Food and Drug Administration
Center for Drug Evaluation and Research
Advisory Committee Conference Room 1066, 5630 Fishers Lane, Rockville, MD.

Summary Minutes of the Pediatrics Subcommittee of the Anti-Infective Drugs Advisory Committee

June 9, 2004

AntiInfective Drugs Advisory Committee Members Present

Steven Ebert, Pharm. D.

Consultants

Joan P. Chesney, M.D.	Victor Santana, M.D.	Naomi Luban, M.D.
David Danford, M.D.	Mark Hudak, M.D.	Richard Gorman, M.D.
Robert Nelson, M.D.	Susan Fuchs, M.D.	Judith O'Fallon, Ph.D.
	Katherine Wisner, M.D.	

Government Employee	Industry Representative
Janet Cragan, M.D. **(CDC)**	Sam Maldonado, M.D.

FDA Participants

Dianne Murphy, M.D.	Shirley Murphy, M.D.	Susan Cummins, M.D.
	Solomon Iyasu, M.D.	

These summary minutes for the June 9, 2004 meeting of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee were approved on June 18, 2004.

I certify that I attended the June 9, 2004 meeting of the Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee, and that these minutes accurately reflect what transpired.

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Thomas H. Perez, M.P.H., R.Ph.
Executive Secretary

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Joan P. Chesney, M.D.
Chair

The Pediatric Subcommittee of the AntiInfective Drugs Advisory Committee, of the Food and Drug Administration, Center for Drug Evaluation and Research met June 9, 2004 Advisory Committee Conference Room, Rm. 1066, 5630 Fishers Lane, Rockville, MD.

On June 9, 2004 the agency provided a report to the committee on Adverse Event Reporting as mandated in Section 17 of the Best Pharmaceuticals for Children Act (BPCA). The products discussed during this portion of the meeting included Hycamtin (topotecan), Temodar (temozolomide), Effexor (venlafaxine), Monopril (fosinopril), Allegra (fexofenadine), Duragesic (fentanyl), Ciloxan (ciprofloxacin), and Vigamox (moxifloxacin). Following this, the agency provided an update on neonatal withdrawal syndrome and congenital eye malformations reported in infants whose mothers used a Selective Serotonin Reuptake Inhibitor during pregnancy. The agency then provided an overview of the Pediatric Research Equity Act (PREA), which was signed into law on December 3, 2003. The last topic was an overview of the Institute of Medicine report, entitled "Ethical Conduct in Pediatric Clinical Trials.

The Subcommittee and invited guests received a briefing document from the FDA in preparation for this meeting.

There were approximately 65 persons present in the audience at this meeting. The meeting was called to order at 8:10 a.m. by the Chair, Joan Chesney, M.D. The Subcommittee members and discussants introduced themselves. Thomas H. Perez, Executive Secretary of the Pediatric Subcommittee of the AntiInfective Drugs Advisory Committee read the Meeting Statement. A welcome, and opening comments were provided by Dianne Murphy, M.D., Director, Office of Counterterrorism and Pediatric Drug Development.

Presentations began at 8:20 a.m. and proceeded as follows.

Adverse Event Reports per Section 17 of BPCA	Division of Pediatric Drug Development Solomon Iyasu, M.D., Lead Medical Officer
Fexofenodine	Jane Filie, M.D., Medical Officer
Topotecan and, Temozolomide	Susan McCune, M.D., Medical Officer
Ciprofloxacin and, Moxifloxacin	Harry Gunkel, M.D., Medical Officer
Fosinopril	Larry Grylack, M.D., Medical Officer
Fentanyl	ShaAvhree Buckman, M.D., Medical Officer David J. Lee, Ph.D., Clinical Pharmacology Reviewer Div. of Pharmaceutical Evaluation II D. Elizabeth McNeil, M.D., Medical Officer, Div. of Anesthetic, Critical Care & Addiction Drug Products

At 10:00 the subcommittee began discussion of question 1, followed by a break at 10:20. The remaining presentation on the topic of **Adverse Event Reports per Section 17 of BPCA** began at 10:35 a.m.

Venlafaxine	Hari Sachs, M.D., Medical Officer

There were no participants for the Open Public Hearing's morning session. At 11:10 Dianne Murphy, M.D. provided the Subcommittee with an update on the status of the evolution of the Pediatric Committee. She also recognized all the past Subcommittee participants for their contributions to the Pediatric Subcommittee soon to be dissolved.

At 11:45 the Subcommittee broke for lunch, and reconvened at 12:40 p.m. The meeting statement for the afternoon's topic was read by the executive secretary and the following presentations followed.

Update on Neonatal Withdrawal Syndrome	Kathleen Phelan, R. Ph., Div. of Drug Risk Evaluation Robert Levin, M.D., Div. of Neuropharmacological Drug Prod. Katherine Wisner, M.D., Women's Behavioral Health CARE

At 2:15 p.m. the subcommittee began discussion of questions 2 and 3. This was followed at 3:15 p.m. by one presentation on the next topic on the agenda.

Update on Congenital Eye Malformations in Infants	Solomon Iyasu, M.D.

The afternoon session of the Open Public Hearing began at 3:25 p.m. with one participant, who provided the following presentation.

Maternal SSRI-Use During Pregnancy And Neonatal Neurobehavioral Outcome	Philip Sanford Zeskind, Ph.D., Research Professor of Pediatrics University of North Carolina - Chapel Hill

After a 10 minute break the meeting continued at 3:55 p.m. with an update and report on the remaining two topics.

Pediatric Research Equity Act (PREA) Update	Shirley Murphy, M.D. Director, Division of Pediatric Drug Development
Overview of IOM Report, *Ethical Conduct of Clinical Research Involving Children*	Robert Nelson, M.D. The Children's Hospital of Philadelphia

The meeting was adjourned at 4:45

Pediatric Sub-committee of the Anti-infective Drugs Advisory Committee Meeting

Questions to the Subcommittee

The Subcommittee discussed the following questions. The meeting's discussion will be made available through the meeting transcripts and placed on the web in approximately three weeks. Transcripts may be accessed at: www.fda.gov/ohrms/dockets/ac/acmenu.htm.

Adverse Event Reporting

1. The risk management strategy for the Duragesic patch that you have heard today is very preliminary. Do you have any suggestions or additional thoughts that you would like to discuss?

   The committee strongly recommends that the Black Box section contain additional language indicating that:
   "inappropriate use may result in serious adverse effects including death" and highlight the need for qualifications of those prescribing the medication.

   In addition the committee suggested the following additional points to consider:
   Patient information should be clear and written at a less sophisticated level, particularly statements regarding continued risk and side effects from the medication after it has been discontinued.
   Format reorganization of the information to highlight important areas.
   Develop additional risk management communications to hospitals, in particular the pharmacy department.
   Consider adding a "Pediatric Exclusivity" category of information for trial information in the labeling for all products that are studied under the Pediatric Exclusivity provisions. The committee also expressed concern that important negative information or even acknowledgement of studies conducted in children is not being noted in all of the labels of products having pediatric studies.
   Consider future development of products labels with embedded electronic links for additional details and documentation.

SSRI/SNRI neonatal withdrawal syndrome

2. The FDA is proceeding with class labeling about neonatal toxicity/withdrawal syndrome related to in-utero exposure to SSRI/SNRIs. Considering the risk/benefit of SSSR/SNRI use in pregnant women with depression versus the risk/benefit to the fetus/newborn, how should this new information on the label be disseminated to child health practitioners and the public? Please discuss the following options.
   a) No further action necessary. Label change is adequate.
   b) Dear Health Care Professional Letter (sponsor responsibility)
   c) Prescribe/health care professional education through professional groups
   d) Public Health Advisory (FDA's responsibility)

   The committee strongly endorsed class labeling for the neonatal toxicity/withdrawal syndrome related to in utero exposure of SSRI/SNRI's. The members also strongly supported a package insert for patients (pregnant or considering pregnancy) which provided detailed information at the 6th to 8th grade level as to what is known about the risk/benefit issues for the fetus/newborn and for the mother when choices have to be made about the use of these agents in pregnancy. The committee did not support a Public Health Advisory.

Strong support from the members was also provided regarding professional education through professional groups regarding the neonatal toxicity/withdrawal syndrome. In addition to Pediatric, Obstetric and Psychiatric Professionals, providing information to Family Medicine practitioners was also strongly emphasized.

3. BPCA does not provide a mechanism for issuing a written request to study drug therapies for pregnant women. There are no population based estimates of SSRI/SNRI exposure data in pregnant women and there are no systematically collected data on neonatal outcomes in infants exposed to these drugs. Furthermore, determining causality for neonatal reactions is challenging as the role of drug discontinuation, direct toxicity (e.g. serotonin syndrome) and/or other drug/substance exposure during pregnancy is often unclear. Is there a need for further research to evaluate and characterize the neonatal effects of in-utero exposure to SSRI/SNRIs? If your answer is yes, in your discussion of research options, please discuss feasibility and potential sponsors for each option.

    a) Continue evaluating/monitoring post-marketing adverse event reports
    b) Population based prospective study of pregnancies exposed to anti-depressants and neonatal outcomes
    c) Retrospective study of neonatal withdrawal syndrome/serotonin toxicity
    d) Randomized controlled trial of treatment of maternal depression. If yes, what research questions should be addressed by the trial?

    The members felt there was an urgency to acquire research data clarifying the nature of the neonatal syndrome. The few available studies don't clearly distinguish between a "behavioral teratogenicity" syndrome resulting from prolonged serotonin exposure in utero vs. a simple "withdrawal syndrome" resulting from in utero "serotonin toxicity." It was felt that retrospective studies would probably not have precise enough focused observations to distinguish between these two syndromes, if in fact there are two separate syndromes.

    Although retrospective studies might provide incidence/prevalence data, the members felt that prospective detailed, longitudinal and long term studies, including if possible, in utero physiologic fetal data are urgently needed. For example, information regarding the long term effects on older children following fetal exposure to SSRI/SNRIs has not been studied in enough detail.

    It was suggested that the NICHD Center for Research for Mothers and Children might be a perfect fit for such studies. Other ongoing epidemiologic studies of infants relative to genetic/teratogenic follow-up were also suggested as ongoing mechanisms to study the effects of these agents on newborn infants.

    Although ideal, the use of randomized controlled trials of SSRIs for the treatment of maternal depression for the specific purpose of defining the effects on the fetus and newborn, is a complex issue which would take much more discussion involving psychiatrists and obstetricians. From one of the speakers the members were made aware of a potential study comparing SSRIs vs. light therapy of depression in pregnancy. Following women who chose no therapy or alternate pharmacologic or light therapy might provide a control group.