

MINUTES OF THE  
**PEDIATRIC ADVISORY COMMITTEE**

Washington DC North Hilton  
Gaithersburg, MD

**Wednesday, March 22<sup>nd</sup>, 2006**

The meeting was convened at 7:30 a.m.

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**Members Present (voting) for March 22<sup>nd</sup>, 2006**

Robert M. Nelson, M.D., Ph.D. (*Chair*)  
Dennis Bier, M.D.  
Robert Daum, M.D.  
Angela Diaz, M.D., M.P.H.  
Deborah Dokken, M.P.A.  
(*Patient Family Representative*)  
John Moore, M.D., M.P.H.  
Thomas Newman, M.D., M.P.H.  
Melissa Hudson, M.D.  
Judith O'Fallon, Ph.D.  
Marsha Rappley, M.D.

**Pediatric Advisory Committee**

**Pediatric Health Organization Representative**

Richard Gorman, M.D.

**Pediatric Advisory Committee**

**Industry Representative**

Elizabeth Garofalo, M.D.

**Executive Secretary**

Jan N. Johannessen, Ph.D.

**FDA Participants**

Dianne Murphy, M.D.  
Robert Temple, M.D.  
Thomas Laughren, M.D.  
Paul Andreason, M.D.  
Rosemary Roberts, M.D.  
Solomon Iyasu, M.D., M.P.H.  
Gerald Dal Pan, M.D., M.H.S.  
Rosemary Johann-Liang, M.D.

**Voting Consultants:**

Paula Knudsen (*Acting Consumer Representative*)  
Robert M. Ward, M.D.  
Benedetto Vitiello, M.D.  
Jorge Armenteros, M.D. (*PDAC member*)  
Cynthia Pfeffer, M.D.  
Daniel Pine, M.D. (*PDAC member*)  
Laurel Leslie, M.D., M.P.H.

**Open Public Hearing Speakers**

Lawrence Diller, M.D.  
W. Douglas Tynan, Ph.D.  
Lawrence Greenhill, M.D.  
Aldelaide Robb, M.D.  
David Fassler M.D.  
Kendrick Moxon  
Ellen Liversidge  
Sam Goldstein, Ph.D.  
Christine Limbers  
Winni Johnson  
Peter Breggin, M.D.  
Carol Watkins, M.D.  
Barbara Hawkins  
Katy Warren  
Fred Baughman, Jr., M.D.  
Grace Jackson, M.D.  
Tamar Osterman  
David Stein, Ph.D.  
Darrel Regier, M.D., M.P.H.  
DuBose Ravenel, M.D.  
Thomas Sullivan, M.D.  
Jim Paicopolos  
Todd Gruber, M.D., M.P.H.  
Julie Zito, Ph.D.  
Vera Sharav  
Allen Jones  
Clinton Libby  
Moirra Dolan, M.D.  
Thomas Kobylski, M.D.  
Sen. Curtis Bramble  
Glen Elliot, Ph.D., M.D.  
Cynthia Wainscott  
Judith Rapoport, M.D.  
Gayle Ruzicka  
James Swanson  
L. Read Sulik, M.D., FAAP  
Sharon Kientz  
Lee Spiller  
Bruce Wiseman  
Jacqueline and Brad Bessner

**Presentations:**

**Committee Role in BPCA Safety Review**

Solomon Iyasu, M.D., M.P.H., OCTAP, CDER, FDA

**One Year Post-Exclusivity Adverse Event Review: Clofarabine (Clolar®)**

Larry Grylack, M.D., OCTAP, CDER, FDA

**One Year Post-Exclusivity Adverse Event Review: Irbesartan**

Alan Shapiro, M.D., Ph.D., OCTAP, CDER, FDA

**Regulatory History of Sibutramine**

Eric Colman, M.D., OND, CDER, FDA

**One Year Post Exclusivity Adverse Event Review: Sibutramine**

Hari Sachs, M.D., OCTAP, CDER, FDA

**Overview of ADHD Portion of the Meeting**

Dianne Murphy, M.D., OPT, OC, FDA

**New Physician's Labeling: Where is the Safety Information?**

Rosemary Roberts, M.D., OCTAP, CDER, FDA

**Update and Overview of FDA activities on ADHD: Summary of June 2005 PAC-Interim Actions and Landmark Events**

Paul Andreason, M.D., OND, CDER, FDA

**General Overview of Recent DSaRM Meeting**

Marsha Rappley, M.D., Dept. of Pediatrics and Human Development, Michigan State University

**Efficacy of Pharmacological Treatment of ADHD**

Benedetto Vitiello, M.D., National Institute of Mental Health, NIH

**One Year Post Exclusivity Adverse Event Review: Adderall XR®**

Susan McCune, M.D., OCTAP, CDER, FDA

**Use of Drugs for ADHD in the U.S.**

Andrew Mosholder, M.D., M.P.H., ODS, CDER, FDA

**Cardiovascular Risk with Drug Treatments of ADHD**

Kate Gelperin, M.D., M.P.H., ODS, CDER, FDA

**ADHD drugs and CV outcomes: Preliminary feasibility results and potential observational studies**

David Graham, M.D., M.P.H., ODS, CDER, FDA

**Psychiatric Adverse Events in ADHD Clinical Trials**

Andrew Mosholder, M.D., M.P.H., ODS, CDER, FDA

**Psychiatric Adverse Events with Drug Treatments of ADHD**

Kate Gelperin, M.D., M.P.H., ODS, CDER, FDA

**Sponsor Presentations:**

**CONCERTA® (methylphenidate HCl) Extended-Release Tablets**

H. Lynn Starr, M.D. – McNeil

Douglas Jacobs, M.D., Associate Clinical Professor of Psychiatry, Harvard Medical School

**Assessing Drug Safety and ADHD Medications, Including Atomoxetine**

Albert J. Allen, M.D., Ph.D. – Global Medical Director – Strattera, Eli Lilly and Company

## Summary of Discussions and Recommendations Pediatric Advisory Committee

### **One Year Post-Exclusivity Adverse Event (AE) Reviews:**

#### Clorfarabine (Clolar®)

Most adverse events reported by the FDA are currently labeled or would not be unexpected in association with the disease or with the concomitant treatments received by the patients in which the adverse events were reported. The FDA recommended routine monitoring of clorfarabine for AEs in all populations.

*Committee Action: The chair asked if any on the committee disagreed with the FDA's recommendation to continue routine monitoring for clorfarabine AEs – there were no objections.*

#### Irbesartan (Avapro®)

The FDA reported that there were no concerning safety signals for irbesartan, and that use is small in the pediatric population with few AE reports. The FDA recommended routine monitoring of irbesartan for AEs in all populations. The FDA noted that data from the exclusivity trial indicating lack of effectiveness in the pediatric population would be included in the labeling.

*Committee Action: The chair asked if any on the committee disagreed with the FDA's recommendation to continue routine monitoring for irbesartan AEs – there were no objections.*

#### Sibutramine (Meridia®)

The FDA reviewed the regulatory history of sibutramine, noting the regulatory concerns and actions taken to mitigate cardiovascular risks and possible fetal toxicity (see response to citizen's petition in briefing materials). The FDA reported that labeling has been updated after exclusivity studies to reflect that data were inadequate to support use in adolescent weight loss and potential adverse events. During the one-year post-exclusivity period, no new pediatric AEs were identified. Previous Office of Drug Safety reviews did not reveal additional cardiovascular risk or an underlying pattern of congenital anomalies. A more formal study of cardiovascular risk, the Sibutramine Cardiovascular Outcomes (SCOUT) Study was initiated in April of 2005 and is ongoing. The agency proposed heightened monitoring for an additional year.

*Committee Action: The chair asked if any on the committee disagreed with the FDA's recommendation to continue heightened monitoring for sibutramine AEs – there were no objections. In addition, the committee expressed the desire to get an update on adverse events associated with sibutramine in the future, after completion of the SCOUT study.*

#### Mixed Salts Amphetamines (Adderall XR®)

Presentation and discussion of the One Year Post-Exclusivity Adverse Event (AE) Review for Adderall was included with other ADHD medications (below).

## **ADHD Products**

*Note: No specific votes were taken in response to the FDA's questions. Rather, the recommendations for inclusion of information on the label were by a consensus assent, or were recommendations of members. Thus, this was a gathering of ideas for the agency to consider for labeling options. However, it is important to note that where an opportunity was given to committee members to discuss the merits of recommending a particular action (e.g. discussion of boxed warnings) and none of the committee expressed a desire to pursue this, it is noted in the record.*

The Chair began by noting that ADHD medications have been shown to be effective in children properly diagnosed with ADHD and therefore will continue to be used.

The deliberations did not reflect the sequence of questions originally presented to the Committee. The Chair collapsed the questions into three areas for the Committee to address the following issues which were covered by the original questions:

1. What was the Committee's assessment of the data?
2. How can the committee, within the framework of FDA labeling, try to foster and improve informed consent, both on the part of the practitioner and parents as they struggle with the decision whether to use or not use these medications. (Are the current messages in the labeling adequate and, if not, how can they be improved.)
3. Are there additional ideas on how to best communicate the messages, and measure risk including "blue sky" ideas?

The Committee addressed the adverse events individually as noted below.

General broad areas of analysis:

- Signs and/or symptoms of psychosis or mania (including hallucinations)
- Aggression or violent behavior
- Suicidal ideation or behavior (suicidality)
- Cardiovascular effects

## **Psychosis/Mania Events (including Hallucinations)**

Several members of the Committee expressed their concerns regarding terminology. The psychiatrists on the Committee were concerned that the term "psychosis" was perhaps being used too broadly, since specific diagnostic criteria were not evaluated in each of the AERS cases. They did, however, agree that the labeling for psychosis was warranted, and could be further clarified

It was noted that symptoms of psychosis or mania were estimated to occur at a rate of 2 to 5 per hundred person-years (observed 1.6 per 100 patient years) for subjects on active drug in registrational randomized controlled trials (as presented by Dr. Mosholder); this was statistically significant compared to placebo (there were zero cases on placebo). This rate (greater than 1%) cannot be considered rare, although it could perhaps be considered infrequent.

The Committee agreed that most cases of hallucinations that were occurring in relationship to the medication did not appear to be a manifestation of a preexisting disease. There was consensus that some of these events were drug related. In discussing adverse event reports from clinical trial data, one of the psychiatrists suggested that some cases may represent hypnogogic hallucinations, relatively common and non-serious sleep-related hallucinations that may occur in some untreated children, but that this could not be determined without seeing the detailed reports. (*Post-meeting note:* Postmarketing case reports were generally not consistent with hypnogogic hallucinations.) There was agreement that psychosis and mania type adverse events, in particular, hallucinations, should be more clearly labeled. The Committee discussed the need to recommend discontinuation of ADHD drug therapy at least temporarily in such situations as an important initial clinical intervention.

The Committee stated that it was important to enhance the current warnings in the labeling regarding psychosis, mania and hallucinations. The message to parents should be to contact the physician if the child has unexpected changes in behavior after initiating therapy. Many such drug-related psychiatric adverse events may be self-limited and resolve with drug cessation. Physician labeling should suggest that medications be stopped, at least temporarily, if such symptoms occur.

### **Aggression Events**

The FDA presentations described the occurrence of treatment-emergent aggression or violent behavior from spontaneous reports. Analysis of the clinical trial data suggested an increased frequency of aggression events relative to placebo for some drugs (methylphenidate transdermal system, Ritalin LA and atomoxetine), but not others [see slides from Mosholder]. The committee noted that aggression is often a feature of ADHD, especially certain subtypes, and that there was evidence from previous double-blind clinical studies showing ADHD medications can generally decrease aggressive behavior [see: D.E. Connor et al, J. Am. Acad. Child Adolesc. Psychiatry, 41:3, March 2002, pp 253-261]. Therefore aggressive behavior should not preclude initiation of therapy; there is a need, however, to obtain an assessment at baseline to determine whether aggression is part of the condition.

Parents need to know to contact the physician if new (treatment emergent) aggression occurs or if symptoms of aggression worsen during therapy. The message is for parents to report any changes (new or worsening) to the physician. Specific wording was not recommended, nor was there a specific recommendation on exactly where this information should go.

### **Suicidality Events**

The Committee did not recommend any changes to the labeling for suicidality at this time. The FDA presentations noted a possible suicidality signal for two drugs. It was noted that Strattera, which has the strongest signal, already has a boxed warning. Modafinil is not yet approved for ADHD, and committee felt it would be up to the committee that discusses approval to discuss whether there was need for labeling.

### **Cardiovascular Events**

The committee members were asked if they felt that based on the data for the pediatric population, there was a need for a boxed warning regarding cardiovascular risks. None on the committee expressed a need for this.

The need for strong warnings regarding the use of the stimulants in patients with underlying structural cardiovascular defects or cardiomyopathies was emphasized. New labeling for the methylphenidate and amphetamine products is already in place or planned.

The Committee discussed the need to inform parents that children with known cardiac anomalies are at a higher risk for sudden death or cardiovascular events, and that the drug therapy could increase this risk. In discussing where in the new label "Highlights" section this warning should go, there were no definitive recommendation made, other than it needed to be prominent.

This risk also exists for children with undiagnosed heart anomalies. Because there is no cost-effective way to identify the few patients with these abnormalities, baseline assessment of family history and symptoms were recommended by Committee members, but not in-depth cardiovascular screening of all patients.

The cardiologist on the committee noted that because non-stimulant ADHD medications can cause a pharmacologic increase in blood pressure and/or heart rate, the FDA should consider having some type of warning on the label for medications that elevate blood pressure/pulse regarding increased risks for children with underlying cardiovascular defects. The rationale was that manipulations that elevate heart rate and/or blood pressure increase the risk of cardiovascular adverse events in children with underlying cardiac defects, and until the results of ongoing studies designed to better define the risk for all ADHD medications in such patients are completed, some type of warning should be included. For the non-stimulant medications, this might include language that contrasts mechanism of action with that of stimulant medications.

Committee members also recommended that parents/patients should be informed to notify their physician if they experience symptoms indicative of undiagnosed cardiac problems after initiating therapy, such as shortness of breath, syncope, palpitations or chest pain.

### **Communicating with Patients**

There was a general discussion of how best to communicate information to patients and encourage the patient-physician partnership in evaluating treatment choices and possible adverse events for ADHD medications. MedGuides and other forms of communication were discussed. The agency noted that Med Guides are used in two instances: (1) there is something troubling about the drug that people need to know before starting medication or (2) to alert physicians and patients to monitor closely for signs of a rare adverse event. The suggestion was made that as an alternative to MedGuides, the agency consider the type of patient information sheet distributed with vaccines, which would explain in lay language such topics as the nature of the disease, various treatment options and consequences of not treating. It was noted that the American Academy of Pediatrics had developed such sheets for a number of medications, but they had been discontinued after several years due to a lack of interest on the part of the practitioners, but that perhaps this idea deserves reconsideration.

### **Summary of Labeling Recommendations for ADHD Products**

*Note: Specific recommendations on this list were not voted on. The list represents compiled recommendations, made by members and reflected in the Chair's summaries of particular discussions. While not voted on, these recommendations were assented to by the group, as no vigorous dissent from these was expressed. Please see the full transcript for detailed discussions.*

#### Aggression:

- Labeling should include the information that (1) aggression can be part of ADHD (2) controlled studies show ADHD medications can decrease levels of aggression, but should warn that (3) new onset or severe exacerbation of aggression should be immediately discussed with the doctor, and physicians should consider stopping the medication.
- The Committee also recommended that a MedGuide or some other form of information sheet should be developed to better inform patients about these medications and to serve as a discussion guide with families and their physicians. Messages should include that discontinuing the drug in certain circumstances is reasonable.

#### Psychosis and Mania (including hallucinations)

- The current cautions in the labeling related to worsening psychosis and mania should be retained, but additional information should be included to more clearly describe the risks.
- Additional information on reports of visual or tactile hallucinations involving insects or insects crawling under the skin should be added to the labels. Reports of auditory hallucinations, including command auditory hallucinations, have also been received during marketed experience with ADHD drugs.
- Quantitative information from clinical trial data should be added indicating that symptoms of psychosis or mania occurred at a rate of 2 to 5 per hundred person-years for subjects on active drug in registrational randomized controlled trials.
- A recommendation that prescribers stop the drug at least temporarily if these reactions occur and monitor patients closely on rechallenge with the same or another medication should be included.

#### Suicidality:

- The committee did not recommend any additional labeling regarding suicidality, since atomoxetine is already labeled and modafinil labeling will be discussed if it is approved.

#### Cardiovascular warnings:

- The committee did not recommend a boxed warning regarding the risk of sudden death or cardiovascular risk for children was needed.
- For normal children, these drugs do not appear to pose an obvious cardiovascular risk.
- The strong warning that FDA requires on the stimulant medications that they increase the risk of sudden death and cardiovascular adverse events in children with

underlying structural cardiovascular defects or cardiomyopathy is warranted. The warning should be included in the new label "Highlights" section.

- A similar warning should be extended to non-stimulant medications that increase heart rate and/or blood pressure, pending the outcome of epidemiological data to clarify this issue. For the non-stimulant medications, this might include language that contrasts mechanism of action with that of stimulant medications.
- There is a critical need for additional pharmacoepidemiologic studies to clarify the risk of cardiovascular events in children (normal and those with underlying cardiac abnormalities) on ADHD medications.

#### General Comments on Labeling

- The Committee discussion noted that the new "highlights" section of the labeling will move the most important information and messages for parents and patients to the front of the labeling.
- The message should be that if children experience sudden or dramatic negative changes in behavior after beginning therapy, parents should contact their doctor.
- MedGuides will provide more information for the consumer on MedWatch, the Agency's adverse event reporting system, including information about the program and the phone number to call. Parents should be encouraged to submit any adverse events experienced to MedWatch.
- The agency or pediatric health organizations should consider developing plain language patient information sheets, similar to those developed for vaccines.

#### Additional Recommendations

- Dr. James Swanson, Professor of Pediatrics at the University of California at Irvine, presented results from a multimodal treatment study with over 500 children undergoing ADHD therapy. His results showed a 1-1.5 cm/year growth difference when patients were on versus off medication. The Committee advised that the agency analyze this data in more depth and consider adding data on growth in the labeling.

The meeting adjourned at approximately 6:30 p.m.

*Please see transcript for details*

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I certify that I attended the March 22, 2006 meeting of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

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Jan N. Johannessen, Ph.D.  
Executive Secretary

\_\_\_\_\_/S//\_\_\_\_\_  
Robert M. Nelson, M.D., Ph.D.  
Chair