U.S. FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ADVISORY COMMITTEE

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MEETING

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TUESDAY,

MARCH 25, 2008

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The meeting convened at 8:00 a.m. in the Grand Ballroom of the Hilton Washington, D.C./North Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland, Marsha D. Rappley, MD, Chair, presiding

COMMITTEE MEMBERS PRESENT:
MARSHA D. RAPPLEY, MD, Chair
DENNIS BIER, MD, Member
AVITAL CNAAN, PhD, MS, Member
AMY J. CELENTO, Patient-Family Representative
ROBERT S. DAUM, MD, Member
MICHAEL E. FANT, MD, PhD, Member
ELIZABETH A. GAROFALO, MD, Industry Representative
MELISSA MARIA HUDSON, MD, Member
KEITH KOCIS, MD, MS, Member
THOMAS NEWMAN, MD, MPH, Member
ELAINE VINING, Consumer Representative
ROBERT WARD, MD, Member

CONSULTANTS PRESENT:

CARL D'ANGIO, MD, Consultant
HENRY FARRAR, MD, Consultant, Pediatric Health Organization Representative
DANIEL NOTTERMAN, MD, Consultant
CRAIG A. SABLE, MD, Consultant
CHRISTY SANDBORG, MD, Consultant

FDA PARTICIPANTS:

CARLOS PENA, PhD, MS, Executive Secretary
FELICIA COLLINS, MD, Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER
JUDITH COPE, MD, MPH, Medical Officer, Office of Pediatric Therapeutics
HENRY FRANCIS, MD
ABRAHAM KARKOWSKY
LISA MATHIS, MD, Pediatric and Maternal Health Staff, Office of New Drugs, CDER
EVELYN MENTARI, MD, MS, Medical Officer, Division of Neurology Products
DIANNE MURPHY, MD, Director, Office of Pediatric Therapeutics, OC
HARI CHERYL SACHS, MD, Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER
LEX SCHULTHEIS
JEFFREY SIEGEL, MD, Medical Officer, OND/ODEII/Division of Anesthesia, Analgesia and Rheumatology Products (DAARP), CDER
KEITH ST. AMAND
AMY TAYLOR, MD, Medical Officer, Pediatric and Maternal Health Staff, Office of New Drugs, CDER

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

8:01 a.m.

Welcome and Introductory Remarks

DR. RAPPLEY: Well, welcome to everyone once again. We are convening the Pediatric Advisory Committee and I'm Marsha Rappley, and I'm chair of the committee, and this is Dr. Carlos Pena, who's Executive Secretary at the Office of Science and Health Coordination, FDA.

We usually start by going around and introducing ourselves and saying who we are and where we are from and the discipline that we represent.

I also want to note for members of the committee who we've worked together for quite some time that actually five people will be rotating off after this meeting today. So, let's have a nice lunch and enjoy each other while we're together.

Okay. Dr. Bier, you want to start?

DR. BIER: Yes, I'm Dennis Bier. I'm

general pediatrician and epidemiologist at UCSF.

MS. VINING: Good morning. I'm Elaine Vining. I'm the consumer representative for the committee.

DR. RAPPLEY: Marsha Rappley from Michigan State University, Developmental and Behavioral Pediatrics.

DR. PENA: Carlos Pena, Executive Secretary to the Pediatric Advisory Committee.

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

DR. D'ANGIO: Carl D'Angio. I'm from the University of Rochester, and I'm a neonatologist.

DR. FARRAR: Hank Farrar. I'm from the University of Arkansas in Clinical Pharmacologist, and I am the representative from the AAP and non-voting member of the committee.

DR. NOTTERMAN: I'm Don Notterman. I'm from Princeton University. I'm a molecular biologist and pediatric critical care.

DR. SABLE: I'm Craig Sable. I'm a pediatric cardiologist from Children's National Medical Center in Washington.

DR. SANDBORG: I'm Christy Sandborg. I'm a pediatric rheumatologist from Stanford University.

DR. MURPHY: Dianne Murphy. I'm the Office Director of the Office of Pediatric Therapeutics at the FDA.

DR. MATHIS: I'm Lisa Mathis. I'm Associate Director in the Office of New Drugs for Pediatric and Maternal Health.

DR. RAPPLEY: Well, welcome to everyone again.

Dianne, do you want to give us the -- oh, you have announcements? Yes, okay.

DR. PENA: Thank you, and good morning. The following announcement addresses the issue of conflict of interest with regards to today's discussion report by the agency on Adverse Event Reporting as mandated by Section 17 of the Best Pharmaceuticals for Children Act.

The Pediatric Advisory Committee will hear and discuss reports by the agency as mandated in Section 17 of the Best Pharmaceuticals for Children Act on Adverse Event Reports for Toprol, Brevibloc, Lotensin, Coreg, Colazal, Eloxatin, Celebrex, and Suprane.

The Pediatric Advisory Committee will also hear about an update on trileptal and the Food and Drug Administration Amendments Act of 2007.

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 interested 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 discussions involve any other products or firms not already on the agenda, for which an FDA participant has a

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

We note that Ms. Amy Celento's participating as the Pediatric Health Care Representative, Ms. Elaine Vining is participating as the Consumer Representative, and Drs. Carl D'Angio, Dan Notterman, Craig Sable and Christy Sandborg are participating as temporary voting members.

We'd also like to note that Dr. Elizabeth Garofalo is participating as the non-voting Industry Representative, acting on behalf of regulated industry.

Dr. Henry Farrar is participating as a temporary non-voting Pediatric Health Organization Representative, acting on behalf of the American Academy of Pediatrics.

With respect to all of the participants, we ask that 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 1 p.m. and I would just remind everyone to turn on your microphones when you speak so that the transcriber can pick everything up and turn them off when you're not speaking.

I'd also just ask to make sure that all cell phones are turned to silent mode.

Thank you.

Agenda Overview

DR. MURPHY: I'm not sure why this spoon is here but we'll just assume that it's not symbolic for anything, and I wanted to also welcome everybody.

I also want to take a few moments this morning because we are in a transition phase. As you saw on the agenda, this afternoon we're going to be providing you an update on what we affectionately call FDAAA, the Food and Drug Administration Amendments Act, which does have great relevance to this committee because you're

one of the very few committees that's actually named in law and legislation advisory committees of the FDA and you have been assigned by Congress a number of additional responsibilities and we're going to go over that this afternoon.

But I wanted to take a moment because we are losing almost that whole side over there, it looks like, of the committee, five members of the committee, and we will be going into this new phase and today, we hope you will recognize that we have a fairly non-controversial day planned for you.

I thought I'd take a moment and go through the process that we have at FDA so that you will know that even though today we don't anticipate any great controversies, that there's been a tremendous amount of effort that has gone into this and we know there's a tremendous amount of effort on your part to look at all this information and to determine whether you agree or disagree with us because that is the reason you are here.

Congress has said, you know, when it comes to safety for pediatric therapies, we want an external group of people who are expert in their field to come in and, if you will, provide us your input as to whether you think we have the right assessment or not.

At other times, we are asking you questions where we're saying we're not really sure and we really want you to help us work our way through what would be the best thing to do.

What I'm telling you today is we don't have a whole lot of that today, but again the point of your being here is to provide us input, if you think that there is something else that we should be doing.

We have a process which, when a product in the past we've granted exclusivity, then there must be a year that goes by where adverse events are collected. At that point in the process, we put together a team and the team involves somebody from the Technical Division who usually sits right there at this meeting who may

wanted to make sure that everybody understood that that's really the new product that you'll be looking at for each meeting which is the review of the adverse events that the Office of Surveillance and Epidemiology has put together and the use review, how much of the product is being used.

We then have a meeting after they've done that to see if there's something that emerged from that review and sometimes we have, as today, we have a couple of things that have come up during the review and they are things that you could -- as you know, you don't have to have causality to put some information in the labeling, and they are adverse events that we think should go in but we would like to hear what you think about it because it's your background and perspective that we're seeking in this information.

Other times, we will have either already involved an epidemiologist or it will become apparent that we need to involve somebody from the Epidemiology staff in the Office of

Safety and Epidemiology, Surveillance and Epidemiology, and in that situation, we will have a much more expanded presentation to you and you've had a number of those.

I think our ultimate one was Tamiflu, we had that brought back three times, in which there is a signal and we can't figure out whether it's a signal from the disease, a signal from the product, a signal from the interaction, whatever. We will have a number of activities that go on, anywhere from just an additional look by the Epi staff or there will be a massive review which you're going to hear about today also in your update, looking at meta-analysis, if you will, of trials.

So, during that -- after that review is provided by the Safety group, we then have to decide what we're going to present to you. Is it going to be an abbreviated review where we don't think there are any signals, we don't see much happening, and we don't want to torture you by reading to you, as you've told us, you don't want

to hear every case history that has been sent in.

We do provide you that material, so that you can make your own assessment, and then we come up with our assessment as to whether we think we need to have an abbreviated review and ask you if we can just return this product to continue monitoring, and you will see that today, we have a number of those products.

When we have a standard review, it's when we are going to take the time to go over the controlled clinical trials that occur because the controlled clinical trials will always have a safety component. We want to make sure that everybody's aware of whatever went on during the clinical trials.

We will then go ahead and present in more detail the deaths and serious AEs. We do this for diseases where there is products that are used to treat conditions or diseases for which there's a high background rate of serious adverse events because you may have a large number of deaths, you may have a large number of serious

adverse events.

It's really hard to sort out what's going on and we just think it's better to go ahead and have you all have the full presentation, in addition to the full package that we provide you. It doesn't mean we're bringing an issue to you, it just means that we think that this is an area that is hard to make an assessment and we want to make sure that you have a full presentation on that because we send you normally at least six to eight products and I know that that takes a bit of work to get through all of those and we think the presentations, we hope, help focus where we think the issues are and so that's the difference for the standard.

You'll notice we really don't have any -- at this meeting, we have only abbreviated and standard. We don't have any of what we call the expanded reviews on which we're spending a whole day.

We do have an update for you and we are doing that in response -- the committee often

makes recommendations where they want follow-up and I don't want to steal their thunder, but you've seen the slides.

Fundamentally, the agency has been in the midst of a massive review of a 199 trials and this committee asked for some follow-up as to what was going on when this product was presented previously, and in this situation, because it's a lot more than pediatrics that's involved, the full review is going to go back to the Neurology Committee and we've asked members of this committee to participate because they're also having members from the Risk Committee and one other committee, I'm sorry, I think there's going to be like four different committees, so there's the full Neurology Committee and then members from other committees, and so that's why we're not bringing the whole thing back to you because it's really -- Pediatrics is a smaller part of this whole big picture.

But that brings me to the other activity of this committee which is you have been

meeting two to three times a year and as you're going to hear the frequency's going to probably have to go up just on safety issues, up to maybe four times a year, but in addition, we value your expertise tremendously for all these other committee activities that have to do with either safety or scientific trial design issues that we ask you to attend to.

So again today, we will be presenting mostly abbreviated and standard reviews to you.

The other thing I wanted to say to you all is that your work at this point, at the end of your last meeting, this committee had reviewed over 70 products and Dr. Judith Cope in her presentation is going to go over for you some of that effort because I think you all deserve to know the full extent of your contribution and actually the work has been put together in a paper that was tentatively just accepted by Pediatrics which focuses on what the Pediatric Advisory Committee's recommendations and activities have been for the last 60 some products that you have

reviewed.

And we're very thankful. I know we say that at the end of every meeting, but I just want to say it again because this is an important committee because you have done such a good job that Congress has now expanded your responsibilities and you'll hear more about that and they usually, I hope, don't do that when they think you've done an awful job.

So, I just wanted to tell you that I think that FDAAA reflected upon the contributions this committee has made in an area that's very difficult because the one thing we've gotten very clearly, the message from you all is you sure wish you had a denominator.

We don't have a denominator and you all have to struggle with that and we struggle with the systems and the data we do have and we really appreciate it.

So, with that, I hope we have -- is Avi here? Well, our Cardiology representative is not here yet, but I think we're going to have to

move on.

So, I'd like to turn it over to Amy Taylor. Dr. Taylor is from our Maternal and Pediatric Health Staff.

Brevibloc (esmolol HCI)

Abbreviated Review of Adverse Events

DR. TAYLOR: Hi. Good morning. This morning, I will start with presenting information on follow-up adverse event information on esmolol.

Brevibloc or esmolol hydrochloride is a selective beta blocker marketed by Baxter Healthcare Corporation. In adults, it is indicated for the treatment of SVT intra- and postoperative tachycardia and/or hypertension. There is no pediatric indication.

Brevibloc was originally approved for marketing on December 31st, 1986, and was granted pediatric exclusivity on August 22nd, 2003.

An adverse event review was presented to this committee on February 14th, 2005. This review was a follow-up to the 2005 meeting as requested.

(Show of hands.)

DR. RAPPLEY: Are there any opposed to this recommendation?

(No response.)

DR. RAPPLEY: So, the committee unanimously accepts this recommendation.

Thank you.

Toprol XL (metoprolol)

Abbreviated Review of Adverse Events

DR. TAYLOR: I will now present information on adverse events for Toprol XL.

Toprol XL or metoprolol succinate is a cardio-selective beta blocker marketed by AstraZeneca for the treatment of hypertension, angina pectoris, and heart failure in adults.

As a result of exclusivity studies, information for use in pediatric patients six years and older was added to the labeling. Pediatric use has been limited, approximately .1 percent of all prescriptions.

The drug was originally approved for marketing January 10th, 1992, and was granted

pediatric exclusivity on July 27th, 2006.

The exclusivity studies consisted of a randomized placebo-controlled dose-ranging study and a 52-week open-label extension study conducted in pediatric patients age 6 to 16 years. These studies included a pop. PK analysis.

The dose-ranging study did not meet its primary endpoint which was a dose response for reduction in systolic blood pressure.

An analysis of the high- and mid-level doses against placebo demonstrated significant decrease in blood pressure. These prespecified secondary endpoints demonstrated effectiveness.

Dose response for reduction in diastolic blood pressure, 1 milligram per kilogram versus placebo for change in systolic blood pressure and 2.0 milligram per kilogram versus placebo for change in systolic and diastolic blood pressure.

As a result of exclusivity studies, the following changes were made to the Toprol XL

labeling. A description of the clinical study results and an adverse event profile in the Pediatric Use Section and a dosing recommendation for pediatric patients greater than 6 years in the Dosage and Administration Section if Toprol XL is selected for treatment.

In the one-year postexclusivity period, there were three reports of serious adverse events. The first case involved an accidental ingestion by a 2-year-old.

The second case involved an in utero exposure of a premature infant delivered at 34 weeks gestation with a moderate heart murmur, bradycardia, and severe difficulty breathing. No further information was available.

The third case was a literature report of a 12-year-old with a renal transplantation on multiple medications who developed severe anemia. The authors attributed the anemia to irbesartan.

There was one reported death which occurred prior to the one-year post-exclusivity

period. This case involved a neonate with an in utero exposure delivered at 36 weeks gestation with limb deformities, pulmonary hypertension with a PDA, abnormal kidney structure and Potter's facies. The patient developed respiratory failure and died on Day 4. The patient's mother was on several anti-hypertensives, including Losartan.

We also conducted an adverse event review since market approval. This yielded 12 reported cases of adverse events. Three of the cases involved congenital abnormalities: a 3-day-old with a patent foramen ovale, a 10-month-old with a hip skeletal abnormality, and a 1-day-old with multiple ulcers in the esophagus and stomach.

There were three reports of accidental or intentional overdoses. There were four reports of pharmacy-dispensing errors. However, since each of these errors involved a different drug, no trend was identified.

There were two additional reports. The first is a 16-year-old with epigastric pain and an elevated amylase. She subsequently

underwent an appendectomy and excision of an ovarian cyst.

The second case involved a 15-year-old with a mild retinal vein occlusion.

In summary, no safety signals were identified since market approval unique to the pediatric population. The exclusivity studies resulted in labeling with dosing information, adverse event information, and a description of the clinical study results.

Pediatric use of the drug was limited, approximately .1 percent of all prescriptions.

This completes the one-year post-exclusivity adverse event reporting as mandated by BPCA. FDA recommends routine monitoring of adverse events for Toprol XL in all populations.

Does the advisory committee concur?

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

Thank you.

DR. RAPPLEY: Does the committee

concur with the recommendation?

(Show of hands.)

DR. RAPPLEY: Is anyone opposed?

(No response.)

DR. RAPPLEY: So, unanimous acceptance of this recommendation.

Lotensin (benazepril)

Abbreviated Review of Adverse Events

DR. TAYLOR: I will now present follow-up adverse event information for benazepril.

Lotensin or benazepril hydrochloride is an ACE inhibitor marketed by Novartis Pharmaceutical Corporation. It is indicated in the pediatric population for the treatment of hypertension in patients 6 years and older.

Lotensin was originally approved on June 25th, 1991, and was granted pediatric exclusivity on July 2nd, 2003.

An adverse event review was presented to this advisory committee on February 14th, 2005. This review is a follow-up of the 2005 advisory

committee meeting as requested.

Since market approval, there have been six reports of adverse events. Two cases were presented in February 2005 involving hyperchloremic metabolic acidosis with hypoaldosteronism in a 4-year-old and an accidental ingestion by a 2-year-old.

Because of the limited reports during the initial reporting period, the advisory committee requested continued focus review of adverse events.

Of the six reported cases since market approval, two were presented in 2005. The remaining four cases will be discussed here. One case was a duplicate. There are three additional cases.

The first case involved a 1-year-old male who was hospitalized with increased serum creatinine and potassium after being on benazepril for nine days.

There were two cases involving congenital abnormalities. The first involves a

newborn with a first trimester exposure to benazepril delivered at 36 weeks with multiple cardiac defects and unilateral rental agenesis with a single dysplastic kidney. The patient died at 19 days due to pulmonary hemorrhage and congenital heart disease.

The second case involves a premature infant whose gestational age was unknown with a first trimester exposure to benazepril. The patient had hypotrophy, premature jaundice, and surfactant pulmonary troubles. A favorable outcome was reported.

It's important to note that Lotensin labeling contains a box warning stating that ACE inhibitors can cause injury and even death to the developing fetus and should be discontinued as soon as possible.

In summary, no safety signals have been identified since marketing approval which are unique to the pediatric population. Pediatric use has been limited, less than 1 percent of all prescriptions.

This completes the follow-up adverse event review as requested. FDA recommends routine monitoring of adverse events for benazepril in all populations.

Does the advisory committee agree?

And again, I would like to thank the people listed here for their help with this review.

Thank you.

DR. RAPPLEY: Does the committee concur with this recommendation?

(Show of hands.)

DR. RAPPLEY: Any opposed?

(No response.)

DR. RAPPLEY: So, unanimous acceptance of this recommendation.

Thank you.

DR. TAYLOR: Thank you.

DR. MURPHY: Marsha, before we go on to the next product, I wanted to -- the committee's heard about a number of anti-hypertensive products very quickly this morning.

I wanted you to be aware that there have now been 12 products, I believe it is, I believe that have been studied for hypertension under this program, and I recently heard Dr. Stockbridge present and he's been at the agency for a long time and he's on the Advisory Committee on Pharmacology who was presenting and said that up until this initiative, these legislative initiatives, he was aware of only one product ever having been studied in pediatrics for hypertension.

So, I think the fact that we've had 12 products studied, you saw a couple of them in a row this morning, is fairly impressive.

As you saw in one of these products, one of the ways that you can show effectiveness is to show a dose response, and there was some issues with that in one of these products today.

I think it's been of interest and we've been very challenged to try to determine why of the 12 products that were studied, half of them didn't work. We know a lot about anti-

hypertensives.

So, we have some working agreements with Duke University and a number of their people have been working with us in analyzing the data, and I just wanted to let you know that the March issue of Hypertension took six of these products, put them into a meta analysis and looked at the various endpoints and dosing, et. cetera, to try to determine why -- if we could come up with an answer as to why we thought we were not seeing responses and also design better trials, if that's what we needed to do.

And I think that it's worth perusing, if you have an opportunity to do that, because they did find some interesting information about dosing and certainly if one of the ways you determine efficacy is a dose effect and you don't do the dosing correctly, you're not going to be able to demonstrate efficacy.

So that the other interesting point with the diastolic endpoint actually appeared to be a bit more useful in pediatrics. So, this was

just to let you know that you got a very abbreviated review. There's a lot of work that's been going on with anti-hypertensive drugs and I think some interesting information coming out and that was, as I said, in the March issue of Hypertension.

Danny Benjamin, Dr. Danny Benjamin was the lead author.

So, thank you.

DR. PENA: The next speaker is Dr. Felicia Collins, Medical Officer in the Pediatric and Maternal Health Staff, Office of New Drugs. Division Representative is Dr. Abraham Karkowsky.

Coreg (carvedilol)

Standard Review of Adverse Events

DR. COLLINS: Good morning. I'm pleased to be able to present to you the one-year postexclusivity adverse event review for carvedilol.

Coreg or carvedilol is a beta adrenergic blocking agent for which GlaxoSmithKline is the drug sponsor.

Original market approval occurred on September 14th, 1995, and pediatric exclusivity was granted on November 8th, 2006.

Prior to the pediatric exclusivity study, carvedilol was indicated (1) for the treatment of mild to severe chronic heart failure of ischemic or cardiomyopathic origin to increase survival and to reduce the risk of hospitalization, (2) to reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have left ventricular ejection fraction of less than or equal to 40 percent, and (3) for the management of essential hypertension.

The next two slides provide some information about the use of carvedilol in outpatient settings. 12.4 million carvedilol prescriptions were dispensed for all age groups during the 12-month postexclusivity period. 0.1 percent of these prescriptions were for the pediatric population. There was a 20 percent increase in the prescriptions for all age groups