MINUTES OF THE
PEDIATRIC ADVISORY COMMITTEE
March 24, 2015

The public meeting was convened 8:00 a.m. to 4:50 p.m. on March 24, 2015.

Members Present (Voting)
Kenneth E. Towbin, MD (Chair)
Michael D. Reed, PharmD
Michael G. White, MD, PhD
Mark Hudak, MD
Susan Baker, MD, PhD
Mary Catelletto, MD
Robert Dracker, MD
Bridgette Jones, MD
Phillip LaRussa, MD

Temporary Voting Members (Voting Consultants)
Geoffrey Rosenthal, MD, PhD
Bonnie Arkus, RN
Antonio Arrieta, MD
David Brent, MD
Jeffrey Campbell, MD
Robert Clancy, MD
Melody Cunningham, MD
Robert Fink, MD
Andrea Holka
Frederick Kaskel, MD, PhD

Temporary Non-Voting Members
Ronald Portman, MD

Designated Federal Official
Walter Ellenberg, PhD

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<th>U.S. Food and Drug Administration (FDA)</th>
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<td>Participants Office of Pediatric Therapeutics</td>
<td>Robert Levin, MD</td>
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<td>Robert “Skip” Nelson, MD, PhD</td>
<td>Norman Hershkowitz, MD</td>
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<td>Judith Cope, MD, MPH</td>
<td>Steven Dinsmore, MD</td>
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<td>Lynne Yao, MD</td>
<td>Kathleen Donohue, MD</td>
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<td>Amy Taylor, MD</td>
<td>Courtney Suggs, PharmD, MPH</td>
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|                  | Peter Diak, PharmD MPH     |                  | Peter Diak, PharmD MPH           |
|                  | Michael Kieffer, PharmD    |                  | Michael Kieffer, PharmD          |
|                  | Courtney Suggs, PharmD, MPH|                  | Courtney Suggs, PharmD, MPH      |

|                  | Nancy Pressly, MS         |                  | Cynthia Bushee, BSN, RN           |
|                  | Eric Chen, MS (OOPD)      |                  | Allison, O’Neill, MA              |
|                  | Doug Silverstein, MD      |                  | Veronique Li, MS, MBA             |
|                  |                            |                  | Timothy Marjenin, BS              |

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Welcome and Introductory Remarks
- Walter Ellenberg, PhD, Designated Federal Official, Pediatric Advisory Committee, Office of Pediatric Therapeutics, Office of Special Medical Programs, FDA
- Kenneth E. Towbin, MD, Chair of the Pediatric Advisory Committee
- Robert “Skip” Nelson, MD, PhD, Deputy Director, Office of Pediatric Therapeutics, Office of Special Medical Programs, FDA
- Dianne Murphy, MD, FAAP, Director, Office of Pediatric Therapeutics, Office of Special Medical Programs, FDA

Presentations

**Center for Drug Evaluation and Research (CDER)**

PAC Presentations:

- **Dymista (azelastine hydrochloride and fluticasone propionate)**
  - Judith Cope MD, MPH, OPT/OSMP/OC/FDA

- **QNASL (beclomethasone dipropionate)**
  - Judith Cope MD, MPH, OPT/OSMP/OC/FDA

Open Public Hearing
- A statement was read by the Chair.

Justified Abbreviated Presentations

**Venofer (iron sucrose)**
- Judith Cope MD, MPH, OPT/OSMP/OC/FDA

**Invirase (saquinavir)**
- Judith Cope MD, MPH, OPT/OSMP/OC/FDA
Center for Drug Evaluation and Research (CDER):
Standard Review of Adverse Event Presentations

Cymbalta (duloxetine hydrochloride)
Amy Taylor, MD, Medical Officer, DPMH/OND/CDER/FDA

Quillivant XR (methylphenidate hydrochloride)
Erica Radden, MD, Medical Officer, DPMH/OND/CDER/FDA

Risperdal (risperidone)
Erica Wynn, MD, MPH, Medical Officer, DPMH/OND/CDER/FDA

Lunesta (eszopiclone)
Erica Radden, MD, Medical Officer, DPMH/OND/CDER/FDA

Oxtellar XR (oxcarbazepine extended-release)
Donna Snyder, MD, Medical Officer, DPMH/OND/CDER/FDA

Revatio (sildenafil)
Amy Taylor, MD, Medical Officer, DPMH/OND/CDER/FDA

Advair HFA (Fluticasone propionate/salmeterol xinafoate)
Ethan Hausman, MD, Medical Officer, DPMH/OND/CDER/FDA

CDER Products: Designated Abbreviated Review

Altabax Ointment (retapamulin) - Michael White, MD, PhD

Center for Biologics Evaluation and Research (CBER)- Abbreviated Presentations

FluMist Quadrivalent (Influenza Vaccine Live, Intranasal)
Judith Cope, MD, MPH, OPT/OSMP/OC/FDA

Fluarix Quadrivalent (Influenza Virus Vaccine)
Judith Cope, MD, MPH, OPT/OSMP/OC/FDA

Center for Devices and Radiological Health (CDRH)

Notification of Conversion to 510K from HDE for the Vertical Expandable Prosthetic Titanium Rib (VEPTR) - Informational Report to the Chair
Amber Ballard, PhD, OSB/PEBIII/CDRH/FDA

Medtronic Activa Dystonia Therapy – Second Postmarket HED Review
Amber Ballard, PhD, OSB/PEBIII/CDRH/FDA, Nathan Ivey, PhD, DEPI/OSB/ CDRH/FDA
Liposorber LA-15 System- Initial Post-Market HDE Review
Veronique Li, MS, MBA, DRGUD/ODE/CDRH/FDA, Doug Silverstein, MD, DRGUD/ODE/CDRH/FDA, Allison O’Neill, MA, DEPI/OSB/CDRH, Cynthia Bushee, BSN, RN, PEB1/DPS/OSB/CDRH

Adjournment

MINUTES:

Dymista (azelastine hydrochloride & fluticasone propionate)
Indication: relief of symptoms of seasonal allergic rhinitis in patients 12 years and older.

Conclusion and Recommendations:
FDA did not identify any new safety concerns. FDA will continue its standard ongoing safety monitoring.

Question to the Committee:
Does the Committee concur?

Committee Discussion:
There was no discussion.

Committee Vote:
Seventeen (17) committee members recommended return to standard, ongoing monitoring for adverse events.

QNASL (beclomethasone dipropionate)
Indication: treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years and older.

Conclusion and Recommendations:
FDA did not identify any new pediatric safety issues. FDA will continue its standard ongoing safety monitoring.

Question to the Committee:
Does the Committee concur?

Committee Discussion:
The committee discussed growth suppression as a problem with this class of products. FDA does require growth studies for these products, but not bone density testing. With new labeling extending the indication to younger children, there will be another pediatric-focused safety review coming up in the next couple of years.

Committee Vote:
Seventeen (17) committee members recommended return to standard, ongoing monitoring for adverse events.
**Venofer (iron sucrose)**

**Indication:** maintenance treatment in patients ≥2 years of age with hemodialysis dependent chronic kidney disease (HDD-CKD); iron maintenance treatment in patients ≥2 years of age with non-dialysis dependent or peritoneal dialysis dependent CKD treated with erythropoietin.

**Conclusion and Recommendations:**
FDA did not identify any new pediatric safety issues. FDA will continue its standard ongoing safety monitoring.

**Question to the Committee:**
Does the Committee concur?

**Committee Discussion:**
Committee discussed off-label use in children less than 2 years old, without reported adverse events.

**Committee Vote:**
Seventeen (17) committee members recommended return to standard, ongoing monitoring for adverse events.

**Invirase (saquinavir)**

**Indication:** treatment of HIV-1 infection in combination with ritonavir and other antiretroviral agents in adults over 16 years of age.

**Conclusion and Recommendations:**
FDA did not identify any new pediatric safety issues. FDA will continue its standard ongoing safety monitoring.

**Question to the Committee:**
Does the Committee concur?

**Committee Discussion**
There was no discussion.

**Committee Vote:**
Seventeen (17) committee members recommended return to standard, ongoing monitoring for adverse events.

**Cymbalta (duloxetine hydrochloride)**

**Indication:** treatment of Major Depressive Disorder (MDD) in adults; generalized anxiety disorder in pediatric patients ages 7-17 years.

**Conclusion and Recommendations:**
FDA did not identify any new pediatric safety issues. FDA will continue its standard ongoing safety monitoring.
Question to the Committee:
Does the committee concur?

Committee Discussion:
A question was raised about the accuracy of the drug utilization data, specifically, whether the data suggesting that the delayed release capsule was being given to the very young was a reporting error. The committee was assured by FDA that the information came from prescription data. The PAC speculated whether these data reflected prescriptions being written for a parent in the name of the child in order to obtain reimbursement.

Committee Vote:
Sixteen (16) committee members recommended return to standard, ongoing monitoring for adverse events. One (1) committee member disagreed.

**Quillivant XR (methylphenidate hydrochloride)**
**Indication:** treatment of attention deficit hyperactivity disorder in pediatric patients ages 6-17 years.

**Conclusion and Recommendations:** The safety review identified no new safety signals, other than those already identified regarding medication errors. FDA will continue its standard ongoing safety monitoring.

Questions to the Committee:
In addition to whether the PAC concurred with continuing ongoing safety monitoring, the PAC Chair formulated the following questions based on the discussion:
Did the committee agree with the following three recommendations?
1. Anger and irritability should be moved to a more prominent place in the labeling.
2. The proper way for the pharmacist to prepare the drug prior to dispensing it needs to be highlighted at the beginning of the instructions.
3. FDA should explore ways in which parents and caregivers could be better informed that, for this product, 1 mg and 1 ml are not equivalent doses.

Does the Committee concur with the recommendation for continuing routing safety monitoring?

Committee Discussion: The committee discussed that this was the only drug on the market that came in liquid form so that it was most often used in children who were unable to take a medication in pill form. It was important to use the syringe that was given for the liquid medication and that the medicine be shaken well before each dose. The committee discussed whether anger and irritability warnings should be moved to an earlier section of the label, that storage and preparation need to be better described, and that parents should be better informed that 1 ml does not equal 1 mg when this drug is properly prepared and dispensed.

Committee Vote:
1. Thirteen (13) committee members agreed with the recommended labeling changes. Three (3) committee members disagreed. One (1) committee member was recused.
2. Sixteen (16) committee members recommended return to standard, ongoing monitoring for adverse events. One (1) committee member was recused.

**Risperdal (risperidone)**

**Indication:** treatment of schizophrenia adolescents with schizophrenia, ages 13 – 17 years, acute manic or mixed episodes associated with bipolar I disorder in pediatric patients, ages 10 – 17 years, and for irritability associated with autistic disorder in children and adolescents, ages 5-16 years.

**Conclusion and Recommendations:**
FDA did not identify any new pediatric safety issues. FDA will continue its standard ongoing safety monitoring.

**Question to the Committee:**
Does the Committee concur?

**Committee Discussion:**
Noting the cases of Torsade de Pointe, the committee asked if there were reports of QT prolongation in the pre-marketing studies of this product. FDA answered that QT studies had been done and that there were no problems with QT prolongation found with this product. The committee inquired why seizures were not an adverse event that was discussed in this review. The FDA’s response was that the focus of this review was on unlabeled serious adverse events, and thus, labeled events, such as seizures, were not discussed in the review. In addition, all serious adverse events are reviewed, and any that were inconsistent with the label (e.g. unusual duration, severity) would have been included. Since none of the seizures were inconsistent (e.g., duration, severity) with the current label, these were not included.

**Committee Vote:**
Seventeen (17) committee members recommended return to standard, ongoing monitoring for adverse events.

**Lunesta (eszopiclone)**

**Indication:** treatment of insomnia associated with ADHD in adults. When it was studied in the 6-17 year old pediatric patients, safety and effectiveness was not established.

**Conclusion and Recommendations:**
FDA did not identify any new pediatric safety issues. FDA will continue its standard ongoing safety monitoring.

**Question to the Committee:**
Does the Committee concur?

**Committee Discussion:**
There was no discussion.
Committee Vote:
Seventeen (17) committee members recommended return to standard, ongoing monitoring for adverse events.

Oxtellar XR (oxcarbazepine extended-release)
Indication: adjunctive therapy in the treatment of partial seizures in children 6 to 17 years of age.

Conclusion and Recommendations:
Hypothyroidism was found to occur in 3 pediatric FAERS cases between August 2009 and July 2014, and Oxtellar XR labeling does not include hypothyroidism. FDA recommends updating Section 6.2, Adverse Events, Postmarketing and Other Experience, of Oxtellar XR labeling to include hypothyroidism. FDA did not identify any other pediatric safety issues. FDA will continue its standard ongoing safety monitoring.

Question to the Committee:
Does the committee concur with the labeling change, and continued routine safety monitoring?

Committee Discussion:
Concern was expressed about the off-label use of this product for bipolar disorder.

Committee Vote:
Sixteen (16) committee members agreed to updating the label and for return to standard, ongoing monitoring for adverse events. One (1) committee member was recused.

Revatio (sildenafil)
Indication: treatment of pulmonary arterial hypertension (PAH) in adults. Revatio does not have an approved pediatric indication.

Conclusion and Recommendations:
FDA recommends continued routine safety monitoring.

Question to the Committee:
Does the committee concur?

Committee Discussion:
The committee discussed that clinical situation surrounding the treatment of pulmonary hypertension in children who have a high risk of sudden death, and the continued use of this drug in the absence of other alternatives. The difficulty of performing these studies was discussed, including the appropriate endpoints.

Committee Vote:
Fifteen (15) committee members recommended return to standard, ongoing monitoring for adverse events. Two (2) committee members were recused.

Advair HFA (Fluticasone propionate/salmeterol xinafoate)
**Indication:** treatment of asthma in patients 12 years and older, though not for the relief of acute bronchospasm.

**Conclusion and Recommendations:**
FDA recommends continued routine safety monitoring.

**Question to the Committee:**
Does the Committee concur?

**Committee Discussion:**
The committee discussed the large study involving 3 sponsors that will have up to 40,000 adult and pediatric patients enrolled in a common protocol design that will allow for a combined meta-analysis. The number of times per day that a patient uses a long-acting beta agonist (LABA) on an as needed basis either alone, or in combination with other medications, was raised as a concern. The 2 fatal cases were discussed, and it was noted that one patient was using the medication many times more than recommended (up to 11 times a day and with other medications). It was discussed that two populations known to the FDA have safety signals for the LABAs—African Americans and the <18 year-old population. The committee discussed that, for these two populations, it is important to assess the safety of LABAs, and whether the benefits of using inhaled corticosteroids outweigh the risks. Hopefully, the studies that are in progress will address these questions.

**Committee Vote:**
Seventeen (17) committee members recommended return to standard, ongoing monitoring for adverse events.

**CDER Products: Designated Abbreviated Review Presentation**

**Altabax Ointment (retapamulin)**
**Indication:** treatment of impetigo due to Staphyloccus aureus (methicillin-susceptible isolates only) or Streptococcus pyogenes in patients 9 months or older.

Michael White, MD, PhD, PAC Designated Reviewer
Recommendation to FDA: Agreed to continuing routine safety monitoring

**Center for Biologics Evaluation and Research (CBER)- Abbreviated Presentations**

**FluMist Quadrivalent (Influenza Vaccine Live, Intranasal)**
**Indication:** prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in ages 2 through 49 years of age.

**Conclusion and Recommendations:**
FDA will continue its standard routine safety monitoring.

**Question to the Committee:**
Does the Committee concur?
Committee Discussion:
The committee discussed off-label use in the under 2 year old because of its ease of use. FDA explained that it was not to be used in under 2 year olds due to the increase risk of wheezing in that age group.

Committee Vote:
Sixteen (16) committee members recommended return to standard, ongoing monitoring for adverse events. One (1) committee member was absent.

**Fluarix Quadrivalent (Influenza Virus Vaccine)**

**Indication:** active immunization for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine in persons 3 years and older.

**Conclusion and Recommendations:**
FDA will continue its standard routine safety monitoring.

**Question to the Committee:**
Does the Committee concur?

**Committee Discussion:**
There was no discussion.

**Committee Vote:**
Sixteen (16) committee members recommended return to standard, ongoing monitoring for adverse events. One (1) committee member was absent.

**Center for Devices and Radiological Health (CDRH)**

**Notification of Conversion to 510K from HDE for the Vertical Expandable Prosthetic Titanium Rib (VEPTR) - Informational Report to the Chair**

**Status:** Pediatric HDE is withdrawn - no longer mandated to do safety reporting to the PAC.

**Medtronic Activa Dystonia Therapy – Second Postmarket HED Review**

**Indication:** an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and segmental dystonia, hemidystonia, and cervical dystonia (torticollis) for individuals 7 years of age and older.

**Conclusion and Recommendations:**
No new concerns regarding safety of the device were identified. Adherence to product labeling may mitigate AEs occurring at the end of the battery life, or with technical malfunction. Strategies for increasing physician awareness of labeling should be considered.

**Question to the Committee:**
FDA recommends continued surveillance and will report the following to the PAC in 2016:
- Annual distribution number
- PAS follow-up results (if applicable)
- Literature review
- MDR review

Does the Committee agree with FDA’s conclusion and recommendations?

Committee Discussion:
The committee commented that while 13 devices were sold, 776 were implanted. There were 23 pediatric HDE reports during this timeframe, but there is no denominator to say how many devices were implanted into the pediatric population or adult population. Of the 23 reports, 4 were regarding battery problems, but without a denominator it is hard to determine the significance of this finding. Because the devices were used for other indications, not just pediatric HDE patients, the committee commented that it is difficult to assess the safety risk of the device. The MAUDE system for adverse events is a passive system. Even though we know about lead and battery problems, FDA does not always get a full report to what was done other than a repair or replacement.

Committee Vote:
Thirteen (13) committee members agreed that the HDE device remains appropriately approved and labeled for pediatric use and recommended return to standard, ongoing monitoring for adverse events. Two committee members abstained from the vote. Two (2) committee members were absent from the vote). One (1) committee member was recused.

Liposorber LA-15 System- Initial Postmarket HDE Review

Indication: treatment of pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis when standard treatment options including corticosteroid and/or calcineurin inhibitors treatments, are unsuccessful or not well tolerated and the patient has a GFR > 60ml/min/1.73m² or the patient is post renal transplant.

Conclusion and Recommendations:
As of January 5, 2015, treatment for FSGS patients has not started. Our review of the published literature and received MDRs since the time of approval has not identified any new or unexpected risks for the pediatric population when compared to the premarket data. FDA concludes that the benefit/risk profile of the Liposorber LA-15 System for the treatment in pediatric FSGS patients continues to support the HDE for which the exemption was granted.

Question to the Committee:
1. Extend the Postmarket Study long term – to obtain long term outcomes?
2. FDA recommends continued surveillance and will report the following to the PAC in 2016:
   - Annual distribution number
   - PAS follow-up results
   - Literature review
   - MDR review

Does the Committee agree with FDA’s conclusions and recommendations?

Committee Discussion:
The committee was interested in where the case studies were conducted and what country reported most of the MDRs. FDA explained that the majority of the case studies came from Japan. The committee expressed concern that the amount of data was insufficient and was reported only for short-term outcomes. No long-term outcome information was presented. The use of biomarkers for measuring risk is controversial. The cause of the disease remains unclear and the need to gather data on genetic factors information is necessary. It was hoped this could be taken to the sponsor with a request to obtain longer term studies.

Committee Vote:
1. Fourteen (14) committee members agreed to extend the postmarket study to obtain long term outcomes. Four (4) committee members are absent for the vote.
2. Fourteen (14) committee members agreed that the HDE device remains appropriately approved and labeled for pediatric use and recommended return to standard, ongoing monitoring for adverse events. Four (4) committee members were absent from the vote.

Adjournment