis based on genus and species, specifically based on species of the two most prevalent organisms I believe both in the trials and more importantly, in disease as seen currently in the United States.

DR. CNAAN: I agree with that. I looked at it and the subgroup analysis is very compelling and shows consistency between the two studies. I think what I'm suggesting is if the 8.4 section had a line sort of pointing in that direction, it would really clarify and help. It's just a suggestion.

DR. MURPHY: And actually some of them do. That was the one thing, that this one doesn't refer. It refers you to the adverse reactions, but it actually has additional information. Sometimes it refers you back to the indications, and it didn't do that, and so that also would have helped.

DR. LINDSTROM: So I hear you saying you don't see a cross-reference to the indication of the clinical study section.

Thank you.

CHAIRPERSON RAPPLEY: Other comments?

Can you put up the slide with the question to the Committee, please? That would be the previous slide.

DR. BROWN: Now I've done something with the computer here. If I can request assistance.

CHAIRPERSON RAPPLEY: I can read it while we're pulling it up. So one year post exclusivity is completed. As a result we have approval for a new indication, and we have labeling changes on usage, dosage, adverse events, clinical pharmacology and clinical studies.

Given that those two things have occurred as a result of the one-year post exclusivity review, the recommendation is that

the FDA will continue its ongoing safety monitoring for terbinafine.

Does the Committee approve of that or support that recommendation? Please, show of hands.

Dr. Cnaan, are you supporting that? Can you show hands again just so I can be sure?

And any opposed?

So there's consensus on this recommendation. Thank you.

DR. MURPHY: And they will take your suggestion under consideration also to have a cross-reference in that section.

CHAIRPERSON RAPPLEY: Yes. So let the record show that we recommend a cross-reference in that section.

DR. MURPHY: Yes.

CHAIRPERSON RAPPLEY: Thank you.

And we move now to our last, and this is the presentation on Aldara, again asking us to move through this concisely.

DR. TAYLOR: Good afternoon. My name is Amy Taylor, and I'm a medical officer with the Pediatric and Maternal Health staff in the Office of New Drugs in CDER, and I'll be presenting the one-year post exclusivity adverse event review for imiquimod.

Aldara, or imiquimod, topical cream is an immune response modifier marketed by Graceway Pharmaceuticals. The product originally received marketing approval in February 1997 and received pediatric exclusivity in December 2006.

Aldara is indicated for the treatment of clinically typical, nonhyperkeratotic, nonhypertrophic, actinic keratosis on the face and scalp in immunocompetent adults, treatment of biopsy confirmed superficial basal cell carcinoma in immunocompetent adults, and treatment of external genital and periana warts, condyloma acuminata, in patients 12 years or older.

Studies in children ages two to 12

years with molluscum contagiosum failed to demonstrate efficacy, and this is listed in the labeling as a limitation of use.

You see here on this side the approved dosing for Aldara. Aldara prescriptions in the pediatric population ages zero to 16 years accounted for approximately 21 percent of total dispensed Aldara prescriptions.

Of the prescriptions dispensed to pediatric patients, 40 percent were dispensed to patients age six to ten years and 38 percent dispensed to patients 11 to 16 years. The top diagnoses were viral warts and molluscum contagiosum.

The exclusivity studies consisted of one single and multiple dose pharmacokinetic and safety study and two efficacy and safety studies in pediatric patients age two to 12 years with molluscum contagiosum.

The pharmacokinetic study found

that absorption of imiquimod following topical application in pediatric patients was comparable to adults.

The efficacy studies consisted of two double blind, vehicle controlled studies in 702 pediatric patients age two to 12 years with molluscum contagiosum. A total of 470 patients were exposed to Aldara. The treatment was up to 16 weeks.

Since the studies failed to demonstrate efficacy, since the vehicle clearance rates were higher than Aldara's, there was no indication for molluscum contagiosum granted.

In general, adverse events in the Aldara group resembled those seen in studies with adults. The most frequently reported possibly or probably related adverse event was application site reaction, which was 31 percent in the Aldara group and 20 percent in the vehicle group. A decrease in white blood cell count and absolute neutrophil count was

observed.

Severe local reactions were reported in the Aldara group with erythema being the most common at 28 percent. The exclusivity studies resulted in labeling changes in the three sections outlined here.

In the indication and usage section under limitation of use, the labeling states that studies in children two to 12 years with molluscum contagiosum failed to demonstrate efficacy.

The pediatric use section of labeling was changed to include a description of the two efficacy studies and their results, adverse events observed during the clinical studies including severe local reactions, as listed earlier in this presentation, and a description of the pharmacokinetic studies and results.

This chart lays out the AERS reports received in the one-year post exclusivity period. There were two pediatric

reports received which were non-serious.

This chart lays out AERS reports received since marketing approval. There were 84 pediatric reports. The reports in pediatric patients since marketing approval reported the uses you see here. Approved uses are underlined. Viral warts and molluscum contagiosum were the most common.

There was one pediatric death reported since marketing approval. The case involved a 16 year old female who committed suicide by gunshot while on the third month of her second course of imiquimod for viral warts. Her total treatment duration was 31 weeks. There was no known history of depression. Suicide is a labeled event.

There were 12 reports of serious pediatric adverse events since marketing approval. The adverse events are arranged by system. There were three neurologic adverse events as you see here, which are labeled events. There were two reported cases of

congenital anomalies. These are unlabeled events, and there was one hematologic adverse event also a labeled event.

There were six cases of localized reactions. The first case involved a seven year old female with a history of cerebral palsy who after two applications for genital warts developed extreme swelling and an inability to void necessitating catheterization in the emergency room. The patient was also diagnosed with a viral infection after developing a sore throat and a low grade fever.

The second case involves a 15 year old female with burning blisters, swelling, and an inability to void after one application for genital warts. She was treated with topical lidocaine.

The third case involves a four year old female with burning pain and an inability to void, fever and flu-like symptoms after three days of treatment for herpes. The

patient was hospitalized two days later.

The fourth case involves a 15 year old female with skin burns, blisters, pain upon urination, fever and fatigue after five days of treatment for genital warts. The patient was hospitalized and treated with antibiotics for the skin burns and blisters.

The fifth case involves a 16 year old female with burning, erosions, and ulcerations after three days of treatment for genital warts. The patient was hospitalized after developing fever, increased white blood cells, and flu-like symptoms.

The last case involves a ten year old male with an application site abscess requiring incision and drainage and antibiotics after one month of treatment from molluscum contagiosum.

The labeling states within the patient counseling information section that female patients that are being treated for genital warts should take special care if

applying the cream at the opening of the vagina because local skin reactions may cause difficulty in passing urine.

In summary, pediatrics accounts for 21 percent of Aldara use. Despite studies showing lack of efficacy, off label use is common, including the treatment of molluscum contagiosum. Pediatric female patients have reported an inability to void secondary to severe local reactions during use in the genital area. The Review Division is planning to update this adverse reaction in the labeling.

In addition to planning to update the labeling related to severe local reactions in females with use in the genital area, FDA will continue its standard ongoing safety monitoring for imiquimod.

Does the Advisory Committee concur?

And I would just like to thank those listed on this slide for their help with this presentation.

Thank you.

CHAIRPERSON RAPPLEY: Thank you.

Open for discussion. Dr. Dure and then Dr. Goldstein.

DR. DURE: A couple of years ago I think Dr. Mathis gave us a lecture on the label and it may not have been you, but it was somebody, and I was under the impression that it was a fairly highly codified document in terms of what the numbers mean.

But this is the first time I've actually seen a 1.4 limitations of use and 1.5 unevaluated populations, and I actually think that's great. I mean, this is sort of what we've been talking about all morning, and yet it's not in the other divisions that we have looked at, at least in their label. So I don't have anything bad to say about Aldara. I mean, it's a great presentation.

But the question is: is there not a level of standardization here within the agency in terms of the label? Because this

seems pretty unique from what we have seen before.

DR. LINDSTROM: You are correct. We do have a lot of guidance or I should say sponsors have a lot of guidance in how they write their package insert in the CFR. Under the section in the CFR that describes what information should and can be included in the indications and usage section, it does discuss limitations of use and unevaluated uses.

We thought that that was particularly important for this product, and so I appreciate your affirmation of the decision to include that information.

DR. MATHIS: And remember that we had two adequate and well controlled studies that were both negative, and I think another important point to make here is that if we look at the prescription practices, 20 percent of the prescriptions are still happening in the majority of patients with molluscum despite that specific language in labeling

saying that this product does not work.

So just an interesting point to people who are out there practicing medicine.

CHAIRPERSON RAPPLEY: Well, I take Dr. Dure's comment as encouraging the agency to encourage that consistently in all new labels.

DR. MURPHY: So what you're saying is that when we have negative studies, that we will be putting the information in the pediatric section; that if we think they're very strong, they're good, it's not inconclusive. It's not one of those where you may be -- in those situations that the Committee is recommending that we look to the Durum Division's use of the limitations of youth section as another place where we have very clear situations to define a limitation of the use in the pediatric population.

DR. DURE: I would say also the 1.5 unevaluated population is we have discussed this, the idea that we have drugs that are

being used in groups that have not been evaluated, and although cognizant of the idea that it may not be working so well because people are using the drug, but this is what this Committee has been sort of looking for.

DR. MURPHY: So, Lisa, you're the chair of the PeRC, and I think that's something that you could take back to them when the actions come to that Committee.

CHAIRPERSON RAPPLEY: And in addition, the comment limitations of use is right up front on page 1 when you open the insert. So I'd like to affirm that, too.

Dr. Goldstein, did you have another comment?

DR. GOLDSTEIN: I had two quick comments. One is where exactly would the additional language regarding the problems with urination and voiding go because it already seems to be in 17.6. Would it be repeated somewhere?

I'm on page 545. this is the new

label.

CHAIRPERSON RAPPLEY: Is our packet starting on page 524 the new label?

DR. GOLDSTEIN: Is that the new label or the old label?

CHAIRPERSON RAPPLEY: You don't know because you don't have our packet.

DR. LINDSTROM: I don't have your packet, but I suspect that you have the new label if you are identifying it by section number.

CHAIRPERSON RAPPLEY: It's the new one because it starts with that limitation of use.

DR. GOLDSTEIN: Okay. Then I guess just to be specific you might want to consider wording rather than "and may cause difficulty in passing urine," "and may cause difficulty or inability in passing urine."

DR. LINDSTROM: I apologize. Could you please repeat your suggestion?

DR. GOLDSTEIN: Yes. The end of

the sentence says "and may cause difficulty in passing urine," but actually somebody needed to be catheterized. So it may cause difficulty or the inability to pass urine. Just a suggestion.

CHAIRPERSON RAPPLEY: Dr. Rakowsky.

DR. RAKOWSKY: Is this also going to be put into the pediatric section or just in 17.6, this wording? I'm not sure. Is that what you're driving at also?

DR. GOLDSTEIN: That's what I'm not clear about either.

DR. MURPHY: Well, it could be either actually because I have to go back and look and see how much of the description was on the adverse events in the peds. section right now. If you want additional, 536, yes, it is. If you want more information about the urination issue, which clearly, we presented to you some pretty severe cases, and that's what you're getting at, if they're actually more severe, that 17.6 would be a possibility

because that would allow you to put more language in than when you're describing the trials. Do you see what I'm saying?

DR. GOLDSTEIN: No, wherever you want to put it is fine with me. We were just curious as to what you were going to do.

And then I just had a follow-up from a previous comment that I made about the safety data and the use data as being reported, that it might be useful to stratify it according to age groups. I was wondering if Dr. Murphy or Dr. McMahon or anybody else on the Committee might comment on the usefulness of that approach because I think this is another drug where if that information were given in that context, it may be helpful to sort out the issues.

CHAIRPERSON RAPPLEY: I think we did make that recommendation to the agency that they consider that whenever feasible, whenever the data allows it.

DR. GOLDSTEIN: I was just

wondering what they thought about it.

DR. MURPHY: I guess I would say if we have enough numbers or we particularly see that there's a sub-population that's particularly effective, I think it's definitely a good suggestion.

As I said though, if we get down into trying to lay out, you know, every sub group with one case or something, I don't think it will be useful for you or us.

DR. GOLDSTEIN: No. Well, actually I disagree on maybe some selective cases. My suggestion was to use the same age groups that are specified when you're applying for the pediatric assessment, and I actually think negative data can sometimes be helpful if it appears nobody is using it in neonates. That might be interesting.

CHAIRPERSON RAPPLEY: Dr. Kocis.

DR. KOCIS: Just some brief comments that even improve the pediatric use section, but I would remove the first section,

the first paragraph on page 536. It goes back to that "have not been established," and I don't think that's relevant, and make Paragraph 2 safety and efficacy a positive statement rather than the negative one or neutral one that have not been established. So it has been approved in children greater than 12 with blah, blah, blah, and then the final third paragraph is -- it's a long paragraph and you get to failed to demonstrate efficacy is the last part of that. So I would put that as the fourth word. Their cream was evaluated and failed to demonstrate efficacy into randomized, blah, blah, blah.

DR. MURPHY: I think what they're trying to say is this was -- actually we were discussing it -- it was hard to find it. So instead of having this generic statement, you're just saying take the statement you have and put it up front in place of that, in essence, right?

CHAIRPERSON RAPPLEY: Ms. Celento.

MS. CELENTO: Just one quick comment. I think it would benefit consumers if you carry through the limitations of use about efficacy not being demonstrated for MC. If you carry that into the med. guide because the med. guide is fairly descriptive about what you could use this for and not use it for, but MC is not listed in there.

DR. LINDSTROM: Oh, thank you.

MS. CELENTO: It's in your med. guide. I'm assuming the patient information section. It's page 547 for us.

DR. LINDSTROM: Thank you for that suggestion. A clarification, that although the patient information, the patient labeling follows the format of a medication guide, it's not actually a medication guide. It does follow that format.

CHAIRPERSON RAPPLEY: So we don't have a medication guide for this particular medication, but Ms. Celento was suggesting that that explicit statement about limitations

of use be included in the patient information as well as in the labeling.

DR. GOLDSTEIN: I apologize. I just want to make one more point for Dr. Murphy, and that is that having an n of zero in some of the patient subgroups may not provide useful information in terms of prescribing data, but it actually can be, I think, very instructive to potential prescribers and may discourage them from doing something without any evidence.

CHAIRPERSON RAPPLEY: And maybe some of that conversation can occur off line.

DR. MURPHY: Yes, because we're not going to be putting use data into the label because that will change. I didn't think that's what you meant. I just wanted to verify.

One other thing about the patient information. I just want to tell the Committee that just like the others have a standard format, to change the standard format

is not easy. So what you're actually suggesting is trying to take the other part of the labeling which went through ten years to get changed and now try to insert a different section into the patient --

CHAIRPERSON RAPPLEY: Perhaps not a different section, but just a comment that there is not effectiveness in --

DR. MURPHY: That we could do. We could figure a way --

CHAIRPERSON RAPPLEY: This is very important for patients to understand as well as professionals.

DR. MURPHY: Yes, we can figure out a place to put it, but that's what I'm trying to say. To create another section would be difficult.

CHAIRPERSON RAPPLEY: So can you flip to Slide 25?

So in addition then to the plans to change the label, which you do see reflected in a new label here, the FDA will continue its

standard ongoing safety monitoring for imiquimod, and is there support for that statement?

Any opposition?

So there's consensus support.

DR. MURPHY: Again, I'm just going to verify that you're concurring with the statement because you're recommending that we do update from the comments I heard --

CHAIRPERSON RAPPLEY: Yes.

DR. MURPHY: -- the local reactions and particularly one specific comment, but in general, the whole Committee is recommending that.

CHAIRPERSON RAPPLEY: Yes. Thank you.

We have to resume from lunch at 1:30, and that is because of our commitment to the open public hearing to begin on time. So I apologize to the Committee for that, but when we have these very good discussions, that's where it takes us. It eats into our

lunch.

DR. MURPHY: Do we have anybody? Do we have anybody for the open public hearing?

DR. PENA: Right now no one has signed up, but it is important to start at that time, Dianne.

DR. MURPHY: Even if nobody has signed up?

DR. PENA: Yes.

DR. MURPHY: We'll follow up on that because I know before we've actually asked and if nobody had signed up and nobody was in the audience --

DR. PENA: So let's talk about this off line.

DR. MURPHY: Yes, we could do it later.

CHAIRPERSON RAPPLEY: So lunch is in the same place as it was yesterday. For the new folks it's in the restaurant which is just to the left as you exit the building, and

it's a room at the far back.

Thank you.

(Whereupon, the above-entitled matter went off the record at 1:05 p.m. and resumed at 1:36 p.m.)

AFTERNOON SESSION

(1:36 p.m.)

CHAIRPERSON RAPPLEY: We would like to resume the meeting, and 1:30 is our time designated for our open public hearing.

We did not have anyone request time, but at this point in time we'd like to ask anyone who desires to speak at the public hearing session to please indicate that by stepping forward to the mic.

So I'd like to state for the record that we have no one who wishes to speak at our open public hearing.

In that case I'd like to move on with our agenda, and Dr. Cope is going to present our speaker.

DR. COPE: Thank you.

I've got the honor to present Dr. Rama Bhat. Dr. Bhat is professor of pediatrics at the University of Illinois, where he has been for the last 30 years since he did his fellowship. He is a Board

certified neonatologist, and he also is a pharmacologist as well.

So he's the Director of the Neonatology Unit and on faculty at University of Illinois, and all of you should have received a copy of his article also in your briefing materials.

Dr. Bhat.

DR. BHAT: Thank you, Dr. Cope, and thank you, Dr. Carlos Pena, for inviting me, and I want to thank the Committee for giving this opportunity to me.

I know your work is very tough, and I want to start by saying that I started neonatology in the mid-'70s when there were only four drugs available for the newborns, and when I looked in 2001 and 2003, I analyzed the number of drugs that premature babies are getting under 750 grams. It used to be 14 drugs before they went home.

So certainly we have come a long way from 1975 to about 2008, and it still

continues to increase rather than decrease, and of course, of that, 85 percent are off label uses. So I think you have a lot of work ahead, and I think you guys at least help me to get some sleep at night when I go that these drugs are probably well worked out and screened by the FDA as analyzed by the Pediatric Advisory Committee, and I thank you for that.

I just want to let you know that I was on the Speakers Bureau for Ovation Pharmaceuticals in 2007. At present I don't have any conflict of interest.

The main objectives for today for the next 20 minutes is to discuss the physiology of the chylothorax and describe the management of the chylothorax and the experience with the actreotide. And this is a new drug that has entered into the field of neonatology during the last five, six years, and we had few cases. I just want to stress here most of the cases that you read in the

literature are single case experiences, and in the last three, four years we have four cases so far which have used this drug.

Chyle is a lymphatic fluid that contains fat, protein, and also lymphocytes and enzymes, lipases and amylases. The specific gravity is about 10.12 to 10.25. It has got a milky appearance which is from the chylomicrons if the baby is taking any fat. Otherwise it will simply look like straw colored fluid. The protein content is about a little more than two grams, and the number of cells are usually more than 1,000 cells with more than 90 percent being lymphocyte, predominantly lymphocytes.

It also contains the albumen and globulin in adults. The amount of the chyle produced is about two to four liters per day, almost about 1.38 mL per kilo per hour. The flow depends upon the oral intake, particularly the fat. The higher the fat intake, higher is the fluid production, and it

is usually sturine.

I just want to give a brief description of the thoracic gut, the anatomy in the next few slides. As we can see thoracic gut starts around the second lumbar vertebra and it ascends up by the side of the aorta, passes through the aortaic hiatus, and then comes through around on the right side of the aorta, and then crosses over and then comes from behind and joins the left -- actually inanimate vein between the junction of the jugular and the subclavian wings.

If you want to look at it in a little bit different way, the lymphatic development, this is an excellent review published in the Nature Immunology reviews by Dr. Oliver, Guillermo Oliver from University of Tennessee, from St. Jude's, a very nice review. The top three figures actually represent the piglets' embryos from anywhere from 3.5 centimeters to about 5.5 centimeter size, and the lower figure actually represents

the human embryo, about nine weeks of gestation already seeing very nice thoracic gut and the lymphatic sacs, the jugular lymphatic sacs.

I want to point out that mainly because in certain conditions like the Down's Syndrome or in conditions like the Turner Syndrome you will see a tremendous amount of large lymphatic sacks developing, and as one can see, in this slide, this is the one variation of cystic hygroma collecting in the neck which is extending sometimes into the axilla, and this is a beautiful diagram by the Netter which we are all very familiar with, just to stress you that there's a whole lymphatic plexus in the subpleural region. So any time there is an obstruction to the thoracic duct either due to the higher pressure or from the thrombosis of the veins where the thoracic duct cannot empty the lymph into the vein, you can have a back pressure, and it an produce leakage and product as the

pleural effusion.

The same thing can happen when an abnormal position with the hyperextension of the neck. Prior to the delivery it can produce an obstructions and produces a bilateral pleural effusion and ascites and the infant can develop actually a hydrops fetalis. These are the so-called non-immune hydrops fetalis, and by the way, we are seeing an increasing number of these in the last 30 years. In the first several years I have not seen this many cases of severe hydrops in utero, and we are diagnosing them more because we have aggressive group of perinatologists who have diagnosed them very early. The majority of them get delivered at 32 weeks, and these are the babies, and I'll show you some X-rays of these babies with really a serious bilateral effusions.

Conunitum chylothorax, we arguing about one to 1,000 deliveries. Instead of increasing the number because of the

increasing diagnosis by the perinatologists, post operative chylothorax, on which I'm not going to dwell too much, we're seeing about 2.5 to about 4.7 percent of cases. There are quite a few good reviews available in the literature with as much as 50 to 80 cases in a series. So one can really review that, and that is probably the most common cause of chylothorax in the postnatal period.

Congenital of the etiology are chromosomal, from Down's Syndrome to Turner's and various malformations or it could be an idiopathic, postoperative from the cardiac surgery or pulmonary or from the T-E fistula surgery.

Traumatic from the birth trauma, and are extrinsic or intrinsic, any kind of an obstruction to the thoracic duct can result in a bilateral pleural effusion and ascites.

Make a diagnosis by the fluid composition, and it is a fusion that will continue to recur, and the chest radiography

which I will show you in a minute shows bilateral massive pleural effusion, and other way to diagnosis is a lymphangiography. You will see the dilated lymphatics, and by looking at the cell count of the fluid and also by the blood counts.

If you follow the blood counts of these babies who have bilateral chest tubes, they invariably become lymphopenic, and that puts them in a very high risk for developing infections, and the cardiac echo just to rule out, make sure that you rule out any cardiac anomalies, and cardio typing is also a must in many of these cases.

A classic picture of an infant with hydrops developed in our institution just about three months ago, and these are cases the obstetricians usually put a pigtail catheter into the pleura to drain the plural fluid so that at the time right after birth the baby can be easily ventilated. Otherwise unless you tap them, it is very difficult.

The lungs are very noncompliant. Most of them don't go to term. They had to deliver them pre-term. Otherwise they will go into severe hydrops and die in utero. So majority of them get delivered by about 32 to 33 week so gestation.

They give the steroids prior to the delivery, tap the fluid, and then deliver these infants. The majority of them have a cardio type dump already prior to the delivery.

This is the same infant following the chest tube insertion. The effusion is completely gone. This infant also required Octreotide Sandostatin up to about nine micrograms per kilo per hour. This is one of the biggest doses that we have used, and this baby subsequently went home. This is the chest X-ray just prior to the discharge, and did very well and is still doing extremely well. All of the chromosome results were normal.

How do you treat? The majority of the cases it's a conservative treatment, more than 80 percent success rate. I'll keep them without any feedings, provide total parental nutrition and a diet rich in MCT once they are stable. I think I want to underline that maybe one of the reasons why we are seeing some of the side effects, if you are too aggressive in feeding these babies very early and putting a lot of bacterial colonization and subsequently developing the necrotizing enterocolitis.

The other way of treating is evacuation, and the last resort is octreotide before the surgery.

Sandostatis is a cyclic octapeptide. Molecular weight is about 1,000 and can be given subcutaneously or intravenously. Bioavailability is 100 percent even when it is given subcutaneously. Volume of distribution is, in healthy volunteers, about 13.6 liters, and you drain yourself to

about 21.6 in patients with acromegaly.

Elimination half-life is about 1.7 to 1.9 hours in the adults. No information available in newborns and especially in the pre-term babies.

Thirty-two percent of the drug is excreted in the urine, and there are no pharmacokinetic studies available in the newborn.

The drug is also being used for acromegaly, Cushing's syndrome, insulinomas, and many of the GI disorders in the adults like secretory diarrhea, Zollinger Ellison Syndrome, post gastronomic dumping syndrome, and a severe GI bleed. The drug has been used with a good amount of success.

In the newborns, of course, the chylothorax which is not responding to the standard medical care, but by that I mean keeping the baby NPO, giving TPN and putting a chest tube drains and waiting for at least a few days. At least if it is draining too

much, I will leave that chest tube, and if not, if there's considerable drainage -- and by that I mean more than 15 to 20 mL per kilo per day -- one will definitely consider treating with octreotide.

Severe neonatal hypoglycemia, a couple of cases have been treated with a nesidioblastosis. These are the babies with the hyperinsulinemia. They have given octreotide. One of these infants actually developed necrotizing enterocolitis.

Mechanism of action, it decreases the splanchnic blood. There are the somantostatic in the sepsis, in the vascular bed, as well as in the lymphatic beds, and the reduction decreases the triglyceride absorption. It inhibits the serotonin, motilin, VIP and the gastrin, gastric hormones, GI hormones. It decreases the gall bladder contractility and the bile flow, thus leading to development of the sludge and the gall stones, reduction in the absorption of

the triglycerides from the gut, and that is one of the main mechanisms why the chyle formation decreases.

It also decreases the gastric and intestinal secretions. So decreased motility, decrease in the stasis in the gut can promote the bacterial overgrowth and can actually produce or develop necrotizing enterocolitis.

This is a review of the octreotide from the neonates up to about three months of age. I have excluded some of the later surgeries, babies having surgery in five months and beyond five months. I excluded those case, included mostly the neonatal chylothorax and some of the difurmatic hernia. Most of those cases had chylothorax post operatively, but basically those babies were born with the neonatal, you know, chylothoraxes, something like about 15, you know, cases that I know of being treated with octreotide.

And the drug has been given as an

IV subcute, and the duration may last anywhere from three days. There is no particular dose that one can actually recommend. Some babies respond to very small doses, and some babies require doses up to ten micrograms per kilo per hour, or about 240 micrograms per kilo per day.

And most of the chylothorax, the effusion stops actually at a dose between anywhere from 80 micrograms per kilo per day up to about 200 microgram per kilo per day. There is a cessation. So one can always question whether it is really the drug that is stopping the chylothorax formation or it is simply the duration. Since when you start giving it for seven to ten days, it may be the natural course of the disease, the chylothorax seizes to accumulate anymore.

This is a study from Dr. Au with the octreotide infusion. You can see with the initiation of the octreotide, actually the drainage actually decreases and subsequently

stops. Usually most of the clinicians will taper the dose over a three to four-day time once the effusion goes to less than ten mL per day.

This is the use of Sandostatin, not octreotide. This is from Beautica, published in the Intensive Care in 2001. You can see the dark dots indicated the Sandostatin infusion rate. When they reach about ten micrograms per kilo per day. Actually you can see the effusion going down almost to nothing.

The side effects are loose stools, nausea, flatulence, hypo or hyperglycemia, liver dysfunction, distended abdomen, hypothyroidism at least for one or two cases with the transient hypothyroidism requiring L-thyroxine supplementation; pulmonary hypertension, one case; and also, they can also produce hypotension.

Serious ones are the necrotizing enterocolitis and a cholelithiasis, and I want to spend a few minutes with the necrotizing

enterocolitis.

The incidence is about .3 to 2.4 cases per thousand live births, but if you look at the intensive care admissions alone, it's about 7.7 cases, 7.7 percent of all the admissions developing NEC in the intensive care nursery. More than 90 percent of the patients are under 1,500 grams, and the annual number of cases in the United States is about 2,500 with the mortality up to ten to 15 percent, but the fulminant necrotizing enterocolitis carries a mortality more than 50 percent. So it's a pretty lethal disease.

The pathophysiology, it's multi-factorial. We can't pinpoint one etiology in this case. Ischemia, immunity and the infection are the three Is. I usually tell the residents to the remember the three Is. That is the infection, immunity and the ischemia.

The previous concept was the asphyxia at the time of birth, so-called

initiation of the diving reflex and subsequently ischemia to the gut and subsequently developing the necrotizing enterocolitis.

That theory is not really very well proven at this time. The more I'd say intraluminal event leading to the subsequently developing necrotizing enterocolitis, almost all of the babies, more than 90 percent of the babies are fed. Breast milk actually has a protective effective. Formula definitely increases the risk for developing NEC because of the bacterial overgrowth is much higher in the formula fed than in the breast fed babies.

And of course, the immature luminal digestion and the bacterial proliferation are the major factors. There are several barrier functions, and actually Dr. Camilla Martin and Alan Walker from Harvard, they have written a very nice review in the Neonatal and Fetal Medicine where the new theories that we are looking at is the premature babies as an

immature gut with an individual mucosal function, whereas in the mature baby there is the gastric acid, adequate gut hormones, and there are an adequate amount of defensive mechanisms that are present with the commensal bacterial like the lactobacillus bifidum which pre-ranks the activation, subsequently prevents the activation of the nuclear kappa factor B and subsequently the release of the various cytokines from the nucleus activation and the gene activation.

That is seen in the premature babies who are fed formula, and these interluminal events actually leads to the subsequent development of the necrotizing enterocolitis.

It's a classic picture of NEC from our own unit about 20 years ago, extensive so-called fominant necrotizing enterocolitis. The surgeons actually did not do anything. They had to just close the abdomen, bring the baby back and, you know, disconnect the baby

from the respirator. So very poor outcome in those cases. If they survive, they have a serious sharp bone syndrome.

In other cases of necrotizing enterocolitis, the patchy areas of the necrosis, you can see with the submucosal air, subserosal air. Sometimes it is a through and through necrosis with the perforation and peritonitis, and the systemic sepsis.

So the treatment is surgical treatment. I missed the octreotide. Okay. I did mention -- I'm sorry -- octreotide dose. I have already given that to you.

Surgical treatment if no response to the octreotide. Some cases will require actually thoracic duct ligation. I don't have that experience, but I know some of our colleagues in Chicago have treated the babies with a several chylothorax requiring thoracic duct ligation or putting a shunt or a pleurectomy of the treatment. This is where they put the ligation in the high up just

before it enters the vein.

And I think what we need to know as far as the octreotide, the pharmacokinetics are not known. We don't have any idea about the dose response relationships. The adverse effects, we really don't have a good idea also. All of the few case reports that we have seen with the hypo and hyperglycemia infection and the necrotizing enterocolitis and gall stones.

There is actually a need for a multi-center randomized controlled studies both in the post surgical isolyzed and the chylothorax. Certainly we are seeing an increasing number from that point. Before this drug becomes in everybody's armamentarium, I think we need to have quite a bit of information at this time.

Thank you for your patience.

CHAIRPERSON RAPPLEY: Thank you very much.

DR. MURPHY: Thank you, Dr. Bhat,

very much.

And I know he has to leave. So if there are questions. We asked Dr. Bhat to present to the Committee because in the last discussion there was some uncertainty and confusion as to how this product is being used off label in the neonates, and if you're going to address the labeling, we thought it would be a good idea if you understand what was going on with this product.

And he thought he had his presentation this morning. He says, oh, he changed his planning once. So we'd like to have you address your questions to him now if you have any.

CHAIRPERSON RAPPLEY: Yes, Dr. Rakowsky.

DR. RAKOWSKY: Two questions actually. How commonly will this be used for chylothorax, say, in the NICU that has a few thousand admissions a year?

I'm trying to go into the