U.S. FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ADVISORY COMMITTEE

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MEETING

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OPEN SESSION

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WEDNESDAY

APRIL 11, 2007

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The meeting came to order at 4:00 p.m. in the Advisory Committee Conference Room, Room 1066, 5630 Fishers Lane, Rockville, Maryland, Marsha Rappley, M.D., presiding.

PRESENT:

MARSHA RAPPLEY, M.D.	Chair
CARLOS PENA, Ph.D., M.S.	Executive Secretary
AVITAL CNAAN, Ph.D., M.S.	Member
ROBERT S. DAUM, M.D.	Member
LEON DURE, M.D.	Member
MICHAEL E. FANT, M.D., Ph.D.	Member
RICHARD L. GORMAN, M.D.	Member

PRESENT (CONTINUED):

MELISSA MARIA HUDSON, M.D.	Member
KEITH KOCIS, M.D., M.S.	Member
JACK STAPLETON, M.D.	Member
ROBERT WARD, M.D.	Member
MARILYN EICHNER	Voting Consultant
PAULA KNUDSON	Voting Consultant
SAMUEL MALDONADO, M.D.	Voting Consultant
GEOFFREY L. ROSENTHAL, M.D., Ph.D.	Voting Consultant

ALSO PRESENT:

SURESH KAUL, M.D., M.P.H.

THERESA KEHOE, M.D.

ROSEMARY JOHANN-LIANG, M.D., F.A.A.P.

LISA MATHIS, M.D.

ANDREW MOSHOLDER, M.D., M.P.H.

DIANNE MURPHY, M.D.

HARI CHERYL SACHS, M.D., F.A.A.P.

AMY M. TAYLOR, M.D., M.H.S., F.A.A.P.

C O N T E N T S

P-R-O-C-E-E-D-I-N-G-S

4:09 p.m.

CHAIR RAPPLEY: Thank you and we're beginning our meeting of the Pediatric Advisory Committee. My name is Marsha Rappley and I'm Chair of the Committee. And I want to welcome everyone and welcome the audience as well. And apologize for my back being to you.

I think it might be helpful if we introduce ourselves just briefly, very briefly. Say our name, where we are from, and the discipline we represent.

I'm from Michigan State University. And my discipline is pediatrics and developmental and behavioral pediatrics.

Bob, do you want to start?

MEMBER WARD: I'm Bob Ward from the University of Utah, a neonatologist and pediatric pharmacologist.

DR. ROSENTHAL: My name is Geoff Rosenthal. I'm from the Cleveland Clinic and I'm a pediatric cardiologist.

DR. MALDONADO: Sam Maldonado. I'm from Johnson & Johnson. My specialty is pediatric infectious diseases. I represent industry.

MEMBER KOCIS: I'm Keith Kocis from the University of North Carolina at Chapel Hill. And I'm a pediatric cardiologist and pediatric intensivist.

MS. KNUDSON: I'm Paula Knudson from the University of Texas Health Science Center. I'm really an IRB person but I'm your consumer representative.

MEMBER GORMAN: I'm Rich Gorman, a general pediatrician from Ellicott City, Maryland, who represents professional healthcare organizations.

MEMBER HUDSON: I'm Melissa Hudson. I'm a pediatric hematologist oncologist from St. Jude Children's Research Hospital in Memphis.

MEMBER FANT: I'm Michael Fant from the University of Texas Health Science Center in Houston. I'm a neonatologist and biochemist.

MS. EICHNER: I'm Marilyn Eichner from Rockville, Maryland. And I am an acting family representative.

MEMBER DURE: I'm Leon Dure from the University of Alabama at Birmingham and a child neurologist.

MEMBER DAUM: I'm Robert Daum. I'm a pediatric ID guy from the University of Chicago.

MEMBER CNAAN: I'm Avital Cnaan. I'm a biostatistician from the University of Pennsylvania

and Children's Hospital of Philadelphia.

DR. MURPHY: Dianne Murphy, Director, Office of Pediatric Therapeutics and previously pediatric ID person.

DR. JOHANN-LIANG: I'm Rosemary Johann-Liang from the Office of Surveillance and Epidemiology.

DR. MATHIS: And I'm Lisa Mathis with the Office of New Drugs, Pediatric and Maternal Health staff.

CHAIR RAPPLEY: Thank you.

So just a couple of housekeeping things. If you're not speaking, it helps if you turn off your mic.

And then second, when we get into the discussion section or if at some point in time people wish to make a comment, you can signal me. I'll try to watch and keep us in order that you indicate you would like to speak.

We're going to try to keep on schedule and break at six. We have four medications to review. The first two come to us to discuss adverse events reports for these two medications granted in the pediatric exclusivity period of time. That's for Fluvastatin and Octreotide.

And then the last two we'll receive updates for both Orlistat and Oxybutynin as requested by previous Pediatric Advisory Committee sessions.

I'd like to turn this over to Dianne at this point in time.

DR. MURPHY: This is the sad part. We get all you excellent individuals to commit time to us and then we get you all trained up and you get experience under your belt and then it is time to say goodbye. So I'd like to do that today.

This is going to be the last official meeting where these individuals will be members of the Pediatric Advisory Committee. We may call people back as SGEs if we need additional expertise in that area. But would Dr. Fant please come up?

As a neonatologist, he's been with us, I think, for three years, Dr. Fant, has been in on some of our more controversial meetings. And we very much thank him for his expertise and time.

And we wanted to present him with a little plaque and a letter from us for the time that he has participated and contributed to our Committee. Thank you very much.

(Applause.)

DR. MURPHY: Do you want to say anything?

MEMBER FANT: Yes, I'll make this brief. Of all of the sort of Committee assignments you get assigned to, I really -- you know, to be honest, this has been the most enjoyable and fulfilling of any that I've been involved with. I think we all have busy schedules. And any time we can devote a significant part of our time to something that at the end of the day you can feel has some real significance and consequence, it is very fulfilling.

And in that sense, I'll always remember this experience as one of the ones I look back on very favorably. And I want to take a brief moment and just thank the FDA staff, particularly Dianne, Jan, Monica Spence who sort of, you know, really kept the logistics simple for us. But the FDA staff -- you know I knew very little about the FDA workings before joining the Committee.

But since then, I've really come to appreciate the complexity of the information that you have to sift through to come to some meaningful decisions, policy decisions. And as one of my old mentors said when I was in graduate school, it is much more difficult to be able to ask the right questions than it is to find the right answer to a question.

And one thing that you guys have always

been able to do is to be able to sift through some very complex information, massive information, sometimes inadequate information, and bring to us some very decent workable questions that allows us then to give you the kinds of input that you are seeking from us.

And so I want to thank you for that. And the professionalism of the staff at the FDA, you know, and sometimes the courage that some of the staff have shown in some of their analyses and making some points, will stick with me.

So, again, thank you.

DR. MURPHY: The next individual we have to say goodbye to is really particularly sad because he's been with us for how long now, Rich?

MEMBER GORMAN: `99.

DR. MURPHY: Since 1999 on and off. And really one of our longest members. Can you come on up here, Rich, please? Dr. Gorman. And he has been our general practitioner, our Academy representative, what other persona have you taken on, Rich, besides --

MEMBER GORMAN: Whatever has been necessary.

DR. MURPHY: Yes, whatever has been necessary. And, again, we'd like to give you this

plaque --

MEMBER GORMAN: Thank you.

DR. MURPHY: -- a small token of our appreciation. And to thank you very much --

MEMBER GORMAN: Thank you very much.

DR. MURPHY: -- for your participation and multiple contributions.

MEMBER GORMAN: I'd like to echo what Dr. Fant had to say because I think he is much more eloquent than I am. The staff here is wonderful. The FDA has given us the opportunity to serve in a way that has advanced the healthcare of children.

And that is an opportunity that we all strive for as pediatricians and rarely get the chance to accomplish. So it is really a pleasure for my having the opportunity to serve on this Committee. And I thank you all.

One of the things my early mentors told me is you should learn something every day. And I can't remember a day that I came home from an Advisory Committee meeting where I didn't learn just one thing but many things.

Thank you.

(Applause.)

DR. MURPHY: Rich? One last thank you.

If you all go to your FDA website, you click on Pediatrics. You will notice now under the Safety, if you click on the Safety, we have posted up on the web the outcomes of all of your deliberations. So people can track whether we are following up with your recommendations.

And I would like Barbara Gould -- would she please stand up in the back? Barbara went through -- please, Barbara, show everybody. She went through every transcript, synthesized it, and made it fit that little box of your entire deliberations.

So there are many people that have worked putting this together and we really do take seriously your recommendations. And with that, I will sit down and turn the meeting back over to Marsha.

Thank you all very much.

CHAIR RAPPLEY: Thank you, Dianne.

Dr. Pena?

EXECUTIVE SECRETARY PENA: Thank you. And good afternoon everyone.

My name is Carlos Pena. And I'm the Exec Sec to the Pediatric Advisory Committee. I have a few notes that I'd like to read before we begin our presentations.

The following announcement addresses the

issue of conflict of interest with regard to today's discussion of a report by the Agency on adverse event reporting as mandated in Section 17 of the Best Pharmaceuticals for Children Act.

The Pediatric Advisory Committee will hear and discuss a report by the Agency, as mandated in Section 17 of the Best Pharmaceuticals for Children Act, on adverse event reports for Fluvastatin and Octreotide.

The Committee will also receive updates to adverse event reports for Orlistat and Oxybutynin which were requested by the Pediatric Advisory Committee or its predecessor, the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee when the reports were first presented.

This statement is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Food and Drug Administration present no potential for an appearance of a conflict of interest at this meeting.

In the event that the discussions involve any other products or firms not already on the agenda

for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such an involvement and their exclusion will be noted for the record.

We note that Ms. Marilyn Eichner is participating as the Temporary Pediatric Healthcare Representative. Ms. Paula Knudson is participating as the Temporary Voting Consumer Representative. And Dr. Geoffrey Rosenthal is participating as a Temporary Voting Member.

We would also like to note that Dr. Samuel Maldonado has been invited to participate as the Non-Voting Industry Representative acting on behalf of regulated industry.

Dr. Richard Gorman is participating as the Non-Voting Pediatric Health Organization Representative acting on behalf of the American Academy of Pediatrics.

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

We have an open public comment scheduled for now 4:20 and I would like just to remind everyone to turn on your microphones when you speak so the

transcriber can get all that is discussed at the meeting today. Thank you.

CHAIR RAPPLEY: Dianne?

DR. MURPHY: Just one last comment and that is as we go through this, as I mentioned earlier in the closed session, the Committee has made many recommendations to us.

One of the last recommendations is that we not read the slides -- all the cases to you. But that we try to focus you by in some way prioritizing, if you will, the cases. So we have tried to do that for you today. And we'll be interested in your feedback if you think it is helpful or not.

Thank you.

CHAIR RAPPLEY: Now we move into our public hearing. Do we have participants for that? Okay, seeing none, then we will move into our presentations for our four medications.

And I'd just like to add that in each set of slides for each particular drug that is presented, towards the end we will be asked a specific question to consider. And that is where we will focus our discussion.

Thank you.

EXECUTIVE SECRETARY PENA: The first

presenter is Dr. Amy Taylor. Amy Taylor is a pediatrician with the Pediatric and Maternal Health staff in the Office of New Drugs. The division representative is Dr. Eileen M. Craig, Medical Officer in the Division of Metabolism and Endocrinology Products.

DR. TAYLOR: Okay. I will be presenting information on Lescol. And I thought I would press this and it would move it. But it doesn't seem to be doing it.

Fluvastatin or Lescol and Lescol XL is indicated in the pediatric population as adjunct to diet to reduce total cholesterol, LDL-C and Apo B levels in adolescent girls who are at least one year post menarche and boys ages 10 to 16 years with heterozygous familial hypercholesterolemia.

Lescol received market approval in December 1993. And Lescol XL received market approval in October 2000. Pediatric exclusivity was granted on December 15th, 2005.

Pediatric use of this drug is limited. It represents less than one percent of all prescriptions. The exclusivity studies were two open-labeled, uncontrolled dose-titration studies in pediatric patients with heterozygous familial

hypercholesterolemia.

These studies resulted in labeling with a pediatric indication, dosing information, adverse event information, and a description of the clinical study results. In the one year post-exclusivity period, no pediatric adverse events were reported.

Seven adverse events in the pediatric population were reported since market approval. They were leukopenia and neutropenia, chorioretinitis, in-utero exposure, intentional overdose, and three reports of accidental overdose.

The review of adverse events since market approval did not identify any safety signals unique to the pediatric population.

In summary, the exclusivity studies resulted in labeling with a pediatric indication, dosing information, adverse event information, and a description of the clinical study results. Pediatric use of Lescol is limited.

No pediatric adverse events were reported in the one-year post-exclusivity period. There were no safety signals identified since market approval unique to the pediatric population.

This completes the one-year post-exclusivity adverse event reporting as mandated by

BPCA. FDA recommends routine monitoring of adverse events for Fluvastatin in all populations.

Does the Advisory Committee concur?

And I wish to thank the people listed here for their help with this presentation.

CHAIR RAPPLEY: Thank you. So this question is open for discussion.

DR. MURPHY: No questions? I need to ask the Division and the Safety Reporter if there are any questions. If there aren't, that's fine. I just want to make sure. You can ask either of them.

Otherwise, I guess, Marsha, the thing is if everybody agrees with the recommendation or not, if you could just get some sense of the Committee.

CHAIR RAPPLEY: So the recommendation is that this be returned to routine monitoring. We were informed earlier in the day that we can return it to routine monitoring or we can ask for it to be specifically monitored in pediatric patients.

What would be the desire of the Committee?

Yes?

MEMBER CNAAN: Routine monitoring means when do we see it again?

DR. MURPHY: You wouldn't unless there was a specific problem that would come up. What this

means is that, as you noticed, this was one of the abbreviated ones that we did not find anything in the review. You -- just to reiterate for the newer members, we did provide you the entire review packet, the use packet, but instead of going over it in public, we've summarized it because we didn't think there was a signal.

However, if the Committee thinks there is something that they are concerned about from reviewing the packet that they want us to come back to them about, we would. Otherwise it goes back to the routine process that all products at FDA would, as you heard earlier, be subject to.

CHAIR RAPPLEY: And that means it will not come back unless there is some additional signal that is noted.

DR. MURPHY: A request by the Committee --

MEMBER CNAAN: Okay.

DR. MURPHY: -- like the other two products coming back.

Bob? Michael?

MEMBER FANT: Yes, is there -- since this is a statin, is there any information that is known in the database in kids with signals with other statins? I mean is there a class issue -- not specific for

this drug but is there a class issue that we might want to look at this drug more specifically.

DR. JOHANN-LIANG: Jo Wyeth, who presented to you before, is the safety Representative for the statins. But as far -- and you can chime in if you'd like -- but as far as I know, we don't have an active pediatric issue -- safety issue regarding statins. I mean the use in kids is very small. And we have not been working up any safety issue, right? Am I --

DR. MURPHY: Can you come to the table and say that please, Jo, so we make it for the record?

DR. WYETH: We reviewed atorvastatin and simvastatin at the last Pediatric Advisory Committee meeting. And there were no signals noted. And that was returned to routine monitoring.

CHAIR RAPPLEY: Bob?

MEMBER WARD: I just want to recommend that we move it back to routine monitoring. And that we try to avoid bringing it back for special pediatric review just out of sort of a hypothetical concern.

MEMBER DURE: Can I just ask one question because the early afternoon session was very helpful but to give Jo sort of the marching orders to keep an eye out for pediatric, is that more work? Does that mean it has to come back to us? Or I mean --

DR. JOHANN-LIANG: In this case, I think returning to the routine monitoring as 71 percent of the outcomes in the past is probably appropriate in my opinion. So it is okay.

DR. MURPHY: But if you wanted her -- I'm just saying because -- I'm not suggesting we do that but for the future, if someone wanted to do that, if that's what you are bringing up, you could do that.

MEMBER DURE: Right. And I guess where I'm trying to go here is that -- when would we -- what are the criteria when we would not refer it back for further pediatric monitoring?

I mean it is more just to get an idea in my own head because we don't know how many people will be using statins I mean with the rise in Type II diabetes in kids and things like that. We don't know what it is going to be like in ten years.

DR. JOHANN-LIANG: Right. So at that time if -- the Safety Advisor who monitored the drug, like with any other drug, and we're hoping that with all the mechanisms in place, if there is a signal with children, that will come up.

And also if you folks or any other things in the literature -- I mean because we do, you know, screen -- signal hunt in other places besides AERS,

that we collectively would be able to bring it back if need so, okay?

DR. MURPHY: So what you are saying, we would return it to routine monitoring with the understanding that we will continue to look at pediatrics and bring anything back that we saw to you all. Is that a summary of what I'm hearing? Thank you.

CHAIR RAPPLEY: Does that sound agreeable to people? Do I see agreement around the table? Would you like to make a comment? Or you are agreeing? Okay, very good. Okay, thank you.

We'll move on to the next medication. And that is Octreotide.

EXECUTIVE SECRETARY PENA: Dr. Amy Taylor is also presenting Octreotide. The Division Representative is Dr. Triskey Hill, Medical Officer in the Division of Metabolism and Endocrinology Products.

DR. TAYLOR: This presentation will focus on background information, including drug use and exclusivity studies, serious adverse events focusing on the gastrointestinal, respiratory, and cardiac systems, the reported deaths since market approval, and concerns pertaining to the off-label use of Octreotide in infants. At the end, we will have

questions for the Committee to consider.

Octreotide, or Sandostatin injection, and LAR depot are somatostatin analogues. Sandostatin injection was approved in October 1988 and the LAR depot formulation in November 1998. Pediatric exclusivity was granted in January 2006.

The adult indications for Octreotide are for the treatment of acromegaly in patients who have had an inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate for the symptomatic treatments of patients with metastatic carcinoid tumors, to suppress or inhibit severe diarrhea and flushing episodes, and for the treatment of profuse, watery diarrhea associated with vasoactive intestinal peptide-secreting tumors. There are no pediatric indications.

Drug use information is difficult to obtain since 54 percent of the use of Sandostatin LAR Depot is in the outpatient clinic setting.

The data resources available to the Agency do not capture this use. In addition, we have no way of knowing the age of the patients for whom it was prescribed in the outpatient clinic setting.

The premier database revealed pediatric

use in .9 percent, or 156 discharges, between July 2005 and June 2006. Sandostatin LAR Depot was associated with a total of seven pediatric discharges for the same 12-month period.

Sandostatin LAR Depot was studied in the pediatric population, a randomized, double-blind, placebo-controlled, fixed-dose six-month study in 60 patients, age six to 17, with hypothalamic obesity resulting from cranial insult, was conducted.

Thirty patients received Sandostatin LAR. The study included a six-month open-label extension study.

The primary efficacy endpoint was the mean change in body mass index from baseline. Patients treated with Sandostatin LAR had a mean change in BMI from baseline of .1 kilogram per meter squared versus 0.0 kilogram per meter squared with placebo. This was not significant. Efficacy was not demonstrated.

This slide presents the most frequent adverse events during Sandostatin LAR treatment in the study. Patients treated with Sandostatin LAR had higher rates of diarrhea, cholelithiasis, and abdominal pain compared to placebo.

There was a higher incidence of new cholelithiasis in this pediatric population compared

to adults with acromegaly and malignant carcinoid syndrome treated with Sandostatin LAR.

The dosing for this pediatric population was 40 milligrams once a month compared to 10 to 30 milligrams once a month in the adult studies.

The open-label extension study was terminated due to lack of efficacy and a high risk of gallstone formation.

Labeling changes which resulted from the exclusivity study include data from the PK portion of the study in the clinical pharmacology section of the labeling and efficacy and adverse event information in the pediatric use section.

There were two adverse event reports in the pediatric population during the post-exclusivity period. Both were serious. One was fatal.

There were a total of 52 adverse event reports in pediatric patients since market approval. Thirty-three of these reports were coded as serious. There were 11 deaths.

Multiple off-label uses were reported. The most common of these reported uses were fistula, hyperinsulinemia, neisidioblastosis, diarrhea, and chylothorax. These are additional reported off-label uses.

Although 33 of the 52 adverse event reports were coded as serious adverse events, a hands-on review demonstrated that there were 36 reports which met our regulatory definition of serious adverse events. Twenty-five of the reports were non-fatal. And 11 were fatal.

Normally once a hands-on review is conducted, we see the number of serious adverse event reports decrease because of duplicate reports. This time, however, we found additional serious adverse event reports to those coded as serious.

I will start with a presentation of the non-fatal serious adverse events and I will focus my remarks on cases that are possibly related.

There were two reports of serious gastrointestinal adverse events which were possibly related to Octreotide use. The first case was a literature report of a newborn male on Octreotide for post-surgical chylothorax which occurred 14 days after surgery to correct a coarctation of the aorta.

The patient had been on intral feedings since post-op day eight. Three days after starting Octreotide, the patient developed clinical signs of necrotizing enterocolitis with abdominal distention, fever, vomiting, and bloody stools. Octreotide was

discontinued.

Antibiotics and parental nutrition was started. The infant did well and was discharged at two months of age.

The second case involves an 11-year-old male with a germinoma on Octreotide, ifosfamide, and cisplatin. Two days later, the patient developed pancreatitis. The pancreatitis resolved after the medications were stopped. Pancreatitis is a rare-labeled adverse event with Octreotide.

There were four reports of serious respiratory adverse events. Three of the reports had a temporal relationship to Octreotide administration, including one case with a positive rechallenge.

The first case involves a three-month-old premature infant with a fistula secondary to short gut syndrome. The patient became hypoxic after one dose of Octreotide. The patient was rechallenged with a lower concentration infusion and became hypoxic again.

The second case is of a two-year-old male with HIV associated diarrhea, AIDS, congestive heart failure, and numerous other medical problems.

After being on Octreotide subcutaneously for two months and then intravenously for two weeks, the patient stopped breathing after administration of

an IV dose. Breathing resumed with stimulation and oxygen.

The third case is a literature report of a six-month-old premature infant with bronchopulmonary dysplasia and a history of necrotizing enterocolitis. The infant was treated with Octreotide for a fistula.

During treatment, the infant had multiple episodes of hypoxia occurring within 30 minutes of Octreotide administration. The patient developed severe pulmonary hypertension and the infant was discharged home on oxygen.

There is one case that is difficult to assess due to underlying condition. This case is an 11-month-old with a history of GI motility problem and other unknown medical history.

While on Octreotide for two months, the patient developed cataracts and pneumonia and a subsequent persistent hypoxia.

There were four reports of serious cardiac adverse events. Two cases reported bradycardia, which is a labeled adverse event. The first case involved a 13-year-old male with a cranial hemorrhage secondary to an arterial venous malformation. The patient developed chylothorax and was treated with Octreotide.

The patient developed sinus bradycardia to

42 during an Octreotide infusion. The bradycardia resolved minutes after the infusion was stopped.

The second case involves an 11-year-old male with bradycardia to 40 during an Octreotide infusion for a bleeding gastric ulcer. The bradycardia was successfully treated with atropine. This report contains limited information.

There were two cases which were difficult to assess. The first case involves a 15-year-old male with Noonan Syndrome who developed sudden chest tightness, difficulty breathing, and pain within 30 minutes of receiving 35 micrograms of Octreotide. The report states that blood pressure and other observations were normal.

The second case involves an eight-month-old male with eosinophilia, dysrhythmia, palpitations, and heart rate change with Octreotide. The patient was treated with defibrillation and drug cardioconversion. No additional information is available.

The next several slides contain information on additional serious adverse event reports. I will not present each case here but if you have any questions regarding a particular case, I will be happy to answer them for you.

There were three reports of serious neurological adverse events. There were three reports involving serious adverse metabolic, nutritional adverse events. There was one case of a medication error and two cases of fever. There were two cases of reported sepsis. There was one case of an abnormal laboratory measurement and one case of dependency. There was one report of a serious blood disorder adverse event and one report of in-utero exposure.

There was one additional published report of a serious adverse event. This case was not reported to AERS. This is a premature infant with hyperinsulinism on Octreotide for five weeks. The patient developed cholestatic jaundice and cholelithiasis. The patient improved with a decrease in Octreotide.

There have been 11 deaths reported in the pediatric population since market approval. One death was reported during the post-exclusivity period. The reported uses associated with these deaths are listed here. I will focus my remarks on cases that are possibly related.

This first case involves a 16 day old on Octreotide for hyperinsulinism. Six days after the start of his second course of Octreotide, the patient

developed clinical signs of necrotizing enterocolitis. During surgery, the patient was found to have extensive NEC. The patient died two hours later.

The second case is a one-month-old female with transposition of the great arteries, status post-surgical repair on Octreotide for chylothorax. She developed abdominal distention and an atrial thrombus after one week on Octreotide. The patient died from necrotizing enterocolitis, sepsis, respiratory failure, and hepatic necrosis. No thrombus was noted on autopsy.

Now that you've heard about three reports of neonates with NEC, two which were fatal and one nonfatal, I want to pause here and present some information on necrotizing enterocolitis and two common off-label uses of Octreotide.

Population-based studies have reported an incidence of NEC of .5 to five per 1,000 live births. Approximately 90 percent of cases are pre-term with six to seven percent of cases occurring in very low birth weight neonates.

Among term neonates, the incidence is .05 to .4 per 1,000 live births. Two-thirds of term neonates with NEC have congenital diseases, for example, congenital heart disease or endocrine

abnormalities.

A study of cardiac intensive care unit admissions found that 3.3 percent of neonates develop NEC. This was independent of whether the neonate had undergone surgery or not.

Among neonates with hypoplastic left heart syndrome, the incidence of NEC was 7.6 percent. Risk factors associated with NEC were hypoplastic left heart syndrome, truncus arteriosus or aortopulmonary window, younger gestational age, and episodes of low output or shock.

The pathophysiology of NEC is poorly understood. Contributing factors include impaired motility, hypoxic-ischemic injury, breakdown of the epithelial barrier, abnormal colonization, and an immature or abnormal inflammatory response.

Overall mortality was reported as 15 to 35 percent. Twenty to 40 percent of neonates require surgery with a 50 percent mortality.

A common off-label use of Octreotide in neonates is for the treatment of chylothorax. It is usually used after a failure of conservative management. There are two types of chylothorax, primary or congenital and secondary resulting from trauma or obstruction.

Some of the risks associated with chylothorax include immunodeficiency, malnutrition, and electrolyte disturbances. Doses reported with Octreotide use for chylothorax are .3 to 10 micrograms per kilogram per hour as a continuous infusion but also subcutaneously or by IV bolus.

Octreotide was used for three to 27 days. Resolution is reported to occur in three to 15 days; however, five to six days is usual. This information is based on the reported experience with 65 patients.

Octreotide is also used off label for congenital hyperinsulinism in neonates. It is usually used for short-term management of hypoglycemia. Due to tachyphylaxis, Octreotide has been effective as a chronic treatment in only a limited number of infants with severe hyperinsulinism.

Reported doses are one to ten micrograms per kilogram per day, subcutaneously in three to four divided doses or by continuous IV infusion. However, doses as high as 40 micrograms per kilogram per day have been used in infants and children.

I will now continue on with the reported deaths since market approval. This next case reported in the literature involves a 15-year-old male with dyskeratosis congenita who underwent a stem cell

transplant.

He developed graft versus host disease on day 15. Two weeks later, he was started on Octreotide for diarrhea. Seven days later, he developed severe hypotension, respiratory distress, and abdominal pain with septic shock.

He died ten days later from diffuse hemorrhagic necrosis of the GI system and diffuse capillaritis of the brain and gut.

The next case involves a three-year-old male with nephrotic syndrome on prednisone. One day after the start of Octreotide, the patient developed a bleeding duodenal ulcer and died the next day.

This case, which was reported in the literature, is a three-week-old premature male with respiratory distress and a history of NEC who was started on Octreotide for an intracutaneous fistula. The patient experienced repeated episodes of hypoxia and was subsequently diagnosed with mild pulmonary hypotension.

The patient improved on supplemental oxygen and was later tolerating room air one week after Octreotide was discontinued. The patient died at six months from liver and renal failure secondary to short bowel syndrome.

This first case is a one-year-old male with a history of hypertrophic nonobstructive cardiomyopathy. The patient received Octreotide for chylothorax. Three days later, the patient developed intermittent second degree AV block which improved after discontinuation. The patient died several months later from underlying cardiac and metabolic storage disease.

The next case was reported during the post-exclusivity period. This was a literature report of a four month old with Noonan Syndrome on Octreotide. Two weeks later after the patient developed abdominal distention and hypoglycemia after Octreotide was stopped. The patient died a few days later from cardiac arrest after pneumothorax, anuria, and hypoglycemia.

The next two slides contain information on additional reports of death. I will not present each case here but if you have questions regarding a particular case, I will be happy to answer them.

There were two cases, not three as you see on the slide, related to hepatobiliary disorder. There were two cases related to miscellaneous disorders.

This review has revealed that Octreotide

is used for a variety of unapproved indications in the pediatric population. Despite the lack of controlled trial data, off-label use of Octreotide in the pediatric population is published widely.

Almost 50 percent of the reports of adverse events received by the FDA occurred in children less than two years of age. The majority of deaths reported occurred in children less than two years of age.

From these reports, we have seen that a wide range of Octreotide doses are used in the pediatric population. Sandostatin injection is used in the majority of the cases. In six reports, continuous infusion was used and this is not an approved method of administration in any population for any indication.

In summary, adverse events seen with Octreotide are serious and not limited to a particular System Organ Class. There was a potential temporal relationship since 27 percent of the reported adverse events occurred within 24 hours of starting Octreotide.

Since market approval, there have been 36 reports of serious adverse events, 25 nonfatal, and 11 deaths. Most cases are difficult to assess due to

underlying condition, concomitant medication, or insufficient information.

There are eight cases that are possibly related to Octreotide use; three reports of necrotizing enterocolitis, which is unlabeled, one report of repeated episodes of hypoxia, one report of repeated hypoxia with rechallenge, and hypoxia is an unlabeled adverse event, one report of pancreatitis, which is a labeled adverse event, and two reports of bradycardia, which is a labeled adverse event.

Almost 50 percent of reports were in children less than two years using Sandostatin injections. The majority of deaths were in children less than two years. Overall, there was no discernible trend between pediatric Octreotide use and reports of death.

This completes the one-year post-exclusivity adverse event reporting as mandated by BPCA.

Before I get to the questions for the Committee, I want to review the information currently in the Sandostatin and Sandostatin LAR labeling. I will start with how they are different.

Sandostatin LAR labeling contains information in the precautions pediatric use section

on the exclusivity study and has limited information on use of Sandostatin in hyperinsulinism.

The Sandostatin injection labeling has no information on the exclusivity study. Remember that the exclusivity study was conducted with Sandostatin LAR. The Sandostatin injection labeling has an in-depth description of use in hyperinsulinism in the precautions pediatric use section. Neither labeling has information on NEC or hypoxia.

This is a slide which was shown earlier in the presentation but I repeated it here to remind you of the information which is in the labeling for Sandostatin LAR.

The next two slides review the information currently included in the precautions pediatric use section of the Sandostatin injection labeling. The labeling states that there have been no formal controlled clinical efficacy safety studies.

The labeling includes a description of efficacy and safety data derived from literature reports of 49 neonates and infants with congenital hyperinsulinism. The information includes the doses used, efficacy reported, and adverse events noted.

The majority of short-term adverse events were gastrointestinal. Long-term adverse events

reported included poor growth, poor weight gain, and gallstones.

We have the following questions for the Committee. Do you recommend changes to the labeling? To the pediatric use sections? Any additions or deletions?

Should the labeling be updated to include information presented on post-marketing adverse events? Should changes be made to both labels? Or just one?

How can this information be disseminated outside of the labeling?

Does the Committee have any other recommendations or comments?

And I wish to thank the people listed here for their assistance.

CHAIR RAPPLEY: These questions are open for discussion.

Bob?

MEMBER WARD: Well, let me just mention some things about NEC and how we think that this drug could be related physiologically or pathophysiologically to NEC.

Mike and I talked about this earlier. We don't fully understand the pathophysiology of NEC. We

have, instead, knowledge about associations. The putative mechanism leading to NEC is that there is mucosal damage and then invasion of bacteria. And the associations with NEC suggest that under-profusion to the body and to the GI tract may contribute to it.

Octreotide can cause vasoconstriction. And so there is a hypothetical way that the two might be linked. The cases presented though, at least two of them had cardiovascular disease that would also reduce blood flow to the intestinal tract. So they are significantly confounded.

And so to attribute it to the Octreotide as opposed to the underlying cardiovascular disease to me is quite unclear. And there is a significant association between these cardiac malformations and the development of NEC in term babies that illustrates really the clinical condition of these patients.

So I think it is very difficult to know -- the other thing I would like to mention is that there were a couple of cases in which the drug was started and the child died within a day. And it simply illustrates intensive care medicine. I mean these are often very sick patients.

And chylothorax, the one that is not on there, is if you don't treat it, they develop

respiratory failure and they die, okay, from the plural effusion. And so we feel somewhat pressed to treat them either with drainage of the fluid and after a period of time with a drug that we think may decrease production of the lymphatic fluid.

So I'm really on the fence about what is the appropriate amount of cause and effect to attribute to the Octreotide in these cases, especially of NEC.

MEMBER FANT: Yes, I agree with that. You know I think we clearly don't have enough information to draw any firm conclusions. But I think what we do know would suggest that, you know, from the standpoint of biological and clinical plausibility, and the risk factors for NEC in the neonatal population, and actually one thing that I was, you know, just sort of -- my concern was heightened for was just the episodes of oxygen desaturations that were occurring and the risk of pulmonary hypertension and, you know, especially kids with chronic lung disease that may have reactive pulmonary vasculature anyway, you know, may suggest that this is a particularly at-risk population.

In reviewing one of the studies that looked at NEC in kids with congenital cardiac

malformations, when they looked at that, you know one of the -- when they did their statistical analysis, you know it seemed that the cardiac defect was independently associated. Again, prematurity was independently associated. And there was an interaction between the two.

And so all of these things in totality would suggest that at least -- oh, and one more thing, you know, there is an abundance of -- I mean I wouldn't say an abundance but there is a lot of random off-label use in the neonatal community, you know. I personally surveyed my own division and, you know, we don't use it that often but when I surveyed a division I used to be a part of, and, you know, it is not used that often but when it is used, it is used for a variety of indications.

And there is not much guidance in terms of the dosing. So, you know, I came to the conclusion that when it is being used, it is being used with, you know, you are sort of walking down -- you are walking through the FDA complex with nothing but a dim flashlight to sort of guide you.

So it's not -- we're often really not walking on sure footing when we are using this drug. And I think the wording probably should be -- or the

labeling should be I guess modified or whatever to just alert the clinical community to what may be signals in certain high-risk babies, you know, kids with heart defects, a lot of whom are slightly premature to begin with, kids who may have underlying lung disease, and alterations and abnormalities in their pulmonary vasculature. They may be more susceptible to the vasoactive activity of Octreotide.

So I think something in the labeling that kind of conveys, you know, a heightened level of alertness on the part of practitioners and perhaps sends a subtle message that we need to be a little extra thoughtful when we use this drug.

CHAIR RAPPLEY: Melissa?

MEMBER HUDSON: Actually I would echo some of what Michael said, too, because it seems like from my perspective, being so distant from neonatology, that these are medically compromised populations for which there is really not an appropriately-labeled use.

And that there should just be a warning that these compromised populations that are prone to hypoperfusion for a variety of reasons, you know, one should be particularly careful because these specific adverse events have been described. And that may be

if you are sort of figuring out what to do as that baby is taking the long trail down, they might actually look at the label and see -- that will alert them to these specific cases.

CHAIR RAPPLEY: Geoff?

DR. ROSENTHAL: I also agree with what my colleagues have said and would just like to reiterate or raise my observation that I think it is being used increasingly. And that it is being used for increasingly obscure indications. And that those indications are, from where I sit, are ones that tend to be indications that don't have other good options.

So chylothorax following heart surgery can be, you know, just a very difficult problem to deal with. And this is one of the Hail Marys.

And I do think it makes sense to somehow let practitioners know that it is not a freebie. That there may be issues with using this in that kind of context.

CHAIR RAPPLEY: Yes, Robert?

MEMBER DAUM: So I guess I'll sort of make a comment on the other side to at least hear more discussion. This is a passive reporting system. And we have a few reports of neonates who got NEC. And premature babies who got hypoxic. And anybody who

sets foot in a nursery will know that both of those things occur in the absence of Octreotide 24/7.

And so I'm not really convinced listening to this that there is an outpouring of concern on the part of the reporters to the system about a particular excess of either of those things. And I have no way to even begin separating normal occurrences in what are probably very sick patients otherwise from the influence of this drug.

And so I guess my position is an agnostic one. I can't tell a thing from what I've heard. And to then turn around and say we're going to change the labeling based on this, I think is going two steps too far out on a small limb.

CHAIR RAPPLEY: Michael?

MEMBER FANT: Interestingly, I agree with what you said. But you have to remember this is a drug that has no label use in the pediatric population. And it is being used. And it is being used for a variety of reasons that -- how did you put it -- increasingly obscure reasons. I mean that is the best way that I can put it.

And we don't have enough information to really know what the truth really is. But I think we have enough information that, I guess, in light of

clinical and biological plausibility, again, we may have some signals that practitioners need to think about before they use this drug.

You know certain situations, you know, like you mentioned, kids with protracted chylothorax, you know when it doesn't resolve spontaneously, you've got very few options to use. And, you know, sometimes you are in a situation where okay, we'll try this or the kid is going to die from something else anyway, you know. And sometimes that is the situation we find ourselves in.

But the notion that Octreotide is necessarily a benign drug, you know, is, I think, it is an inaccurate notion. And I think at least these signals -- the potential signals that are starting to show up that we need to look at and practitioners who are taking care of kids who may be at risk -- at a potential risk in terms of susceptibility to these adverse events, they just need to have something to think about.

Now if I'm a neonatologist and I have a kid with malignant chylothorax, you know, that is not resolving, you know, I really don't care what the label says, I'll probably use it, you know, because you don't have any other option. And I think any

practitioner would.

So I really don't think it would change the practice of thoughtful practitioners. But it may give the non-thoughtful practitioners something to think about.

CHAIR RAPPLEY: Keith and then Leon.

MEMBER KOCIS: Certainly these cases are not going to be causational with regard to the fact that these are extremely complex, extremely sick children who have had a very high likelihood of death. And I want to throw one other mechanism in there which was the thrombosis that we've seen throughout the autopsy findings and other things.

These children are at high risk for a thrombosis, imbalance of coagulants and anticoagulants, hypoproteinemia, catabolism, et cetera, et cetera. So I think my point would be that the combination of at-risk children and Octreotide does, at least in my opinion, reach a certain level of a concern that notification needs to go out there because of one, an increasing use, two, lack of other therapies that we might want to use in these children in sort of a now a movement towards using this.

Certainly in one of my journals that is published, some positive results which are concerning

to me. And certainly anecdotally I've used it for secondary chylothorax in post-op cardiac kids with unenthusiastic endorsement for the drug. I really haven't seen it work all that well. So, of course, we need randomized control studies. We'll say that.

But I think at this point, there is an increasing use in at-risk children and there are very serious lethal, fatal complications from that. And I think we need to put that warning out there. If you are going to use it in these children, you need to be aware of that, a heightened early warning to that.

And also one other thing, particularly with the chylothorases issue, we have other therapies that many times do work. And if you wait long enough, temporally related, they do resolve, at least in the secondary chylothorax issue.

And I think the sense is, and certainly if you were to read this paper, you might be moving towards Octreotide before basic therapy of MPO, TPN, and other things that have lower risk -- not zero risk but lower risk -- until we have better data.

CHAIR RAPPLEY: Leon?

MEMBER DURE: Yes, first of all, Dr. Taylor, I wanted to applaud you because you summarized some pretty complicated stuff there. But one thing I

didn't hear explicitly was in all these adverse events, were the patients being treated specifically for chylothorax? Because is there some other reason -- you've alluded to it but I don't see these patients so I don't know.

And just -- and I'll finish up -- then the other question is is there is a labeling issue here because the labels are different. And what are you -- do you have a suggestion for how to address that? Now I'll stop.

DR. TAYLOR: Well, I'll answer the first question. And then maybe have Theresa address the second question.

You may recall there was a slide that had the uses reported for the 52 adverse event reports. And there was a nice long list. And so those were actually why Octreotide was used in each of those reports.

CHAIR RAPPLEY: That's Slide 13 and 14.

PARTICIPANT: Did they all have chylothorax?

DR. TAYLOR: No, that's what I'm saying. Chylothorax was just one of the reported uses among the many.

MEMBER KOCIS: Hyperinsulinism is one of

the ways we use it, probably almost as frequently as we do for chylothorax.

DR. TAYLOR: Avital?

MEMBER CNAAN: I wanted to go a little bit actually on the label. I would like to suggest that on the injection label, the exclusivity study description does need to be added because I think it is a little bit misleading that that information, that negative information essentially is missing from the injection description.

Otherwise I agree with the statement about causality is not there. It is association and concurrent things. And we also don't have a true denominator. From everything I'm hearing here, the denominator is increasing even as we speak. So we have to be careful how we put that language.

DR. KEHOE: I'll address the question of adding the LAR exclusivity to the injection label. One of the difficulties with that is what actually drove the LAR study was two smaller studies with Sandostatin injection that showed that it did achieve weight loss in hypothalamic obesity subjects.

So we have a little bit of disparity there. And I'm not sure it would be appropriate to put the Sandostatin LAR data in the Sandostatin

injection label since there are differences in how the drugs, you know, appeared to achieve efficacy.

And I think as far as making the labels identical, it will be difficult if not impossible to do because the drugs are used for, you know, very different conditions.

I think most of what we are talking about here in the critical care setting is the injection formulation. And so, you know, changing the precaution section of the injection formulation which, right now, gives a lot of information that is very old and has probably been there since possibly 1988. And not really been updated.

But to take out some of that and then put in some of the precautions that you are suggesting, I guess one of the questions I would like to hear from the Committee is when you talk about warnings and precautions, which section of the label do you think this warrants?

Does it warrant talking about it in the pediatric section of the precaution section of the label? Or does it actually warrant a warning, which I heard the word warning used from somebody. But that would be an important distinction.

CHAIR RAPPLEY: Bob?

MEMBER WARD: I really have trouble though with concluding cause and effect at this point in time. There certainly is a putative mechanism that would fit, a vasoconstriction added on to other factors contribute -- that also have produced hypoperfusion. And so I just think we have to be careful at how much confidence we put in cause and effect.

I think putting something in there that warns about the association that has been observed, especially in patients who have other factors, predisposing to hypoperfusion, makes sense. But to conclude that it is cause and effect, I just don't think we have the data to do that.

CHAIR RAPPLEY: Rich? And then Robert. And then Michael.

MEMBER GORMAN: This is one of the times when the emerging worries section on the FDA's, that whole concept of being able to express ambiguity or not having reached a conclusion from the FDA has been so wonderful in terms of what we can do because I think this is exactly the kind of thing where this would fit well into that emerging concern section that you have.

I don't think this rises to the level of

changing labeling because I don't think causality is and I don't think frequency is known. And I'm not sure then what I would say in a label that I would then want to be relatively factual. I think this goes into the emerging worries section.

And I think that the pediatric intensive care, pediatric surgery, and pediatric neonatology community is fairly good at communicating things internally.

And I think that this risk could be communicated internally to them -- disseminated in means that are not labeled and would probably be much more effective both at their national meetings and in those Dear Doctor letters that you love to send. We do read them, by the way, occasionally.

CHAIR RAPPLEY: Robert?

MEMBER DAUM: That approach sounds like fresh air to me, to be honest. And I guess I want to come back to your comment because I certainly defer in expertise in this. But you said the association that has been observed. And I guess what I'm trying to say is I don't think any association has been observed.

If we want to have -- I mean these are passive reports where you are trying to dissect out what they may have been related to. So I would

support a call for research to look into this. But I don't think that belongs on the package label.

I would certainly support a concern about off-label use but I'm always concerned about off-label use. But the idea of an emerging problem note is, I think, probably about all this amounts to right now.

I honestly don't think the data we've heard could say anything more than that.

CHAIR RAPPLEY: Michael?

MEMBER FANT: Again, I agree with everything that has been said. You know I think some of the, you know, at least when I and probably others on the Committee use certain words they may carry different significance with people in the Agency. So when you say, you know, warnings and things like that, you know, sometimes we are thinking more generally than some specific mechanism that you guys have worked out.

But I think some wording within the drug information section of the PDR that everybody looks at when they look up a drug, you know, whether that is a little short narrative under the pediatric section, whether it is an emerging concern within the pediatric section, something that just sort of communicates some concerns that have been raised.

And you can even add that, you know, no clear association has been determined. I mean you can do that. But I think it is -- for the reasons articulated before, I think it is important information to get out.

CHAIR RAPPLEY: Yes?

DR. KEHOE: Then would a statement in the precaution section under pediatrics that Sandostatin LAR or Sandostatin injection is not indicated for use in children -- would that be sufficient to -- and then go on, you know, to describe -- to be sufficient to put the brakes on uses that you may think -- the ever-expanding uses?

CHAIR RAPPLEY: No, I'm going to respond to that -- that we see that all the time and we still use drugs off label because we can't wait for the studies to be done. So I don't think that would be adequate.

MEMBER WARD: You know one of the case reports came from one of my colleagues in which treated with Octreotide, the chylothorax went away. Stopped the Octreotide, the chylothorax came back. Started the Octreotide, the chylothorax went away again. He concluded that it was effective for -- and this was a child with congenital chylothorax rather

than acquired.

So, you know, I have trouble with saying that it is not effective. But in the context of -- we have no studies, however, to meet the level of a regulatory endorsement or labeling for it. And I think we need that. We need to establish a dose and a dose response -- the basics.

PARTICIPANT: She didn't say it was not effective. She just said that there was no indication.

CHAIR RAPPLEY: Dianne?

DR. MURPHY: I'm trying to sort through what we're hearing. So I thought maybe that might be -- and maybe -- is Tony still in the audience? Because we need to talk about what would get on an emerging -- I don't know that this would -- you know what I'm saying is the whole other stuff where you don't put anything in the label, often you are doing that because you are working towards something. And you want people to know before you get to the final point.

And, you know, so I think we'd have to separate out that that would mean you are not going to put anything in the label, what are you going to wait for, okay? Then the Committee could say come back.

So I'm trying to lay it out. That's one -- what I hear one category is.

We wish there were studies, you know, maybe make that known, try to communicate internally. See if it would merit going forth. Again, because of the paucity of data, I'm not sure how that would be. But I don't want to rule that out.

I'm just trying to lay out what would go up on the website as an emerging issue. And then the Committee could say come back after X amount of time and we look at this again. That is one thing I'm hearing. And people please add on after I get through.

The second is that I think it has been made clear because we were passing notes back and forth over here, you are not suggesting a warning, okay. You are suggesting that -- the other voices that we are hearing is that we put something in the label that informs the physician that these events are occurring. And in a certain population that is maybe more susceptible but we have no causality relationship.

And we do put that in -- somebody brought that up -- we do put that in the label that we are not saying that this is cause and effect. And those who

went through some of our other products, you know, that we -- so your decision here, I think, is are you at the level yet where you think just informing physicians about this is something the Division should do in the precaution section is what it sounds like thus far or should you wait?

Are there other categories that are coming out here?

CHAIR RAPPLEY: I've heard today then two positions. One is that there is enough information presented that we need to communicate a concern to the profession. And the second is that it is still just speculative. And that it doesn't reach the threshold to communicate through a label or otherwise.

Can we have a decision at that point if we -- depending on how we decide whether or not we need to communicate more information to the profession, then we can decide how best to do that.

Avital?

MEMBER CNAAN: Can I add one more thing? I'm also hearing that the dose is unknown since it is not indicated. Is there any room to do at least a small dose response study? This is not a population for a big Phase III study but possibly a small dose response that might help us?

CHAIR RAPPLEY: Just to follow up on that, are we in a position to ask the sponsor to do further studies?

DR. MURPHY: There is no exclusivity. So I guess this might fall into our category of if the Europeans want to get exclusivity, if they want exclusivity in Europe, would they be willing to answer a question that the people across the pond, their colleagues across the pond have?

I don't know. There's no leverage to go to the sponsor and ask them to do another study at this point. I mean I guess -- and I'm just thinking off the top of my head here -- I mean if this got to be such an issue it might be to their benefit to go out and do something to try to answer that question.

Any other thoughts from the Division?

DR. KEHOE: You know I guess it also doesn't necessarily have to be done by the sponsor. It could be driven by the neonatal community, the physicians saying we need this data to be able to make informed decisions of a drug that is already being used.

And maybe then it is the professional society that will drive this study being done, not necessarily the company.

CHAIR RAPPLEY: But realistically, that message goes out and then there has to be funding appropriated for that kind of a study. And somebody has to submit a proposal to study it. So that is a very long pipeline.

So I'd like to go back to the point at which we need to decide whether or not the level of concern is great enough that we need to alert the profession.

Yes, Keith?

MEMBER KOCIS: As I said before, I think we've reached threshold. We are using a drug that has maybe benefit, maybe not. It has -- it is being used in extremely high-risk patients, which is how it is going to be used, except for the chubby kids that want to lose some weight.

And then it is being used with concomitant drugs and other things. And these are serious, fatal side effects that I think need to be reported as not causative but associated with its use and blah, blah, blah, blah, blah, certainly disclaiming any causation because there is definitely no data to prove that. But these are occurring.

CHAIR RAPPLEY: Does somebody want to summarize the other opposite position? Yes, Melissa?

MEMBER HUDSON: Do we have any way to know if you are disseminating information through the website versus a label, which is likely the more effective route to reach clinicians? Like do you have any metrics on that? Because I feel strongly that this information needs to be disseminated even though there is no causality that has been demonstrated.

DR. JOHANN-LIANG: I mean I think there has been a number of different types of surveys and studies that have been done trying to look at, you know, what did the box achieve, what did medication guides achieve. But I don't think there has been any direct comparisons of all those different metrics to see which is better than the other.

So generally if there is a very concerned concern, we try to go multiple routes obviously. And then we try to think about who would be most important to reach. Is it the clinician? The provider writing the script? Is it the healthcare provider in the hospital? I mean there are different situations. Is it the parent?

Is it the -- so -- and these metrics have different populations that it is reaching. So that is something to consider.

I just wanted to add one thing in regards

to this labeling issue. For something for you all to consider. As I discussed during the training time, in regards to safety, you know we don't have to have absolute proof and substantial evidence to say we are concerned. I mean it is usually -- you know we look at reports in AERS and obviously so many of these things have, as Amy had pointed out, they are difficult to assess. They are sick babies. And et cetera.

So however often when there are -- when you go through the case series from AERS, and that is all you really have, and you are concerned, we very often say this has been observed. You know there is no -- we're not saying this is cause. We can't establish that. We're just saying there is enough of a concern. This is something that people need to know.

Usually they don't go to the section of warnings as regulatory. But in the post-marketing this has been observed. And this is something we want the clinicians, the healthcare providers to know. That is for the labeling section. So I hope that's helpful.

CHAIR RAPPLEY: Thank you.

So I think we need to bring this question

to closure. And do we need to take a vote on this? Do we have -- let me just say that -- yes, okay, go ahead, Robert.

MEMBER DAUM: The people who are pushing for notifications, would they be able to say what it is that we are going to disseminate because, again, looking at this list of things, there are about 20 different ones. One of them has one case of Noonan Syndrome with sudden chest tightness. I mean what is it that we are going to say if we did say something?

CHAIR RAPPLEY: If you would allow me to summarize and then add or contradict if I don't portray this correctly, that the people who have expressed concerned is that there is a particular risk for certain high-risk infants and for certain age groups. And that it is a level of concern that is high enough that we should be getting this information out to those who take care of these children.

MEMBER DURE: I don't understand this. I mean to say there is a risk for certain infants, which ones? I mean if you only name the ones --

CHAIR RAPPLEY: Specifically they said --

MEMBER DURE: -- yes, but if you only name the ones that we have here, you may miss some. I mean it's almost too specific what you are saying.

CHAIR RAPPLEY: Oh, I thought you were telling me it was too general. Sorry.

MEMBER DURE: Well, no, I mean because you are enumerating certain conditions. And I mean if the goal is to heighten awareness here, then I just like the idea of saying it has been observed that, you know, there have been bad outcomes in, you know, neonates with bad disease.

MEMBER WARD: Let me just support what you said, Leon. I think saying that we have observed this in high-risk infants who have disorders, cardiovascular disorders and prematurity associated with hypoperfusion, systemic hypoperfusion, to me is an objective description of what we have seen and heard.

But, again, I just can't buy yet the cause and effect. Maybe it is there. Maybe it is not.

CHAIR RAPPLEY: So then the suggestion is that we add to the label the observation that these outcomes have been observed in children with these certain conditions.

Yes, Avital?

MEMBER CNAAN: We've replaced one because we had a term baby with congenital, not pre-term, with it being either pre-term or congenital, as was

described, not the combination. Just to be clear.

CHAIR RAPPLEY: Yes.

DR. MALDONADO: This is just a question for the experts in neonatology or anybody else. If that text goes in the label, how do you think that text will modify behavior? Because I just don't know how -- I cannot picture that.

CHAIR RAPPLEY: Well, I think, you know, we've had the discussion in this Committee before about using the label to modify behavior. And the point of the label is to provide information rather than to try to modify behavior. That's my understanding.

MEMBER FANT: Yes, and to specifically address it, I really, you know, I don't think it will modify behavior any more than any good information or any information would influence one's decision-making. And that is all it is is providing information.

CHAIR RAPPLEY: We do need to come to closure. So, Bob, if you want to add one more comment?

MEMBER WARD: I just think it may modify behavior. One of the principles of managing NEC is to stop feeding as soon as there are symptoms. And noting that there may be an association with treatment

with Octreotide, as soon as an infant exhibits symptoms that you have usually better outcomes -- not always but usually better outcomes, more bowel preserved. But that is the only thing I can imagine, Sam.

CHAIR RAPPLEY: So then if I can summarize again, that we want to add the information that these outcomes have been observed in children who have cardiac disease and other predisposition to low-perfusion states.

MEMBER KOCIS: I just don't want to narrow it just to low cardiac output, too, because I mean we can probably come up with a summary based on the case reports -- I wouldn't focus it --

CHAIR RAPPLEY: Okay.

MEMBER KOCIS: -- just to that.

CHAIR RAPPLEY: And can rely then on the Agency to draft that language?

DR. MURPHY: I was going to say I think we've got a feel for -- and believe me, they'll go back and forth between the Office of Safety and the Division and try to come up with something.

And I guess the only other -- the last thing then is the consideration of trying to make the labels -- rather than negative information on the one

exclusivity study should go into the injection even though it wasn't studied in that population. And that is just something we'll have to discuss internally.

Because we have to deal with this from a moiety point of view, too. But to be fair to the sponsors, you know, your product wasn't studied. Then, you know, why is that information going on that label. It gets back to the whole concept of we have to assess what is important information we think to the populations using those labels.

CHAIR RAPPLEY: So that is an Agency decision.

DR. MURPHY: I think we've heard some people think that we should and that we should at least reassess the situation.

CHAIR RAPPLEY: Okay.

DR. MURPHY: And then I think we can say that we will reassess the situation and consider it.

CHAIR RAPPLEY: Are people agreeable with that?

Keith, did you want to add?

MEMBER KOCIS: Yes, going back to the obese child study, and it is sort of a segue into another drug we will be looking at, but is there enough warning based on that study where there was 33

percent cholelithiasis in those children, if we identified that at-risk, I mean higher than what it was in the adult studies for that drug and that indication, I mean it's outside my area of expertise, but that struck me that we are looking at another drug with a similar profile that maybe in children there is a higher -- while it is clearly known that cholelithiasis occur, have we identified in the label under the pediatric labeling for that indication sort of a higher level of risk?

And I know that is a little different than what we have discussed but that did come to mind when I was reviewing all this.

CHAIR RAPPLEY: Okay.

DR. MURPHY: I think we just got that added to our list of things to look at, too.

CHAIR RAPPLEY: All right. Very good.

One more comment, Geoff?

DR. ROSENTHAL: My only other point is that I, for one, would like to hear more about this drug in the upcoming meetings.

CHAIR RAPPLEY: When should we bring it back?

DR. MURPHY: That was my next question.

CHAIR RAPPLEY: Okay, great.

DR. MURPHY: Did you want us to just send you the label or whatever is the decision? Or did you want us to bring it back? So --

CHAIR RAPPLEY: I heard your questions as wanting more information about say a year from now?

DR. ROSENTHAL: That sounds right, yes. That sounds great.

CHAIR RAPPLEY: Okay. Rather than approving any label change. We leave it to the Agency to draft the language.

DR. MURPHY: Okay.

CHAIR RAPPLEY: Unless I hear other -- no? Okay. Very good. Thank you.

And thank you, Dr. Taylor, that was very good.

So we move to orlistat.

EXECUTIVE SECRETARY PENA: Presenting for orlistat is Dr. Hari Sachs. Dr. Sachs is a Pediatric Medical Officer with the Pediatric and Maternal Health Staff in the Office of New Drugs.

DR. MURPHY: Actually, don't go away, Division, please. Before we go to the next drug, our Office of Safety actually pointed out that we wanted to make sure you all address the very last question.

CHAIR RAPPLEY: I'm sorry.

DR. MURPHY: That's all right.

CHAIR RAPPLEY: Were there any other comments or suggestions? It gets back to did we wrap up? Were there any other kind of studies? You know we heard some information on that, that people wanted some dose -- to try to at least -- that was getting at the efficacy-type of issue. So --

DR. JOHANN-LIANG: Yes, this is a discussion with, you know -- and I know, Dr. Rappley, we have brought out the issue of how it is going to take time, funding for clinicians to get together. But something to consider, something that may be very simple, and this really has to do with a registry-type of issue, maybe as I think the doctor over there -- my eyes can't -- had pointed out about getting clinicians together.

And something very simple, like a network, by internet, whatever, but just to start -- if there is increasing use of this product for all sorts of off-label use, it would be nice to know for what, what doses are being used, you know is it helping the kids? For what indications?

CHAIR RAPPLEY: So you are suggesting that that recommendation from this Committee carries some weight and helps make that happen? Okay.

PARTICIPANT: We can work on that.

CHAIR RAPPLEY: Yes.

PARTICIPANT: There are several contacts that can help.

CHAIR RAPPLEY: Okay. So I think you can take it from this Committee that we would like to see carefully controlled studies that examine both indication, efficacy, and dosage, as well as safety.

DR. MURPHY: Sorry.

CHAIR RAPPLEY: No, that's fine. No, please do that, yes. Right. And I did not mean to imply that we shouldn't do more studies. I didn't mean that at all.

Okay, thank you.

DR. SACHS: Okay, we're going to move from the littlest guys to the adolescents. And I'll present an update on orlistat and cholelithiasis.

Some of you may recall that at our Advisory Committee in February of 2005, we concluded that reports of cholelithiasis during the pediatric trial and the incidence of cholelithiasis in post-marketing surveillance warranted continued monitoring although the relationship to the therapy versus the underlying obesity and rapid weight loss was unclear.

Just to refresh your memory, orlistat is a

lipase inhibitor that is marketed by Roche. It was approved initially in 1999. Pediatric exclusivity was granted in 2003. And an over-the-counter switch has occurred just a few months ago.

Orlistat inhibits the absorption of dietary fats which may be related to gallstone formation. Orlistat is one of several products now that has dual marketing status. That is both as a prescription product and an over-the-counter product.

Xenical is the prescription product and it is indicated for adolescents and adults over 12 years of age for obesity management in conjunction with weight loss. And this is predicated on having a certain body mass index, depending on the presence or absence of risk factors.

The dosage is the same in adults and adolescents. It is 120 milligrams three times a day. As the nonprescription product, Alli, is indicated just for adults for weight loss when used with a reduced-calorie or low-fat diet and the dosage is half of that of the prescription product.

This is an update from the use from the last meeting. The dispensed prescriptions for all age groups have continued to decrease. And orlistat is still prescribed mainly in adults with pediatric

patients accounting for less than one percent of all prescriptions.

Since our last meeting, the Office of Surveillance and Epidemiology has performed an analysis of the AERS database to look at cases of cholelithiasis and acute cholecystitis and identified 37 domestic cases of which only one was a pediatric case.

And that was the case we did describe at our last meeting, an adolescent who had been receiving treatment as part of one of the trials. There were no additional pediatric cases since February of 2005.

OSE has concluded that there may be an association between cholelithiasis and orlistat use in all populations and has initiated a review of all weight loss products to get some perspective on this risk. And there does not actually appear to be a safety concern specific to children or adolescents.

Since our last meeting, the labeling has been updated as well. To the precaution section has now been added the statement that substantial weight loss can increase the risk of cholelithiasis and that came from a trial of Type II diabetes prevention in which the treated group had a greater incidence of gallstones. However, that incidence was really

similar if the degree of weight loss was accounted for.

The post-marketing section now also includes reports about pancreatitis, which, as you guys know, may or may not be related to gallstones.

So in summary, there is still actually minimal use in pediatric patients. There were some additional cases of cholelithiasis identified in adults but none in children. Our labeling does reflect an increased risk of gallstone formation with substantial weight loss.

And the FDA, at this point, recommends a return to routine monitoring of adverse events for this drug in all populations. But just so you know, that now will include monitoring for nonprescription products, which is a requirement for the future although the implementation and format for that has not yet been determined.

What do you guys think?

CHAIR RAPPLEY: Thank you. Open for discussion. Does the Committee concur with the recommendation? Very good. We concur.

DR. SACHS: I'd just like to acknowledge all these folks that actually were behind the scenes for this slide presentation as well. Thank you guys.

CHAIR RAPPLEY: Thank you very much.

So we'd like to move on to oxybutynin. And Dr. Maldonado will be recusing himself from this discussion. Thank you.

EXECUTIVE SECRETARY PENA: The presenter for oxybutynin is Dr. Andrew Mosholder. And he is a Medical Officer with the Division of Drug Risk Evaluation. The Division Representative at the table is Dr. Suresh Kaul, Medical Officer in the Division of Reproductive and Urologic Products.

DR. MOSHOLDER: Good afternoon everyone. In the next few minutes, I'm going to summarize our review of central anticholinergic effects with the drug oxybutynin.

All right, just by way of background, oxybutynin, which is marketed under the trade name Ditropan or as a transdermal patch as Oxytrol is a tertiary amine anticholinergic. It is an antimuscarinic compound that was approved for marketing about 30 years ago, available in several formulations, orally in tablets, syrup, and extended release tablets. All of those are available generically as well. And also transdermal patch, Oxytrol, which is not available generically.

The indications briefly are bladder

instability, neurogenic bladder, overactive bladder, and detrusor over-activity. And pediatric exclusivity was granted about five years ago, February 2002.

In June 2003, pursuant to the pediatric exclusivity, there was a review of pediatric adverse event reporting. And there were actually very few reports for analysis. I believe there were only five.

So this Committee requested additional monitoring. And there was a follow-up review pursuant to that request completed last September for the November meeting of this Committee.

And it was noted that CNS adverse event reports were being reported proportionately more frequently for the pediatric group than for the adults. And so the Office of Pediatric Therapeutics asked us to do an in-depth review of this and a comparison of the pediatric and adult CNS event reports.

Just to go over what is in the labeling currently. For pediatric labeling, first of all, Oxytrol, the transdermal preparation, is not labeled for pediatric use. Ditropan is labeled for patients five years and above with dosage specified for patients over five years. And the Ditropan Extended Release XL is labeled for patients six years and

above.

There are some statements in the current labeling about CNS effect. The drug may produce drowsiness. Several adverse reaction terms are listed. And in the overdose section, CNS excitation is one of the adverse events. But nothing more elaborate in the current labeling.

And to review the use of the product, in the United States, there is over a million patients who received Ditropan or the generic versions in 2006. And this is about 4.9 million prescriptions dispensed last year.

Almost two-thirds of the prescriptions were for patients aged 60 and above. And in terms of pediatric use for the years for which we have data, going back to 2002, from the Verispan source, which is where these data are from, consistently it has been about four to five percent of the total use in the United States.

And of the pediatric use, if we look at that, we find that about 12 percent of pediatric prescriptions were off label by virtue of either the age of the patient being under six years or for the patch, any pediatric use. I should add this calculation was revised somewhat from what appears in

the document in your briefing package.

So we conducted an AERS search January 12th of this year. We selected adverse event terms which were thought to represent the central anticholinergic syndrome as has been described in the literature. And the complete list of terms is in the briefing document.

This search returned a total of 347 reports, 145 of them were excluded either by virtue of being duplicates or for other reasons -- if there was another obvious cause of central nervous system event such as illness or perhaps another drug. This left 202 cases, of which 180 had age information. And there were 37 pediatric cases and 143 adult cases that served as our case series for analysis.

Now if you go back and look at all AERS reports for oxybutynin, you find that 12 percent of them involve a central nervous system event of some type. But if you look at all pediatric AERS reports for the drug, almost one-third of them involves a central nervous system event compared to 11 percent of the adult AERS reports.

Looking further at the 37 cases, most of these were from the U.S., I should add, 33 of them were reported by healthcare providers. The age range

was rather broad but the median was around six years.

The most common AERS preferred term, or PT as we refer to it, was hallucinations followed by agitations, sedation, confusion, amnesia, which is a term for memory impairment. And as we described in the briefing document, two of those memory impairment cases actually were very well documented with neuropsychological evaluations and abnormal dreams.

And 23 of these reports reported positive dechallenge, meaning that the symptoms abated when the drug was discontinued. In four cases, there was a positive rechallenge. Six involved a hospitalization. Fourteen of the 37 had a past psychiatric or a neurological history of some type.

And 17 were judged to be off-label either by virtue of the patient's age, indication of nocturnal enuresis, which is not one of the labeled indications, or dosage above 20 milligrams.

To give you an example of some of the cases, this is just briefly some of the more better described or persuasive cases. First there was a four-year-old boy who received a single dose and developed vivid hallucinations.

A six-year-old girl with incontinence from trauma who, following a dose increase, became

agitated, developed hallucinations, a personality change, and these symptoms went away when the drug was discontinued.

An eight-year-old girl with overactive bladder, treated for a few weeks, who developed confusion, hallucinations, mood changes, delusions, and so forth. Again, these symptoms resolved within a few days of discontinuation.

And the final case is a literature case, the citation is in the briefing document, but this was a four-year-old girl who received a ten milligram dose for enuresis, again, off-label use, developed visual hallucinations and the following day the hallucinations returned after the next dose. And then when the drug was discontinued, they did not recur.

So we were curious as to how the pattern of age distribution among the AERS reports for CNS events matched the use of the drug by age. And what this displays is in the row -- the front row is the percent of prescriptions by age for the most recent year. And in the row behind is the percent of the total domestic CNS adverse event reports.

And I realize these are comparing different time frames so this is really just to give you an idea. You don't want to make too much of this

but you see that they match up pretty well except there is sort of a bump at the lower ages for the CNS cases. So it is a discrepancy versus the amount of use in that population.

So comparing the adult and the pediatric CNS case reports, there were some qualitative differences that we discovered. First of all, hallucinations were the most common in the pediatric group. And also were very common among the reports in the 60 and above group. And relatively less frequently represented in the reports from the ages in between.

Agitation was reported more often among the pediatric cases. And in contrast, sedation was reported more often among the adult cases. And in the 60-plus age group, confusion was the most frequently reported CNS event.

So in conclusion, we found that from AERS we were able to identify case series which we feel represents central anticholinergic effects of the drug. A significant proportion of all the spontaneous reports for oxybutynin do involve a CNS event.

The current labeling does not explicitly describe the potential for central anticholinergic effects or the qualitative differences in the types of

events that have been reported. And so my Division is recommending that the labeling for CNS effects be strengthened.

And here let me skip ahead to acknowledge the many people who assisted with this. In particular, Paula Gish, who couldn't be here today, but who was the primary analyst for the AERS case series.

So the questions for the Committee, first does the Committee recommend that the labeling include more information for prescribers about adverse CNS effects? And also any other comments or suggestions, we'd be glad to hear from you. So thank you very much.

CHAIR RAPPLEY: Open for discussion.

Thank you.

MEMBER WARD: Could I ask, well, first, Andrew, is there an association between dose and the hallucinations? Because I don't think I saw that but maybe I missed it.

DR. MOSHOLDER: Well, not per se, although some of the cases did involve either super therapeutic or actual overdosage.

MEMBER WARD: Okay.

DR. MOSHOLDER: So I think we would sort

of presume this is dose-related. And in particular, it is well known, overdosage of anticholinergic compounds would create this effect. But we didn't do really -- there wasn't really enough to work with for formal dose-relatedness. And it is very hard to get that kind of data out of spontaneous reports, too.

MEMBER WARD: Yes, I was looking for it and I couldn't find it -- a recommendation that the label say if the CNS adverse events occur that the drug should be stopped. And this particular population benefits from being dry. And not from voiding.

And it seemed to me reasonable that it say instead that the dosage be reduced, you know, rather than stopping the drug.

And for the urologists, could you clarify this issue about overactive bladder versus detrusor instability because on page 14 under 3.2, they look like they are interchangeable under Bullet No. 3.

DR. KAUL: Before I do that, let me make some comments for the members of the Committee. I know we are running short of time but I will make it fast.

We have to understand that it is an old drug which has been marketed since 1975. And it has

been there for the last 32 years. And what we have seen here is 37 cases. And out of 37, we have 19 cases which are off-label use. That makes it 51 percent.

And it is a pretty safe drug. And it is also efficacious. It has been used by millions of users, 1 point some million just last year. And we do -- the Division acknowledges the fact that we do need to strengthen the label.

We have -- out of the four which were just presented here, hallucination, confusion, agitation, and sedation, out of those four, we have three already in the label in the adverse section. And the only one missing out is agitation. And the Division is totally in agreement to include that in the label.

What section? I cannot comment at this time. But somewhere in the label, it will show up. And any other strengthening of the label or the language or the verbiage suggested by the Committee, we will go with that.

CHAIR RAPPLEY: Yes, Geoff?

DR. ROSENTHAL: I have a more of a methodological question. As we try and, you know, find threads that would help us support causal relationships, I think it is very helpful that you

presented, you know, the number of patients who had a positive dechallenge and a positive rechallenge.

Are there ever data available, not just in this particular case necessarily but in other contexts as well, for the negative rechallenges? You know if we have positive rechallenge data, presumably the observations would be available for other patients who are rechallenged and for whom the response is not positive.

Are there any data for this case? Or in general?

DR. MOSHOLDER: I believe six of these cases, the notation was that they did not discontinue the drug. But I think the more -- so I think the more extreme cases, usually the response is to discontinue the drug.

And I don't recall seeing any cases where a dose reduction was tried first. But, I mean, your point is well taken. It is hard to develop precise data from those type of case series.

CHAIR RAPPLEY: Leon?

MEMBER DURE: Yes, I guess what I'd say is that it is not surprising to me that you have a fairly high incidence of people with neurologic impairment. At least the paradigmatic patient that I see who is on

Ditropan is a myelomeningocele or spina bifida or something like that. And they have central nervous system issues, anyway.

It is a little counterintuitive, though, because, as a neurologist, we typically think of children being more tolerant, at least from a CNS perspective of anticholinergics. I mean they can take Artane and huge doses compared to adults.

But I don't have any problems with a little bit of tweaking of the label. I mean I think it is very reasonable to be more specific about some of this.

DR. KAUL: We, as a Division, have no problem with that. We are going to.

DR. MOSHOLDER: Yes, if I could follow up on your comment, that's interesting because when we looked at the literature, actually what you see in the textbooks is that children are more sensitive to anticholinergic effects. And, in fact, in the atropine labeling, there is a statement to that effect.

What we couldn't find was any systematic data that really supported that. So that is why we got curious to look at the reporting pattern.

MEMBER DURE: It is a big deal what age

you are doing because there are so many changes in acetylcholinesterase and butylcholinesterase from, like, birth to ten. So it is very difficult to sort out.

CHAIR RAPPLEY: Is there enough information here to warrant a special comment about very young children? Children less than five and their being more prone to these hallucinations?

DR. KAUL: Below five is off-label use.

CHAIR RAPPLEY: Right.

DR. KAUL: And the current label says six and above.

CHAIR RAPPLEY: Right. I am aware of that. And that the information shows it is being widely used off-label. And that those children, in particular, had a proportionately higher reaction with hallucinations. I'm just wondering if that is worth mentioning in the label.

DR. MURPHY: I think that's what we are asking you.

CHAIR RAPPLEY: Yes. And I'm asking the group.

MEMBER DURE: I'll go out on a limb and say no. I mean, I think -- I don't know what is approved for children below five for detrusor

instability. And this is a population that, you know, that needs treatment. So these drugs are going to be used.

And if we -- again, if you just tweak the label some, I don't know if there is quite enough there to say that it is a special population under five.

CHAIR RAPPLEY: Yes?

DR. MURPHY: Can we get an idea of tweak? No, I mean that's fine. If you want to leave it at that, I just want to make sure because we've got -- this reminds me of the ADHD discussion, if you guys will remember where the words are in the label. But the question is do we want to add another word or do we want to say more than that.

So I guess I'm just trying to get from "tweak," do we mean just add another word or two or is there anything else? We don't -- what we're also hearing from you is that you have to look at the benefits of having this drug available. And we don't clearly want to put something such as stop the drug. I think we've heard that.

But that this dose effect might be something to think about. That if you are having -- something on the label about if you are having these

effects, particularly in younger children, consider lowering the dose or calling your doctor or something like that. Is that on the table?

Or you don't even want us -- I go back to Dr. Dure, you don't even want us to do that?

CHAIR RAPPLEY: We have several people who want to comment. So Avital, Robert, Melissa, and then Bob.

MEMBER CNAAN: Let me put a suggestion based on the almost last -- Slide No. 11 with the bar graph which would be to group the entire less than 16 and not separate by five or six or anything. As a group at risk a little bit for hallucination plus the dose modification rather than dose discontinuation and stop there. And not deal, for this Committee, with the elderly side. I think it goes a bit out of our purview.

CHAIR RAPPLEY: Robert?

MEMBER DAUM: So I like the language that was in this memo that was circulated to us with an executive summary at the beginning. I think the tweaking is pretty good right there. And maybe I'll read it very quickly.

DR. MURPHY: Sure, yes.

MEMBER DAUM: It's pretty short. Thank

you, Dianne.

Oxybutynin has the potential to cause anticholinergic central nervous system effects and these adverse effects have been reported post-marketing. Post-marketing reports describe a variety of CNS anticholinergic effects with hallucinations and agitation prominent among pediatric cases and confusion, hallucinations, and sedation prominent among reports involving geriatric use.

Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. If patients experience anticholinergic CNS effect, drug discontinuation should be considered -- not done -- considered.

So we should bandy this around a little bit. But that is pretty close to what I would like.

MEMBER WARD: I would argue for dose reduction before dose discontinuation.

CHAIR RAPPLEY: Or you could have dose reduction or discontinuation.

MEMBER WARD: Yes.

CHAIR RAPPLEY: And Melissa was next. And then Richard.

MEMBER HUDSON: They have already made my

comments.

CHAIR RAPPLEY: Okay. She said her comments were already made.

Rich?

MEMBER GORMAN: I would also like to -- these patients are often on multiple medications. So while they are changing their medications in conjunction with their entire medical regime because there may be other anticholinergic effective agents that they are using at the same time.

DR. KAUL: Absolutely right, because some of the cases we reviewed in this presentation, they had confounding medications as well as a confounding other co-morbid medical conditions.

CHAIR RAPPLEY: Any other comments or suggestions?

Keith?

MEMBER KOCIS: I just would say, you know, without going back and reviewing all the clinical trials but with the information we have, we have no dosing information, yea or nay. But it's, as we talked earlier, it is pretty straightforward. It is an anticholinergic drug. That is how it works. Expect this to happen.

And then let the doctors do what is right

for the patient. Be it stop it, be it reduce it, be it alter their combination of medicines. But I would try to not be too specific because that is not the data we have been given. And there is 30 years of data out there that I certainly haven't reviewed before I'd make some statements about that.

CHAIR RAPPLEY: Okay.

DR. MURPHY: OSE Division? Okay? One question?

CHAIR RAPPLEY: Yes?

DR. MURPHY: One of the things about the dechallenge and rechallenge, that might be something that we will look at maybe in some of the future reports -- and maybe making sure we have those.

I think we have done that for you all in the past. But we also mention if there are negative dechallenges. And so I hear that might be something that would be useful for you all to make sure we focus on that.

DR. JOHANN-LIANG: I think negative dechallenge, we sometimes have information. I mean, patients are treated through that. But negative rechallenge, it is very hard. To get positive rechallenge, you know that's once in a while.

DR. MOSHOLDER: Yes, this is summarized on

page nine of the --

DR. MURPHY: I know. And that's why -- what I'm saying, Andy, is that you all almost always do it in your reviews. And I think what we are going to need to do is focus -- make sure we put it in the presentations because we give them so much material that sometimes we just need to refocus it.

DR. MURPHY: Carlos, can you remind us when we should report tomorrow morning?

CHAIR RAPPLEY: I was going to ask Carlos because I didn't bring that with me. And I don't want to tell you the wrong time.

EXECUTIVE SECRETARY PENA: The taxis will be picking everyone up at seven-thirty in the morning.

DR. MURPHY: Okay.

EXECUTIVE SECRETARY PENA: The taxis are waiting outside right now to take you back to the hotels.

DR. MURPHY: But the meeting starts at eight or eight-thirty? Because we've got eight-thirty. So is that correct? Somebody is saying eight-thirty, is that correct?

EXECUTIVE SECRETARY PENA: If it starts at -- let me check --

DR. MURPHY: We will send you --

EXECUTIVE SECRETARY PENA: -- I will check it in two minutes.

DR. MURPHY: -- an email, I guess.

MEMBER WARD: That was actually -- the last email was eight-thirty.

DR. MURPHY: Okay. We're going with eight-thirty.

MEMBER WARD: I'll try to get the taxis moved back a half an hour.

DR. MURPHY: Okay. Thank you all very much. We appreciate your advice and see you tomorrow morning.

(Whereupon, the above-entitled meeting was concluded at 6:12 p.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Pediatric Advisory Committee

Before: Marsha Rappley, M.D.

Date: April 11, 2007

Place: Rockville, Maryland

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Christina Warner