MINUTES OF THE
PEDIATRIC ADVISORY COMMITTEE

Holiday Inn/Gaithersburg, Grand Ballroom
2 Montgomery Village Road, Gaithersburg, Maryland

Tuesday, November 18th, 2008

The meeting was convened at approximately 8:00 a.m.

Members Present (voting) for March 25th, 2008
Marsha Rappley, M.D. *(Chair)*
Amy Celento (*Patient Health Care Representative*)
Avital Cnaan, Ph.D., M.S.
Carl D'Angio, M.D.
Leon Dure, M.D.
Hank Farrar, M.D. (*Pediatric Health Organization Representative*)
Brahm Goldstein (*Industry Representative*)
Melissa Maria Hudson, M.D.
Keith Kocis, M.D., M.S.
Kathleen Motil, M.D.
Daniel Notterman, M.D.
Geoff Rosenthal, M.D.
Alexander Rakowsky, M.D.
Elaine Vining (*Consumer Representative*)

Temporary Voting Consultants
Mark Hudak, M.D.

Executive Secretary
Carlos Peña, Ph.D., M.S.

U.S. Food and Drug Administration (FDA) Participants
Judith Cope, M.D., M.P.H.
Lisa Mathis, M.D.
Ann McMahon, M.D.
Dianne Murphy, M.D.
William Boyd, M.D.
Thomas Laughren, M.D.
Mitchell Mathis, M.D.
Ozlem Belen, M.D.
Norman Hershkowitz, M.D., Ph.D.
Phillip Sheridan, M.D.
Devanand Jillapalli, M.D.
Carole Davis, D.O., M.P.H.

Jill Lindstrom, M.D.
Naomi Lowy, M.D.

Open Public Hearing Speakers
None

Presentations
Welcome and Introductory Remarks
Marsha Rappley, M.D., Chair, Dean, College of Human Medicine, Michigan State University
Carlos Peña, Ph.D., MS, Executive Secretary, Office of Science and Health Coordination, Office of the Commissioner (OC), FDA
Agenda Overview
Dianne Murphy, M.D., Director, Office of Pediatric Therapeutics (OPT), OC, FDA
Zyvox (linezolid) Report Requested at the November 16, 2006 Pediatric Advisory Committee meeting (report in the briefing packet)
Betoptic S (betaxolol) and Timolol (timolol) Abbreviated Process
Risperdal (risperidone) Standard Review of Adverse Events
Felicia Collins, M.D., Medical Officer, Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), FDA
Zyprexa (olanzapine) Standard Review of Adverse Events
Felicia Collins, M.D., Medical Officer, OND, CDER, FDA
Levaquin (levofloxacin) Standard Review of Adverse Events
Elizabeth L. Durmowicz, M.D., Medical Officer, OND, CDER, FDA
Lamictal (lamotrigine) Standard Review of Adverse Events
Felicia Collins, M.D., M.P.H., Medical Officer, OND, CDER, FDA
Ambien (zolpidem) Standard Review of Adverse Events
Elizabeth L. Durmowicz, M.D., Medical Officer, OND, CDER, FDA
Lamisil (terbinafine) Standard Review of Adverse Events
Patricia Brown, M.D., Medical Officer, OND, CDER, FDA
Aldara (imiquimod) Standard Review of Adverse Events
Amy Taylor, M.D., Medical Officer, OND, CDER, FDA
Sandostatin (octreotide) Expanded Review of Adverse Events-Outside Speaker Presentation
Rama Bhat, M.D., Professor of Pediatrics, Director of Neonatology, University of Illinois at Chicago Medical Center
Sandostatin (octreotide) Expanded Review of Adverse Events
Amy Taylor, M.D., Medical Officer, OND, CDER, FDA
Ethics Discussion
Robert "Skip" Nelson, M.D., Ph.D., Pediatric Ethicist, OPT, OC, FDA

Sponsor Presentations
Sandostatin (octreotide) Expanded Review of Adverse Events-Sponsor Presentation
Todd Gruber, M.D., M.P.H., Head, U.S. Medical Function, Novartis

Summary of FDA Questions, Committee Discussion, Vote and Recommendations

Zyvox (linezolid) Report Requested at the November 16, 2006 Pediatric Advisory Committee meeting (report in the briefing packet)

Question to the Committee

- Follow-up Report contained in the background package. Are there any questions?

Committee Discussion

The Advisory Committee discussed the clinical study on QT prolongation requested by the Review Division and its application to all age groups. The committee requested that they receive the QT Prolongation report that is noted by the review.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed that they had no additional recommendations to the follow-up Report contained in the background package.

Betoptic S (betaxolol) and Timolol (timolol) Abbreviated Process

Question to the Committee

- FDA will continue its standard ongoing safety monitoring for these products. Does the committee concur?

Committee Discussion

The Advisory Committee discussed information in labeling concerning the use of this product in the pediatric population and the availability of data from the trial on the degree of lowering of intraocular pressure in the pediatric population would be useful in labeling.

Committee Vote

- Twelve (12) committee members unanimously agreed to standard ongoing safety monitoring for these products.

Risperdal (risperidone) Standard Review of Adverse Events

Felicia Collins, M.D., M.P.H., Medical Officer, OND, CDER, FDA

Question to the Committee

- FDA will continue its standard, ongoing safety monitoring for oral risperidone. Does the Advisory Committee concur?

Committee Discussion

The Advisory Committee discussed adverse events related to product use, off-label use, including risks and benefits, age subgroups, product labeling, and long-term use effects.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously supported more than the standard, ongoing safety monitoring for oral risperidone.
- Twelve (12) committee members recommended the following:
    1. Additional follow-up regarding on-label and off-label product use of this class of drug products with specific attention to age and indication for which the product is being used;

2. Additional follow-up regarding metabolic syndrome, growth, sexual maturation, and hyperprolactinemia
3. Studies, which may be collaboratively developed with NIH, on long-term effects in the pediatric population of this class of products ;
4. Additional follow-up on extrapyramidal side effects in the pediatric population;
5. Additional evaluation of this class of antipsychotic medications and concomitant drug use;
6. Committee is not recommending any public communication before additional discussion which should occur after receipt of data from above recommendations.

- Twelve (12) committee members agreed to withhold further recommendation on labeling until this additional information is provided to the Advisory Committee.

Zyprexa (olanzapine) Standard Review of Adverse Events
Felicia Collins, M.D., M.P.H., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA recommends, in view of the potential metabolic effects with the use of olanzapine, especially in pediatric patients to continue to evaluate the safety of olanzapine and decide if any additional risk-management regulatory action is needed. Does the Advisory Committee concur with this approach?

Committee Discussion
The Advisory Committee discussed the need for additional information, as discussed with risperidone, on use of this product in the pediatric population, obtaining more information from new database resources, and off-label use considerations.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed on the need to continue to evaluate the safety of olanzapine and additional risk-management regulatory actions concerning the monitoring of metabolic changes. Committee agreed with FDA's continued surveillance of metabolic syndrome.
- Please see the recommendations for risperidone.

Levaquin (levofloxacin) Standard Review of Adverse Events
Elizabeth L. Durmowicz, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA recommends continuing routine, ongoing post-marketing safety monitoring. Does the Advisory Committee concur?

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to routine, ongoing post-marketing safety monitoring and recommended adding the following text to the warning section (5.8) about prolongation of QT, "and other agents that cause an increase in QT".

Lamictal (lamotrigine) Standard Review of Adverse Events
Felicia Collins, M.D., M.P.H., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA is working to include suicidality data in the labeling of 11 antiepileptic drugs, including lamotrigine. FDA will continue to monitor medication errors related to name confusion. FDA will continue its standard, ongoing safety monitoring for lamotrigine. Does the Advisory Committee concur with this approach?

Committee Discussion
The Advisory Committee acknowledged that FDA has already worked with other sponsors on labeling products regarding risk of suicidality for antiepileptic drugs.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to standard, ongoing post-marketing safety monitoring.

Ambien (zolpidem) Standard Review of Adverse Events
Elizabeth L. Durmowicz, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA recommends returning to routine/standard safety monitoring for all patients. Does the Advisory Committee concur?

Committee Discussion
The Committee noted that the pediatric statement in the prescribing labeling information is inconsistent with the MedGuide and recommended FDA consider harmonizing the pediatric statement about not using these products in children.

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to routine/standard safety monitoring for all patients.

Lamisil (terbinafine) Standard Review of Adverse Events
Patricia Brown, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- FDA will continue its ongoing safety monitoring. Does the Advisory Committee have any additional comments?

Committee Discussion: Members recommended that the pediatric section would be clearer if it referred back to the Indication Section as it is unclear that the product was approved for a pediatric indication. Additionally, the Pediatric Use Section 8.4, should have a cross-reference to the pediatric studies described in Section 14 (Clinical Studies).

Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to ongoing safety monitoring.

Aldara (imiquimod) Standard Review of Adverse Events
Amy Taylor, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- In addition to planning to update the labeling related to severe local reactions in females with use in the genital area, FDA will continue its standard, ongoing safety monitoring for imiquimod. Does the Advisory Committee concur?

Committee Discussion:
The Committee recommended that more specific language should be added to the label concerning the adverse event "inability to urinate". The committee suggested FDA utilize Section 1.4, "Important Limitation of Use" to communicate that a product not be used in the pediatric population in a certain way. They also suggested for all product labeling, that Section 1, "Indications" should have a subsection as referenced with this product, "1.5 Unevaluated Populations", which specifically noted when there had been no studies in the pediatric population. Additionally, the Committee recommended that the Patient Information Sheet include a similar statement concerning lack of effectiveness in <12 year old patients as mentioned in the professional component of labeling.
Committee Vote and Recommendations

- Twelve (12) committee members unanimously agreed to ongoing safety monitoring and the addition of the information concerning inability to urinate.

Sandostatin (octreotide) Expanded Review of Adverse Events-Outside Speaker Presentation
Rama Bhat, M.D., Professor of Pediatrics, Director of Neonatology, University of Illinois at Chicago Medical Center
Committee Discussion

- The Advisory Committee discussed product use in the medical and teaching facilities and duration of use.

Sandostatin (octreotide) Expanded Review of Adverse Events-Sponsor Presentation
Todd Gruber, M.D., M.P.H., Head, U.S. Medical Function, Novartis
Committee Discussion

- The Advisory Committee thanked Dr. Gruber for his presentation.

Sandostatin (octreotide) Expanded Review of Adverse Events
Amy Taylor, M.D., Medical Officer, OND, CDER, FDA
Question to the Committee

- One approach FDA is considering is to (1) revise labeling to clarify there are no approved pediatric indications and (2) remove the description of the 49 published case reports from the octreotide Injection labeling. FDA will continue its standard, ongoing safety monitoring for octreotide. Does the Advisory Committee concur with the stated approach?

Committee Discussion

The Advisory Committee discussed approaches on educating the community on product use, need for gathering additional data, and partnerships with other stakeholders on obtaining additional data.

Committee Vote and Recommendations

- Eleven (11) committee members unanimously agreed (1 member not present) to the following recommendations to FDA:
    1. Revise the label to include the statement "Safety and effectiveness have not been demonstrated in children";
    2. Harmonize existing labeling concerning the pediatric population, specifically to remove the forty-nine (49) case reports cited in the octreotide injection labeling;
    3. Include in the label information about serious pediatric adverse events reported to the Agency and acknowledge that no causal association has been established;
    4. Work with NIH and/or other stakeholders to develop a systematic prospective/retrospective review for information on actual use and adverse events of off-label use in the pediatric population.
    5. Once information is collected and reviewed, FDA should provide a follow-up report to the Committee.

Ethics Discussion

Robert "Skip" Nelson, M.D., Pediatric Ethicist, OPT, OC, FDA

Committee Discussion

- The Advisory Committee thanked members of the Pediatric Ethics Subcommittee and accepted the report from the Pediatric Ethics Subcommittee.

The meeting adjourned at approximately 4:15 p.m.

Please see transcript for details

I certify that I attended the November 18th, 2008 meeting of the Pediatric Advisory Committee and that these minutes accurately reflect what transpired.

Carlos Peña, Ph.D., M.S.
Executive Secretary

Marsha Rappley, M.D.
Chair