

MINUTES OF THE APRIL 12, 2016 PEDIATRIC ADVISORY COMMITTEE from 8:00am-5:15pm

<p><u>Members Present (Voting)</u> Mark Hudak, MD (<i>Chair</i>) Michael G. White, MD, PhD Susan Baker, MD, PhD Mary Cataletto, MD Amy Celento, BS Avital Cnaan, PhD Robert Dracker, MD, MHA, MBA, CPI Jonathan Mink, MD, PhD</p>	<p><u>Temporary Voting Members (Voting Consultants)</u> Melody Cunningham, MD Marc Moon, MD Kenneth E. Towbin, MD Frederick Kaskel, PhD, MD Peter Havens, MD, MS Jonathan Davis, MD Jeffrey Campbell, MD, MS Christy Turer, MD, MHS Sarah Hoehn, MD, MBe Leslie Walker-Harding, MD Alexander Rakowsky, MD</p>
<p><u>Non-Voting Members</u> Ronald Portman, MD</p>	<p><u>Designated Federal Official</u> Marieann Brill MBA, RAC, MT (ASCP)</p>

U.S. Food and Drug Administration (FDA) Participants

<p><u>Office of Pediatric Therapeutics</u> Robert “Skip” Nelson, MD, PhD Judith Cope, MD, MPH LCDR Kenneth Quinto, MD, MPH</p> <p><u>CBER</u> CAPT Craig Zinderman, MD, MPH</p> <p><u>CDRH</u> Vasum Peiris, MD, MPH John Laschinger, MD Douglas Silverstein, MD Cynthia Bushee, BSN, RN Kelly Bauer, BSN, RN Carolyn Neuland, MD Courtney Millin, PhD Timothy Marjenin, BS Changfu Wu, PhD George Aggrey, MD, MPH Colin Anderson-Smits, MPH Andrew Miller, MS</p>	<p><u>CDER</u> Courtney Suggs, PharmD, MPH Kimberly Swank, PharmD Carmen Cheng, PharmD Vicky Chan, PharmD, BCPS Travis Ready, PharmD Sarah Kang, PharmD, BCPS Margaret Rand, PharmD, BCOP Kelly Cao, PharmD Sarah Camilli, PharmD, BCPS Martin Pollock, PharmD Danijela Stojanovic, PharmD, PhD Timothy Jancel, PharmD, BCPS, (AQ-ID) Nabila Sadiq, PharmD, BCPS LCDR Justin Mathew, PharmD Jennie Wong, PharmD Yuliya Yasinskaya, MD Elizabeth O’Shaughnessy, MD Sharon Hertz, MD Joyce Korvick, MD Ethan Hausman, MD John Alexander, MD, MPH Donna L. Snyder, MD</p>	<p><u>CDER</u> LCDR Erica Radden, MD Amy Taylor, MD Mona Khurana, MD Robert Levin, MD Norman Hershkowitz, MD, PhD Phillip Sheridan, MD Tiffany Farchione, MD Gregory Reaman, MD Rigoberto Roca, MD Leah Crisafi, MD LCDR Grace Chai, PharmD Patty Greene, PharmD Kusum Mistry, PharmD CDR Ida-Lina Diak, PharmD, MS Karen Long, PharmD Joann Lee, PharmD CAPT Corrinne Kulick, PharmD Kusum Mistry, PharmD</p> <p><u>CDER staff on the phone</u> Andrew Dmytrijuk, MD Lynda McCulley, PharmD, BCPS Lisa Soule, MD David Moeny, MD Ronald Orleans, MD Rita Ouellet-Hellstrom, PhD, MPH</p>
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Welcome and Introductory Remarks and Award Presentations

- Mark Hudak, MD, Chair of the Pediatric Advisory Committee
- Robert “Skip” Nelson, MD, PhD, Deputy Director, Office of Pediatric Therapeutics, Office of Special Medical Programs, FDA
- Marieann Brill, MBA, RAC, MT (ASCP), Designated Federal Official, Pediatric Advisory Committee, Office of Pediatric Therapeutics, Office of Special Medical Programs, FDA

Presentations

Chris Feudtner, MD, PhD, MPH, FAAP, Chair of the American Academy of Pediatrics, Section on Hospice and Palliative Medicine, “Opioids and Children: Framework for Labeling Drugs to Promote Appropriate Treatment of Pain.”

Sharon Hertz, MD, Director, Division of Anesthesia Analgesia and Addiction Products (DAAAP), Center for Drug Evaluation and Research (CDER), FDA, “Analgesia Development for Pediatric Patients.”

Open Public Hearing

An opening statement was read by the Chair, Mark Hudak, MD.

1. An email was sent to FDA and summarized for the public regarding concerns about vaccines for children and infants. The Chair noted the email for the record.
2. Craig Butler, National Executive Director, Cooley’s Anemia Foundation
The following were requested:
 - A label change that establishes guidelines for stopping Exjade or Jadenu during periods of febrile illness, and
 - Continued FDA pediatric safety monitoring of Exjade
 - A timeline for further action on follow-up by FDA on these issues.

Presentations

Center for Biologics Evaluation and Research (CBER)

Abbreviated Presentations

FluLaval Quadrivalent (Influenza Vaccine)

LCDR Kenneth Quinto, MD, MPH, OPT/OC/FDA

FDA Question to the Committee:

FDA will continue its standard ongoing safety monitoring. Does the Committee concur?

Committee Discussion:

No discussion.

Committee Vote:

Eighteen (18) committee members agreed with the FDA’s plan to continue standard ongoing safety monitoring.

FluLaval (Influenza Vaccine)

LCDR Kenneth Quinto, MD, MPH, OPT/OC/FDA

FDA Question to the Committee:

FDA will continue its standard ongoing safety monitoring. Does the Committee concur?

Committee Discussion:

No discussion.

Committee Vote:

Eighteen (18) committee members agreed with the FDA's plan to continue standard ongoing safety monitoring.

Fluzone Quadrivalent (Influenza Vaccine)

LCDR Kenneth Quinto, MD, MPH, OPT/OC/FDA

FDA Question to the Committee:

FDA will continue its standard ongoing safety monitoring. Does the Committee concur?

Committee Discussion:

No discussion.

Committee Vote:

Eighteen (18) committee members agreed with the FDA's plan to continue standard ongoing safety monitoring.

Center for Drug Evaluation and Research (CDER)

Abbreviated Presentations

SKYLA (levonorgestrel-releasing intrauterine system)

Judith U. Cope, MD, MPH, OPT/OC/FDA

Conclusion of the Slide Presentation:

There were 16 unique cases with serious adverse events, from 4/4/2013 through 8/31/2015. Of the cases reported, there were included bleeding pattern alteration, IUD expulsion, pregnancy and pelvic inflammatory disease. These events are consistent with the known risk in the labeling and no increased severity was observed. No pediatric deaths were identified. No new safety concerns were identified.

FDA Question to the Committee:

FDA will continue its standard ongoing safety monitoring. Does the Committee concur?

Committee Discussion:

The committee discussed the need for performing studies of bone mineral density changes in adolescents, including long-term follow-up studies, from exposure to progesterone-only contraceptives. This concern is less of an issue with SKYLA, as it is an IUD with low systemic exposure to progesterone.

Committee Vote:

Seventeen (17) committee members agreed with the FDA's plan to continue standard ongoing safety monitoring. One (1) committee member abstained from the vote.

Xeloda® (capecitabine)

Judith Cope MD, MPH, OPT/OC/FDA

Conclusion of the Slide Presentation:

Sixteen adverse event cases in pediatric patients received from April 30, 1998 (drug approval date) and August 31, 2015 were evaluated. Two disease-related deaths and one fatal surgical complication were reported. The small number of reports is consistent with low use in pediatric patients due to lack of efficacy. There is no evidence from these data that there are new pediatric safety concerns with this drug at this time. We recommend routine pharmacovigilance monitoring.

FDA Question to the Committee:

FDA will continue its standard ongoing safety monitoring. Does the Committee concur?

Committee Discussion:

No discussion.

Committee Vote:

Eighteen (18) committee members agreed with the FDA's plan to continue ongoing safety monitoring.

Standard Presentations

MYCAMINE (micafungin sodium)

LCDR Erica Radden, MD, Division of Pediatric & Maternal Health (DPMH), Office of New Drugs (OND), CDER, FDA

Conclusion of the Slide Presentation:

The safety review identified no new safety signals. Overall the serious adverse event cases were highly confounded or had limited information to assess causality.

FDA Question to the Committee:

FDA recommends continuing ongoing surveillance. Does the Committee concur?

Committee Discussion:

No discussion.

Committee Vote:

Eighteen (18) committee members agreed with the FDA's plan to continue ongoing safety monitoring.

Noxafil® (posaconazole)

Amy Taylor, MD, DPMH, OND, CDER, FDA

Conclusion of the Slide Presentation:

A review of the safety signal of posaconazole and vincristine drug interaction is being conducted. FDA is evaluating this safety signal to determine if, and how, labeling may be modified, and will provide a report to the PAC.

FDA Question to the Committee:

- 1) FDA recommends continuing ongoing surveillance. Does the Committee concur?

Committee Discussion:

The PAC discussed the need to review the labeling of Noxafil with respect to drug-drug interactions with other products which are metabolized by CYP3A pathway. Among these drugs are vincristine and midazolam, and other benzodiazepines.

Question formulated by the Committee from the discussion:

- 2) Is the committee in agreement with the FDA that they review the interaction between vincristine and Noxafil and strengthen the label, if necessary?

Committee Votes:

- 1) Eighteen (18) committee members agreed with the FDA's plan to continue ongoing safety monitoring.
- 2) Eighteen (18) committee members agreed that FDA review and report back to the PAC regarding drug interactions between Noxafil and vincristine and/or midazolam, as well as other drugs which are metabolized by the CYP3A pathway (other benzodiazepines), and consider an appropriate labeling change.

Precedex™ (dexmedetomidine hydrochloride)

Amy Taylor, MD, DPMH, OND, CDER, FDA

Conclusion of the Slide Presentation:

No new safety signals were identified.

(Note: the order in which the committee voted on the questions is depicted numerically)

FDA Questions to the Committee:

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

Committee Discussion:

Committee discussed having a future advisory committee meeting due to their concerns about the increasing use of dexmedetomidine in infants and young children. The meeting would be set within the broader context of concerns about the use of general anesthetics and sedatives, which may cause neuroapoptosis following exposure in infants and young children. FDA agreed with the need for a meeting once further data are available on dexmedetomidine exposure in juvenile animal models, and from on-going clinical and epidemiological studies of general anesthesia in infants and young children. Ideally, this meeting would be able to be planned in the next few years.

Question formulated by the Committee from the discussion:

- 1) Is an Advisory Committee meeting needed to review the concerns about the increasing use of

dexmedetomidine use in infants and young children set within the broader context of concerns about the use of general anesthetics and sedatives, which may cause neuroapoptosis following exposure in infants and young children?

Committee Votes:

- 1) Eighteen (18) committee members agreed that an Advisory Committee is needed to review further data on dexmedetomidine, and also on the broader concerns about use of general anesthetics and sedatives in infants and young children.
- 2) Eighteen (18) committee members agreed with the FDA's plan to continue routine, post-marketing safety monitoring.

Aciphex® Sprinkle™ (rabeprazole sodium)

Amy Taylor, MD, DPMH, OND, CDER, FDA

Conclusion of the Slide Presentation:

In September 2015, FDA reported a potential signal of a risk of systemic lupus erythematosus (SLE) in proton pump inhibitors. Also, FDA identified potential safety signals of vertigo and blurred vision.

FDA Question to the Committee:

FDA recommends adding vertigo and blurred vision to prescribing information for all dosage forms of Aciphex®. Does the Committee concur?

Committee Discussion:

Committee questions on where the adverse events would be added to the label were answered by FDA medical staff who stated that the information about vertigo and blurred vision would be placed in the Postmarketing Experience Section 6.2 of the label. The information regarding lupus will come back to the committee as more information is available.

Committee Vote:

Eighteen (18) committee members agreed with the FDA recommendation to add vertigo and blurred vision to prescribing information for all dosage forms of Aciphex®.

Risk-Based Assessment Proposal for CDER Products

LCDR Kenneth Quinto, MD, MPH, OPT/OC/FDA

Conclusion of the Slide Presentation:

OPT plans to implement the new risk-based assessment process for CDER products in time for the September 2016 PAC Safety meeting.

Committee Discussion:

In general, committee member comments about the new process were positive. The committee made some constructive suggestions with respect to posting the reviews to facilitate access, review and comment.

Vyvance Capsules (lisdexamfetamine dimesylate)

Mona Khurana, MD, DPMH, OND, CDER, FDA

Conclusion of the Slide Presentation:

A possible signal for alopecia will undergo further FDA review with results to be presented at future PAC meeting.

FDA Question to the Committee:

- 1) FDA recommends continuing ongoing surveillance. Does the Committee concur?

Committee Discussion:

The committee discussed the potential safety signal of alopecia and FDA's plan to investigate this further and to bring information to them at a later date. They also recommended that FDA explore the use of a claims database (as published in a 2011 New England Journal of Medicine article) to obtain further information on the question of suicidality.

Questions formulated by the Committee from the discussion:

- 2) FDA will conduct a review of the safety signal of alopecia and will report back to the committee at a future date. Does the committee agree?
- 3) The committee recommended that FDA explore the use of claims database (as published in a 2011 NEJM article) to obtain further information regarding the question of suicidality. Does the committee agree?

Committee Votes:

- 1) Eighteen (18) committee members agreed with the FDA plan to continue ongoing surveillance.
- 2) Seventeen (17) committee members agreed with FDA's plans to review the safety signal for alopecia and bring the information to the committee at a future date. One (1) committee member disagreed with this plan.
- 3) Eighteen (18) committee members agreed that FDA should explore the use of the claims database to obtain information regarding suicidality.

SYMBYAX (fluoxetine hydrochloride and olanzapine)

Mona Khurana, MD, DPMH, OND, CDER, FDA

Conclusion of the Slide Presentation:

No new pediatric safety signals were identified.

FDA Question to the Committee:

- FDA recommends continuing ongoing surveillance. Does the Committee concur?

Committee Discussion:

No discussion.

Committee Vote:

- Eighteen (18) committee members agreed with the FDA's plan to continue ongoing surveillance.

Seroquel® (quetiapine fumarate) & Seroquel XR® (quetiapine fumarate extended-release)

Donna Snyder, MD, DPMH, OND, CDER, FDA

Conclusion of the Slide Presentation:

No new safety signals were identified.

FDA Questions to the Committee:

FDA recommends continued routine monitoring. Does the committee concur?

Committee Discussion:

No discussion.

Committee Vote:

Eighteen (18) committee members agreed with the FDA's plan to continue routine monitoring.

Sabril® (vigabatrin)

Donna Snyder, MD, DPMH, OND, CDER, FDA

Conclusion of the Slide Presentation:

No new safety signals were identified.

FDA Question to the Committee:

FDA recommends continued routine monitoring. Does the committee concur?

Committee Discussion:

No discussion.

Committee Vote:

Eighteen (18) committee members agreed with the FDA's plan to continue routine monitoring.

Center for Devices and Radiological Health (CDRH)

Initial Post-Market HDE Review

Impella RP System

John Laschinger, MD, Structural Heart Devices Branch, Division of Cardiovascular Devices, Office of Device Evaluation (ODE), CDRH, FDA

Conclusion of the Slide Presentation:

FDA recommends continued surveillance and will report to the PAC in 2017.

FDA Question to the Committee:

FDA recommends continued surveillance and will report the following to the PAC in 2017:

Annual distribution number

PAS follow-up results

Literature review

MDR review

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

Committee Discussion:

No discussion.

Committee Vote:

Eighteen (18) committee members agreed with the FDA's conclusions and recommendations.

Annual Post-Market HDE Reviews

Medtronic Activa Dystonia Therapy

Courtney Millin, PhD, Division of Postmarket Surveillance, Office of Surveillance and Biometrics, CDRH, FDA

Conclusion of the Slide Presentation:

There were 56 MDRs reporting 39 unique events associated with use of the Activa neurostimulator in pediatric patients. A return or worsening of dystonia symptoms (loss of therapeutic effect) was the most frequently reported pediatric patient problem. The most frequently reported device problem was impedance issues. No new device or patient problems were identified.

FDA Question to the Committee:

FDA recommends continued surveillance and will report the following to the PAC in 2017:

Annual distribution number

PAS follow-up results

Literature review

MDR review

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

Committee Discussion:

Reasons for what might cause explantation of the device were discussed. The FDA was asked if growth in the pediatric population was found to be the reason that the device leads were dysfunctional and explanted. FDA was unable to calculate the duration of use. Therefore, no trends were found for the reasons of explanting the device leads.

Committee Vote:

Sixteen (16) committee members agreed with the FDA's conclusions and recommendations. Two (2) committee members were recused from the vote.

Liposorber®LA-15 System

Douglas Silverstein, MD Division of Gastro-Renal, and Urological Devices, Renal Devices Branch, ODE, CDRH, FDA

Conclusion of the Slide Presentation:

As of January, 2016, four pediatric patients have received therapy for focal segmental glomerulosclerosis (FSGS) with the Liposorber® LA-15 system. Of the three patients that finished a

complete course of therapy, all exhibited reduction in urine protein/creatinine, while showing stabilization or improvement in glomerular filtration rate (GFR). While some adverse events were not insignificant, none were thought to be device-related, but rather consistent with that observed in the underlying disease or with associated devices (catheter).

FDA Question to the Committee:

FDA concludes that the benefit-risk profile to date supports continuation of the PAS and recommends continued surveillance. FDA will report the following to the PAC in 2017:

Annual distribution number

PAS follow-up results

Literature review

MDR review

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

Committee Discussion:

Committee discussed the risks versus the probable benefit that the pediatric population would encounter when being supported by the Liposorber®LA-15 System. There was discussion on how to preserve the renal function when other options are not available to the pediatric patient, and this option helps to maintain the growth and development of the child.

Committee Vote:

Fourteen (14) committee members agreed with the CDRH conclusion and recommendation to continue surveillance. Four (4) committee members were absent at the time of the vote.

Adjournment

Mark Hudak, MD, Chair