DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ADVISORY SUBCOMMITTEE

OF THE ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

SECTION 17, BEST PHARMACEUTICALS FOR CHILDREN ACT ADVERSE EVENT REPORTING

Thursday, June 12, 2003

3:45 p.m.

Holiday Inn Gaithersburg
The Ballrooms
2 Montgomery Village Avenue
Gaithersburg, Maryland

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C O N T E N T S

P R O C E E D I N G S

Call to Order, Introductions

DR. CHESNEY: We would like to start with introductions because there are some new people at the table. It looks like the left side of the table is depleted, so we will start at the right.

Dr. Murphy, I don't know if you and Dr. Cummins need to introduce yourselves or we can move on.

DR. MURPHY: I think you can move on.

Solomon, you need to introduce yourself.

DR. IYASU: Good afternoon, My name is Solomon Iyasu. I am a team leader with the Division of Pediatric Drug Development, pediatrician, epidemiology. I will be talking about adverse events today.

DR. CHESNEY: Thank you. Continuing around the table?

DR. CHEN: Hello. My name is Min Chen. I am Associate Director of the Office of Drug Safety, CDER.

DR. HIRSCH: I am Mark Hirsch. I am the medical team leader in urology.

DR. PARKS: I am Mary Parks. I am the Deputy Director, Division of Metabolic and

Endocrine Drug Products.

DR. FUCHS: Susan Fuchs, Pediatric Emergency Medicine Physician, Children's Memorial Hospital, Chicago, a member of the committee.

DR. O'FALLON: Judith O'Fallon, statistician, Mayo Clinic Cancer Center, Rochester, Minnesota.

DR. LUBAN: Naomi Luban, pediatric hematologist-oncologist, Director of Transfusion Medicine and Laboratories, Children's Hospital and George Washington University School of Medicine, member of the committee.

DR. DANFORD: David Danford, Department of Pediatrics, Joint Section of Pediatric Cardiology, University of Nebraska Medical Center and Creighton University in Omaha.

DR. NELSON: Robert Nelson, pediatric critical-care medicine at Children's Hospital, Philadelphia.

DR. CHESNEY: Joan Chesney, Division of Pediatric Infectious Diseases at the University of Tennessee, Memphis Health Science Center.

MR. PEREZ: Tom Perez, Executive Secretary to this Committee.

DR. GORMAN: Rich Gorman, pediatrician in

private practice in Ellicott City, Maryland.

DR. MATTISON: Don Mattison, NICHD.

DR. IP: Stanley Ip, Department of Pediatrics, New England Medical Center.

DR. ANDREASON: Paul Andreason, psychopharm leader, Division of Neuropharmacological Drug Products, FDA.

DR. STASKO: Robert Stasko, medical officer, Division of Neuropharmacology.

DR. NEWMAN: Tom Newman, Departments of Epidemiology and Biostatistics and Pediatrics at UCSF.

DR. CHESNEY: Thank you.

Mr. Perez is going to read the conflict-of-interest statement for this meeting.

Meeting Statement

MR. PEREZ: Thank you. The following announcement addresses the issue of conflict of interest with respect to this meeting and is made part of the record to preclude even the appearance of such at this meeting. All participants have been screened for interests related to the product to be discussed, their sponsors' competing products and their sponsors.

In accordance with 18 U.S.C. 208(b)(3),

the following participants have been granted waivers that permit them to participate in the discussions; Dr. Joan Chesney for owing stock in the sponsor of Zoloft and Lipitor, value between $52,000 and $100,000 and for owing stock in a firm that makes a competing product to Zoloft. The stock is valued from $5,001 to $25,000.

Dr. Richard Gorman for owing stock in the parent company of the sponsor of Ditropan. The stock is valued between $50,000 and $1.00 to $100,000.

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 involvement and their exclusion will be noted for the record.

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

Thank you.

DR. CHESNEY: Thank you.

Our main speaker for this afternoon is Dr. Solomon Iyasu. He is going to discuss the adverse-event

reports for four drugs, I understand.

Adverse Event Reports

DR. IYASU: Good afternoon.

[Slide.]

I know this is very late in the day. I will try to make it as painless as possible. In the next hour and a half, I will be presenting to you the one-year post-exclusivity adverse-event review for four drugs.

As you recall, I presented preliminary data for Zoloft in the last meeting. Today, I will present the review of full year adverse-event reports of Zoloft and Ditropan and preliminary results for Zocor and Lipitor.

[Slide.]

As you well know, reviewing and reporting the reports for the Pediatric Advisory Subcommittee is mandated by Section 17 of the BPCA. We discussed this during our last meeting.

[Slide.]

Sertraline, or Zoloft, was granted exclusivity on February 1, 2002. It is a selective serotonin-reactive inhibitor. In adults, it is indicated for the treatment of major depressive disorder or CV panic disorder, post-traumatic

disorder, premenstrual disorder, social anxiety disorder. In children, it is indicated for the treatment of obsessive-compulsive disorder in age six years and older.

[Slide.]

How frequently is this drug being used? To answer this question, I will present data from two data sources; the IMS Health or National Prescription Audit Plus which provides data on projected frequency of dispensed prescriptions by retail pharmacies. Data is gathered from a sample of 22,000 randomly selected pharmacies in the U.S. The pharmacies in the sample represent about 40 percent of the pharmacy stores and approximately 45 percent of prescription coverage.

The second database is National Disease and Therapeutic Index which provides projected frequency of total mentions or appearances during patient visits to the office-based practice. The data are gathered from a panel of 2,000 to 3,000 office-based physicians in the Continental U.S.

A drug mention can result from a prescription written, a refill authorized, a sample given, the drug administered in the office and so on or any combination of these.

[Slide.]

Data from the NPA Plus indicates that total dispensed prescriptions for all ages increased from 21 million in 1998 to 31 million in 2002. Family medicine, internal medicine and psychiatry were the top three specialties prescribing Zoloft in and accounted for most of the increase during this time period.

The pediatric specialty were responsible for close to 400 dispensed prescriptions during 2002. Frequency of Zoloft mentions during patient visits to office-based practice increased slightly between 2000 and 2002 in children zero to sixteen years of age.

Two thirds of the mentions were in adults and children. Zoloft was used more in male children than females while the opposite is true in the adult population. In 2002, there were close to 700,000 drug mentions in all pediatric-aged children representing about 8 percent of total Zoloft mentions or appearances.

[Slide.]

There are very important limitations of drug-use databases. NPA Plus did not provide, for example, demographic information and NDTI

projections can be unstable due to small sample size when use of a drug is less prevalent.

[Slide.]

Before I go into the actual review of the adverse events reported for this product, I would like to dwell a little bit on the adverse events limitations and the limitations of the database that we have at FDA.

Oh; I think have a different slide here. This is the labeling information which you have. Do you have it in the packet? I understand that the labels are in the package so this is a summary of what the label says regarding pediatric information. Adverse events are generally similar to those seen in adults and the other adverse events in pediatric patients included hyperkinesia, twitching, fever and so on as indicated on this slide.

In the precaution section of the label, there is mania, hypomania, weight loss, risk of seizure and suicide mentioned as precautions in the Precaution Section. In the Pediatric Section, there is information about decreased appetite and weight loss from studies that were done in the pediatric population and recommendations to do

regular monitoring of weight and growth for children who are taking this medication.

[Slide.]

Let me dwell, then, on the adverse-event reporting system and its important limitations before I go into the actual review. AERS is a spontaneous and voluntary system as opposed to an active surveillance system. Therefore, underreporting adverse events is an important limitation. The extent of underreporting may vary by drug and length of time a drug has been in the market. Another limitation is reporting bias. There tend to be more reports, for example, for new drug entities which have just come into the market. Often the quality of the reports is poor and in conflict which makes is very difficult to adequately assess the relationship between the event and the suspect drug.

There are no real numerators or denominators and, therefore, it is not possible to estimate the true incidence rate of events or exposure or risk. Numerators are ascertained. Denominators can only be projected for many of these drugs. Unlike in clinical trials, they are one kind of reliably estimated risk because there

are no control groups to compare to.

It may be a good signal generator or detector for rare unlabeled serious adverse events. However, it is poor at detecting the depth and strength of the signal especially when the background rate of an event is high or unknown. The veracity of a causal attribution based on the AERS data is often questionable. It is soft data at best, but often that is all we have.

So, with that introduction to the AERS database, let me go to the actual report.

[Slide.]

Let me turn to this report, the one-year report, that is on the table here. When looking at this table, the numbers are not going to add up for two reasons. First, the totals in the first row include reports with unknown age. Second, these counts may include duplicate reports. Fortunately, duplicates are easy to sort out by a careful review. The numbers in parentheses on this table are adverse-event reports from the U.S. alone.

Therefore, the AERS search for the one year after granting exclusivity generated a total of 1,249 reports worldwide of which 847 were from the U.S. alone. Among pediatric-age patients,

there were 51 adverse-event reports of which 40 were serious and five were reports of death. While the pediatric deaths is a duplicate report upon hand review, minor review; that is, having four unduplicated pediatric deaths in the final analysis

[Slide.]

Adverse-event reports are categorized according to preferred terms. This slide presents the top ten most frequently reported adult and pediatric adverse events in decreasing frequency of occurrence. Note that adverse events not previously described or not on the label are marked by an asterisk. This includes, for the pediatric patients, maternal drugs affecting the fetus, complication of maternal exposure and memory impairment.

[Slide.]

I would like to turn my attention to the demographics of the 49 unduplicated pediatric adverse-event reports for the one-year after exclusivity. Looking at the age distribution, there were nine reports among infants less than one month old. All the reports under one month old can loosely fall under the category of maternal exposures of the fetus. A little less than half of

the reports were in children older than twelve years. 21 were in females and 27 in males.

[Slide.]

Based on the predominant adverse events reported in each case, the 49 pediatric cases could generally be summarized in the following five categories. However, it must be emphasized that most reports involved more than one drug and possible confounding by underlying medical disorders.

There were thirteen patients with psychiatric events most commonly characterized by aggression, hostility or hallucinations. Ten patients had neurologic events. Most of the events, however, were extrapyramidal movement disorders. There were 13 cases with congenital events in the context of exposure by maternal use. These included congenital malformations and neonatal withdrawal syndromes.

[Slide.]

There were nine patients whose adverse events were due to either an overdose or accident or intentional medication error or suicide. Five nonfatal overdoses, of which three cases were accidental ingestions, two were intentional

overdoses in adults and children. Of the three fatal cases, two completed suicides and one case was an accidental toxicity.

There were four other cases that cannot fit into any category. So this is, in general, putting them into different adverse-event profiles.

[Slide.]

An examination of outcomes revealed, as I said before, four unduplicated pediatric deaths. There were nineteen hospitalizations and 26 that were life-threatening or required interventions or medically important events.

Just a reminder, there is a regulatory definition for what a serious adverse event is. It is defined as any adverse drug experience occurring at any dose that results that in any of the following outcomes; a death, a life-threatening adverse drug experience, an in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity or a congenital anomaly or birth defect.

[Slide.]

Let's turn to the diagnosis or indication for use recorded in the adverse-event case reports.

The commonest indication for use is depression in sixteen patients. You will recall that Zoloft is not approved for depression. It is approved for OCD.

Although few, it appears that it was also used for ADHD, OCD, vocal-cord disorder, stress emotional disorder, anxiety and adjustment disorder. There were a large number of in utero exposures. We also had several for which indication for use was either accidental or unknown.

[Slide.]

Let me discuss the cases that led to the four deaths. A premature baby born to an HIV-positive mother who was using Zoloft and multiple other meds during pregnancy. The baby died after developing pneumothorax and septic shock. The death was probably unrelated to Zoloft in this case. I am just presenting the summary.

[Slide.]

Patient No. 2, an adolescent child committed suicide following a one-week trial of sertraline for depression. The patient remained significantly depressed during therapy. This report is an update provided during 2002 to an

initial report that was provided to FDA in 1997.

Two days ago, the sponsor provided us additional information regarding this patient which became available as a result of litigation. The information suggests the patient exhibited serious behavioral and emotional problems including anger, aggression, social withdrawal, suicide ideation for the six months prior to initiation of therapy or also to the event.

As a known suicide risk in major depressive disorder is labeled and there is a Precautions Section of the drug label. The information to date, including what we got recently, is suggestive of the event being related to the underlying condition of depression. The role of sertraline, if any, is unclear in this case.

[Slide.]

This report is from a relative of the deceased. An adolescent child committed suicide after using Zoloft without prescription about six times during the ten-year period. The intention was to get high. He was introduced to Zoloft by a student ten days prior to the event. There was no prior history of depression. However, the patient

reportedly had hallucinations the night before and, on the morning of the event, it is also reported that the patient stayed home due to fever that morning. This is probably a drug-abuse situation with a possible overdose although there was no information in the case report about dose.

So it is unclear if sertraline is causally related to this death or not.

[Slide.]

I just want to bring to your attention, which is on the label, Zoloft label and suicide risk Precaution Section, the possibility of a suicide attempt is inherent in the major depressive disorder and may persist on until significant remission occurs. Close supervision of high-risk patients should accompany the initial therapy. Prescriptions for Zoloft should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

[Slide.]

In summary, most of the pediatric events involve multiple drug exposures, had confounding medical disorders, generally were similar to adult events and most were labeled or previously

described events except maternal drugs affected the fetus, complications of maternal exposure and memory impairment. Even memory impairment can probably be the same as concentration impairment.

There were two suicides in adolescents, one with a history of depression and the other without a history of depression. The causal relationship between these two events is unclear.

[Slide.]

So the question that we would like to pose to the committee is any feedback on this report because, although there were 49 unduplicated reports, there was little to suggest that this was causally related to the drug. So I invite any comments and questions or clarifications on this product and this report.

[Slide.]

I would like to acknowledge Carol Pamer, Laura Governale for their contributions because they did most of the safety review.

DR. CHESNEY: Dr. Nelson?

DR. NELSON: The 392,000 prescriptions in the past year, I assume, is just the number of prescriptions. I guess two questions; A, what is the capture of that particular database relative to

national usage and, B, can one take that and at least divide by 30, since most plans only give you 30 pills per prescription, at least to get a relative number, at least a low number, of the number of actual people behind those prescriptions as opposed to number of prescriptions?

DR. IYASU: They used data that I mentioned comes from the pharmacy data which is really dispensed prescriptions. It doesn't necessary apply to use. It covers only about 40 percent of the pharmacies in the country and 45 percent, I think, of the prescriptions. So, if you were to try to calculate how many tablets, it would be difficult, probably, from this database.

DR. NELSON: But, at least from that, you could at least double it to get an idea of national usage, at least roughly.

DR. IYASU: I am not sure that you can do that. I don't know what the accuracy or validity of doing that would be because I haven't really calculated. We don't have a national database that covers--so there really is a comparison that we do. But you can have a rough calculation and put some confidence limits around that and see how good the estimates are.

I haven't done it so I can't give you a straightforward answer.

DR. CHEN: I think Dr. Nelson's question was about person-year calculation to get an estimate of the exposure. The data we have, the prescription data, is already in a projection so we can get that rough estimate again as far as person-year exposure data to be used as a denominator if we want to calculate anything. Right?

DR. NELSON: I guess that is a more sophisticated way of stating my question.

DR. CHEN: Maybe Laura would like to add a little bit more about drug use data specifics.

DR. GOVERNALE: As Dr. Iyasu stated previously, what we are getting from the National Prescription Audit is the number of prescriptions from the pharmacy databases. This number is projected to the national level so the numbers that were quoted are the nationally projected estimates of prescription volume.

DR. CHESNEY: Dr. Danford, you were next.

DR. DANFORD: I am interested in the thirteen either birth defects or fetal problems that came to light. Was there a particular pattern among those that you could recognize as a specific

problem with the drug?

DR. IYASU: Among the four cases of malformations which were all related to maternal exposure, we could not establish any causal relationship. But there were two cardiac defects, one limb reduction and then there was another face anomaly.

Given that we have some information about the effect of this drug on birth defects, there are no human studies to suggest that there is an effect of that kind, unexpected. But, again, the AERS database is not the best place to try to establish some causal relationship. But, from the human studies, there is no signal that suggests that there are birth-defect effects from the drug.

DR. CHESNEY: Dr. Luban?

DR. LUBAN: I presume that the drug is contraindicated in pregnant women?

DR. IYASU: Right. It is contraindicated and that risk and benefit has to be weighed before this drug is given to pregnant women but it has not been studied in pregnant women.

DR. CHESNEY: Dr. Gorman.

DR. GORMAN: We have approved many drugs, or BPCA has approved many drugs. How were these

four drugs selected for our review today?

DR. IYASU: The law states that we have to provide a review of all the drugs that have gotten exclusivity. The selection in based on the dates on which these drugs have gotten their exclusivity determination done. If they were given on a certain date, then they are put on the list. So, on the anniversary of that granting of the exclusivity, then we are obliged to provide that review within three months or so, depending on how extensive the review is

So that is how they come into the picture. Two of these drugs, for example, were approved in February and the statins were approved on February 22, two of them. So all four of them have completed their one year plus the time that we need to review the data. That is how they got selected into the presentations this time.

DR. CHESNEY: I don't see any other questions. Should we go ahead, then?

DR. MURPHY: Our neuropharm representatives are leaving so this is your last chance, ladies and gentlemen, before they depart, if you have any more questions about Zoloft. I just wanted to point that out. Okay.

Sorry, guys. I just wanted to make sure they understood that you would not be staying around.

DR. GORMAN: One more question. Is this pattern of neonatal withdrawal syndrome seen with the other agents that we are not getting reported on today, and the same thing with the facial abnormalities and limb-length discrepancies. Is that when you look at all the selective serotonin reuptake inhibitors, that looks more convincing than just with Zoloft alone?

DR. ANDREASON: If I heard you correctly, you said the withdrawal syndromes or the discontinuation?

DR. GORMAN: The neonatal discontinuation.

DR. ANDREASON: The neonatal discontinuation. Pretty much with the neonatal discontinuation syndromes, they seen to be fairly constant across the group with some hint that the longer half-life SSRIs are not showing as many cases. But, again, it is hard to tell because this is an AERS database. There are cases reported kind of across the board. Whether these represent discontinuation or toxicity followed by discontinuation is, at this point, difficult to say

because sometimes symptoms are showing directly after birth which would not give an adequate amount of time for the drug to wash out and have that be a withdrawal or a discontinuation syndrome.

As far as the cranial-facial abnormalities, I am not sure on that one. I would assume that they are. Is Andy here? Andy, could you speak to the cranial-facial abnormalities?

DR. ANDREASON: This is Andy Mosholder who reviewed many of these drugs. He is with the Office of Drug Safety now.

DR. MOSHOLDER: Off the top of my head, I am not sure I can contribute anything about cranial-facial anomalies with SSRIs. I think fluoxetine has been the best studied in the literature and there hasn't been any association established in terms of congenital anomalies to date that I am aware of. But I am not sure of the others in the class have been studied to the same extent at this point in time.

DR. IYASU: Thank you.

[Slide.]

My second talk is a review of the adverse-event reports involving oxybutynin or Ditropan.

[Slide.]

Ditropan was granted exclusivity on February 3, 2002 and is an antispasmodic and anticholinergic agent. In adults, it is indicated for the treatment of bladder irritability associated with voiding in patients with an inhibited neurogenic bladder. In children, Ditropan is indicated for the treatment of detrusor muscle overactivity in association with a neurogenic condition such as spina bifida.

The tablet in syrup are approved in children five years or older and the extended-release form is for ages 6 and older.

[Slide.]

Drug-use data for 1998 to 2002 shows that total dispensed prescriptions increased from 3.5 million in '98 to 6.5 million in 2002 in all ages. The oral form was the predominant form dispensed. Urology and internal medicine were the two top specialists responsible for most prescriptions.

The pediatric specialty accounted for about 82,000 dispensed prescriptions during 2002.

[Slide.]

The frequency of drug mentions or appearances during pediatric patient visits in office-based practice decreased to 82,000 down from

138 in 2002 and 105 in 2000. Children between the ages of two and eleven represented over 70 percent of the use. Overall, the use was much higher in females than males in pediatric and adult patients. However, there were gender and age differences in the leading indications for use.

In males age two to eleven years, the leading indications were frequency of urination and polyuria. In age twelve to sixteen, it was for incontinence of urine. In females age two to sixteen years, the leading indications were other bladder dysfunction such as hyperactive bladder, paralysis of bladder or neurogenic bladder.

[Slide.]

In the office-based setting, the top three physician specialties prescribing Ditropan were urology, pediatrics and nephrology.

[Slide.]

During the year following exclusivity, there were a total of 40 adverse-event reports, five of which were in pediatric patients. All the pediatric events had serious outcomes. There were no pediatric deaths.

[Slide.]

This slide shows the ten most frequent

adverse-event reports listed in decreasing order of frequency. Adverse events not previously described or not on the label are marked by an asterisk. In adults, the drug being ineffective was the most common reported events. This is unlabeled. In pediatric patients, although several reported events are not labeled such as depression, hallucinations, panic reaction, abnormal behavior, anger, anxiety, aggression. However, the number of events are just too few and uninterpretable.

[Slide.]

However, when we looked at the reports from the drug-approval date which was 1975 to March 19, 2003, there were 745 adults and 74 pediatric reports. This slide shows the unlabeled events only. In adults, the most common, again, was drug ineffective. Other events were pruritus and the condition aggravated.

There were also unlabeled events in pediatric patients, several of which are psychiatric events such as personality disorder, thinking abnormal, agitation and so on. But, again, the numbers were not that great. We did not do a detailed analysis in review of the case reports since '75.

[Slide.]

The five reports for the post-exclusivity period were in patients between the ages of two and eleven years of age. Two were female and three were male. The administered doses ranged from 5 to 37.5 milligrams per day.

[Slide.]

This slide shows the diagnosis for which Ditropan was used as recorded in the case reports, one each for enuresis, nocturnal enuresis, neurogenic bladder and detrusor muscle spasms. There was no information for one patient.

[Slide.]

I will briefly discuss each of the five pediatric reports. A school-age child in Ditropan and Desmopressin, which is a synthetic antidiuretic hormone agonist, was used in the treatment of primary nocturnal enuresis. The patient was hospitalized with low osmolality, hyponatremia, weight gain which mostly may have been the effects of the Desmopressin.

There were three medically significant events. A school-age child on Ditropan had a seizure after taking Benadryl. The patient was treated in the ER and Ditropan was resumed. The

patient is seizure free.

Next was a fragile preschool-age child with a history of tracheostomy, ventricle-peritoneal shunt on Ditropan syrup via G tube. The patient became unconscious and Ditropan was discontinued. The only other information we have is the catheterization increased from four to six times a day during therapy.

[Slide.]

The next case is a preschool child born with brain damage who developed behavioral and psychiatric events after six to twelve months of treatment with Ditropan for bed wetting. After Paxil was added, the patient became violent and a danger to one's self and others and developed personality changes. Paxil was discontinued and resumed at half dose after the patient became depressed and suicidal. The symptoms improved but the bed wetting persisted.

The patient was put on Detrol and Paxil following which Ditropan was discontinued and eventually bed wetting improved as the patient matured.

[Slide.]

The next case is an anxious school-age

child put on Ditropan for nocturnal enuresis but developed several psychiatric symptoms. The patient was put on Atarax and Ditropan was discontinued after a month.

[Slide.]

In summary, all the five pediatric reports had serious outcomes. However, several adverse-event terms were unlabeled as indicated before. Most of the psychiatric events primarily were reported from the two patients with possible underlying psychiatric conditions. The pediatric events cannot be solely attributed to Ditropan use because of concomitant drug use, possible overdosing or confounding medical conditions.

Once again, the limitations of the AERS data makes attribution of causality very difficult when one is considering the clinical question of did the suspect drug cause the event. From an epidemiologic standpoint, causality is a public-health question that requires a population-based approach to adequately answer the question. Postmarketing reports are limited in this aspect unless you have a large number of signals.

[Slide.]

The question, then, to the committee is,

because of the small number of reports that we have for the one year, should we consider an additional one year of AERS follow up.

DR. MURPHY: This applies to both products, we are asking this.

DR. CHESNEY: Would anyone feel strongly that we should not ask for an additional year of follow up? In other words, we would ask for another year of follow up. I think everybody agrees that we would like an additional year of follow up for both drugs.

DR. IYASU: Okay. Thank you. Any comments or questions? Let me go to the next one.

[Slide.]

My last presentation is a review of adverse events of simvastatin or Zocor, events that were reported to the FDA during the one year after pediatric exclusivity was granted.

Exclusivity for this drug was granted on February 22, 2002. Simvastatin is a lipid-lowering agent. In adults, it is approved for use in coronary heart disease with hypercholesteremia. In children, it is indicated for the treatment of heterozygous familiar hypercholesterolemia as an

adjunct to diet to reduce total cholesterol, low-density lipoproteins and Apo B levels in boys and postmenarchal girls age ten to seventeen years.

This condition occurs at the prevalence rate of 1 in 500 and is associated with an increased risk of premature coronary heart disease in adulthood. Adjunct therapy is used if, after the adequate trial of dietary therapy, LDC-C remains equal to or more than 190 milligrams per deciliter or it is equal to more than 160 milligrams per deciliter and a family history of premature heart disease or two or more CVD risk factors are present.

[Slide.]

Based on data from NPA Plus, total dispensed prescriptions for Zocor have increased from 18.5 million in 1998 to 28.8 million in 2002 for all ages.

[Slide.]

In 2002, there were a projected 4,000 drug mentions or appearances in office-based practice for the pediatric age group zero to sixteen years of age. There were no mentions of this drug during 2000 and 2001. Hyperlipidemia was the lead indication in this setting.

[Slide.]

Now, counts of adverse events during the year after exclusivity shows that there were a total of 1,309 reports in all ages including domestic and foreign sources. Most were in adults. There were eight reports in the pediatric age groups. However, a careful of review of the case reports revealed four of the age reports were in adults. That is leaving four pediatric reports for review. One of the four was a pediatric death.

[Slide.]

Today, I will only present a summary preliminary review of the pediatric cases. This is really a preliminary report. There were four unlabeled and unduplicated events with serious outcomes including one death. However, the number of reports are too few again for a meaningful interpretation. All the pediatric events reported to FDA were from foreign sources.

Preliminary review indicates that the events cannot be solely attributed to Zocor use. Two cases were exposed in utero. Both were delivered by C-section because of fetal distress. The first case was exposed to Zocor in the first trimester only. There were no other concomitant

maternal medications. The baby is a healthy, normal weight term baby.

The second in utero exposure involved multiple concomitant maternal medications, prematurity and resulted in postnatal death from complications of prematurity. The rest of the pediatric reports had concomitant medications and confounding medical conditions. As I stated earlier, the reports are too few and the causal link to Zocor cannot be made from the available information for any of the events I discussed above.

[Slide.]

The question for the committee, again, is because of the small number of reports and relatively low pediatric use, should we consider then an additional year of AERS follow up.

DR. CHESNEY: Can I speak for the rest of the committee and say we would appreciate another year of follow up.

DR. IYASU: Thank you.

Let me go to the last report

[Slide.]

The next drug is Lipitor. It was granted exclusivity on February 22, 2002, the same day as

Zocor. I will get you out of here in five minutes. The label for the drug is in your package. The approved indications in adults and children are summarized on this slide and they are similar to what it is for Zocor.

[Slide.]

The next two slides are the use data for Lipitor. The total dispensed prescriptions for Lipitor are increasing, 24.8 million in '98 to 65.7 million in 2002.

[Slide.]

Frequency of drug mentions for pediatric patients in office-based settings are also increasing from 9,000 in 2000 to 14,000 in 2002. Pediatric use represents less than 1 percent of all Zoloft mentions during the year. The most common indication, again, is hypercholesterolemia.

[Slide.]

During the one year after exclusivity was granted, there were a total of 966 adverse-event reports. However, there were no pediatric reports during the year so I have nothing to report.

[Slide.]

I would ask the same question now as for the other drug.

DR. CHESNEY: We would like more information.

DR. IYASU: Thank you.

DR. CHESNEY: Thank you very much. This brings us to the open public hearing.

Open Public Hearing

DR. CHESNEY: I understand that nobody has signed up for the open public hearing. Is there anybody from the public who would like to speak? Yes? I think the time is generally about three to five minutes.

MS. McDONALD: My name is Sheila McDonald. I am a Member of the Board of Directors of the Child and Adolescent Bipolar Foundation. Ms. Judith Cornelius is also a member of the Board of Directors of the Child and Adolescent Bipolar Foundation which is a national organization of 12,000 families raising children with bipolar disorder.

As you can imagine, our mission is to educate families, professionals and the public about early-onset bipolar disorder and to advocate for increased research on the nature, causes and treatment of bipolar disorders in children.

Parents report that before diagnosis,

serious adverse drug reactions have occurred. These parents report to us on our website constantly and they have reported that, as a result of single drug-therapy treatment with SSRIs alone, there have been adverse events. Whenever there are adverse events reported to us, we ask that they send it to the formal system.

However, many families report that, as an adjunct to appropriate treatment with new stabilization therapy, SSRIs can be an important tool in helping to improve the quality of our children's lives. So we feel, importantly, that clinicians and families need this important safety data to help guide appropriate use of these and other medications and we urge increased attention to safety studies in children and to improve the adverse drug-event reporting system. We are hopeful that the SSRIs will be continued to be looked at as an adjunct to appropriate treatment.

Thank you.

DR. CHESNEY: Thank you. Would anybody from the agency like to respond?

DR. MURPHY: No, except to say that we will continue to be looking at the SSRIs.

Chair/Committee Final Comments

DR. CHESNEY: I think that brings our afternoon open session to a close. Is that correct? Would you all like to make final remarks? I would like to thank Dr. Iyasu and your colleagues for doing all this follow-up information for us. I think, even though we are not represented by very many here, it is very, very important information. So we really appreciate all the effort you all have put into it.

DR. MURPHY: I think any feedback from the group--I think one of the things we are going to have to do is not have it at the very last, which we tend to. I think that is probably one of the things I would begin to suggest we change a little bit. Any suggestions from the committee on how to make it more useful to them, again, in the context that we have limited resources. You saw our one safety person is dedicated totally to peds, so we have many people who have also assisted and cooperated, and help us. Office of Drug Safety has committed significant time and effort to this.

Knowing, within that context, we just don't have unlimited resources. If there is any other way that we can make this more useful, we would like to hear from you.

DR. CHESNEY: I think, in a very pragmatic sense, it would be nice to get this information before we come and particularly to have the pediatric adverse effects that have been reported, everything about the pediatric use in the drug insert highlighted. It took me a while to find the Zoloft information. If that was highlighted and if it were possible to get the report you just gave us beforehand, so we could be formulating questions and absorbing it better than at the end of the day.

I would agree with you, Diane, maybe it would be possible to do it early in the session or in the middle of a session or take time out to do it because I do feel badly that there are not more people here to hear it. But I am also glad that there is nothing that we--it sounds like there is nothing we need to be particularly alarmed about this time.

DR. MURPHY: We, again, would like to say thank you very much to everybody, and particularly to you guys and ladies that hung in here to the very end.

DR. CHESNEY: We understood there was a limousine to take us if we stayed later. Thank you all, very much, for all the work that you did as

background information. We just have a very, very easy job compared to what you do and so thank you very much for all you do.

[Whereupon, at 4:39 p.m., the meeting was adjourned.]