MINUTES OF THE PEDIATRIC ADVISORY COMMITTEE (PAC)

The public meeting was convened 10:00 am – 5:35 pm EDT, September 15, 2020

Members Present (voting)	**Temporary Voting Members**
Kelly Wade, MD, PhD (*Chair)* Premchand Anne, MD, MBA, MPH, FACC David Callahan, MD Melody Cunningham, MD, FAAHPM Randall Flick, MD, MPH Peter Havens, MD, MS Sarah Hoehn, MD, MBe, FAAP Richard Holubkov, PhD Roberto Ortiz-Aguayo, MD, MMM Randi Oster, MBA Wael Sayej, MD Christy Turer, MD, MHS, FAAP, FTOS Benjamin Wilfond, MD	Angela Czaja, MD, MSc Robert Dracker, MD, MHA, MBA, CPI Gwenyth Fischer, MD, FAAP Bridgette Jones, MD, MS Olcay Jones, MD, PhD Jeffrey Lukish, MD, FACS, FAAP James McGough, MD Gianna McMillan, DBe Jennifer Plumb, MD, MPH Jeffrey Strawn, MD **Non-Voting Members** Jennifer Goldman, MD, MS Ronald Portman, MD, FAAP **Designated Federal Officer (DFO)** Marieann Brill, MBA, RAC, MT(ASCP)

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

Office of Pediatric Therapeutics (OPT)	**CDER Office of Surveillance and Epidemiology**	**Center for Biologics Research and Evaluation (CBER)**	**Center for Devices and Radiological Health (CDRH)**
Susan McCune, MD **Center for Drug Evaluation and Research (CDER) Division of Pediatric and Maternal Health** Ethan D. Hausman, MD	Doris Auth, PharmD Carmen Cheng, PharmD Lisa Harinstein, PharmD Ivone Kim, MD Mohamed Mohamoud, PharmD, MPH Andrew D. Mosholder, MD, MPH **CDER Office of New Drugs Division of Psychiatry** Qi Chen, MD, MPH	Barbara Buch, MD Adrienne Hornatko-Munoz, RAC Narayan Nair, MD Jonathan Reich, MD, MS Dorothy Scott, MD Craig Zinderman, MD, MPH	Vasum Peiris, MD, MPH Mark J. Antonino, MS Shani Haugen, PhD Priya Venkataraman-Rao, MD

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Welcome and Introductory Remarks

- Kelly Wade, Chair, PAC opened the meeting. Dr. Wade directed those participating in the meeting and the audience to the FDA press contact Gloria Sanchez-Contreras, Press Officer, OC/OEA/OMA. Her email (gloria.sanchez-contreras@fda.hhs.gov) and her telephone number (301-796-7686) were provided. Dr. Wade also directed the industry and press to the PAC email inbox (PAC@fda.hhs.gov).
- PAC members introduced themselves and provided their affiliations.
- Marieann Brill, Designated Federal Officer (DFO), read the usual, customary, and required disclosures and conflict of interest statement.
- Susan McCune, Director of OPT gave opening remarks.
    - Dr. McCune announced the general topics for discussion for the September 15th PAC Meeting
    - Personnel announcements:
        - Welcome to a new member to the PAC: Dr. Jennifer Goldman, Associate Professor, University of Missouri Kansas City and member of the Department of Pediatric Infectious Diseases and Clinical Pharmacology at Children's Mercy Hospital in Kansas City
        - Celebrating the career and upcoming retirement of Sheila Reese, RN
        - Introductions of 3 new members of OPT involved with the PAC: Ester Hatton, Jeanine Best, and Margaret Caulk
    - Web-Posted Reviews
    - Update on montelukast labeling, including reassessment of benefit-risk for allergic rhinitis and box warning for neuropsychiatric adverse events
    - PREA noncompliance letters: CDER=46, CBER=2

CDER: Standard Review of Adverse Event Presentations

1. **"Pediatric Focused Safety Review Vyvanse (lisdexamfetamine dimesylate)" – presented by Ivone Kim, MD, DPV, OSE, CDER (via pre-recorded video) with backup by Carmen Cheng, PharmD, DPV, OSE, CDER**

   Dr. Kim presented the safety review for Vyvanse, prompted by a new formulation (chewable tablets) approved in 2017. Drug use trends over the most recent 12-month period ending in June 2019 showed the majority (61%) of prescriptions were dispensed in the 12-17 year-old age group. The FAERS case review from the period of July 1, 2015 through April 20, 2019 yielded 23 unlabeled serious pediatric cases, including 3 completed suicides in adolescents and 20 non-fatal cases. The suicide cases contained inadequate information to conclude there was a causal association with Vyvanse. In addition, there was insufficient evidence to determine a causal association with Vyvanse and many of the other unlabeled non-fatal adverse events. There was a potential safety signal of acute dystonic reactions, which was further queried with respect to ADHD stimulants or atomoxetine, both in FAERS and in the medical literature. Insufficient evidence was found to support a postmarket safety signal of acute dystonia associated with ADHD stimulants or atomoxetine.

2. **"Pediatric Focused Safety Review Mydayis (mixed salts of single entity amphetamine) and Adzenys ER (amphetamine extended release)" – presented by Mohamed Mohamoud, PharmD, MPH, DPV, OSE, CDER**

Dr. Mohamoud presented the safety review for Mydayis and Adzenys ER. Both drugs were labeled for pediatric patients with ADHD (Mydayis for ages 13-17 and Adzenys ER for ages 6-17) in 2017. Drug use trends show most use in the 6-12 year-old age range (61%), with a total of ~1 million pediatric patients receiving amphetamines in 2018. The FAERS case review from the period of January 1, 2006 through May 15, 2019 yielded 6 cases for discussion. There were 2 fatal cases, one in a 15-year-old who developed exertional heat stroke and the other a 13-year-old with a completed suicide. In both cases, the extent of the causal association with amphetamines was difficult to determine given the available information. There was a single case of dystonia in a 7-year-old, which prompted a further search for a drug-drug interaction (DDI) involving ADHD stimulants and antipsychotics. A series of 36 cases was identified in FAERS, with evidence to support a DDI between methylphenidate and risperidone. This DDI involving acute hyperkinetic movement disorder will be incorporated into the drug labeling for methylphenidate and risperidone products.

Open Public Hearing

- 1 speaker
    - Dr. Diana Zuckerman (President, National Center for Health Research): Discussed concerns with limitations and adequacy of adverse event (AE) reporting, including that many FAERS reports are incomplete and patients want information on the likelihood and severity of AEs. FDA can utilize Sentinel to further investigate AEs. Dr. Zuckerman brought up concerns with the AEs identified with Vyvanse, and the lack of information on their likelihood and severity. She also discussed Orencia, and the labeling change for angioedema. She suggested that the interaction with TNF antagonists needs better description in the labeling. Finally, she discussed FLOURISH, and asked why the post-marketing data are scant and why the successes are fewer than in the pre-market data. FDA describes that the data in the labeling show benefit outweighs the risk however, data do not support this statement.

Voting

- Vyvanse – FDA identified acute dystonia as a potential signal in the pediatric focused safety review. A subsequent signal review for acute dystonia and ADHD medications did not identify sufficient evidence to support a signal for acute dystonia and ADHD medications at this time. FDA recommends to continue ongoing, postmarket safety monitoring. Does the Pediatric Advisory Committee concur?

  Vote Results: **Yes: 21** **No: 1** **Abstain: 0**

- Mydayis – FDA will incorporate DDI of acute kinetic movement disorder in all risperidone and methylphenidate product labelings in Drug Interaction section. FDA recommends continuing routine, ongoing postmarket safety monitoring of Mydayis. Does the Pediatric Advisory Committee concur?

  Vote Results: **Yes: 20** **No: 2** **Abstain: 0**

- Adenzys ER – FDA will incorporate DDI of acute kinetic movement disorder in all risperidone and methylphenidate product labelings in Drug Interaction section. FDA recommends continuing

routine, ongoing postmarket safety monitoring of Adzenys ER. Does the Pediatric Advisory Committee concur?

Vote Results: Yes: 20 No: 2 Abstain: 0

CDER: Standard Review of Adverse Event Presentations (continued)

3. **"Pediatric Focused Safety Review Orencia (abatacept)" – presented by Lisa Harinstein, PharmD, DPV, OSE, CDER**

   Dr. Harinstein presented the pediatric focused safety review for Orencia, initiated due to the 2017 labeling for juvenile idiopathic arthritis (JIA) ages 2-17 years. Drug use in patients <18 years of age was low, at approximately 2% of all prescriptions in 2018. The FAERS review from July 7, 2009 through December 18, 2019 yielded 2 pediatric cases for discussion: 1 case of inflammatory bowel disease and 1 case of angioedema. The angioedema case prompted a safety review in all ages, which yielded 82 additional cases in adults. Angioedema was added to labeling as an adverse event in June of 2020.

Voting

- Orencia – Angioedema was identified as a potential signal, assessed in a concurrent signal review, and added to labeling in June 2020. Low use of abatacept in pediatric population. Pediatric reported adverse events are consistent with known adverse events described in labeling. FDA recommends to continue ongoing, postmarketing safety monitoring. Does the Pediatric Advisory Committee concur?

Vote Results: Yes: 21 No: 0 Abstain: 1

Center for Biologics Evaluation and Research (CBER): Standard Review of Adverse Event Presentation

4. **"Gamunex-C [Immune Globulin (Human), 10% Caprylate/Chromatography Purified]: Hypersensitivity Reactions in Patients Receiving Certain Product Lots" – presented by Craig Zinderman, MD, MPH, Division of Epidemiology, OBE, CBER**

   Dr. Zinderman presented the pediatric focused safety review for Gamunex-C, initiated due to the approval of an expanded indication for subcutaneous administration in pediatric patients with primary humoral immunodeficiency (PI). There were 95 total pediatric AEs during the review period from December 2015 to August 2019, including 2 deaths and 41 non-fatal serious AEs. Most notably, there were increased hypersensitivity-type AE reports with specific lots. Voluntary lot withdrawals were initiated by the Applicant. FDA communicated potential serious risk with public safety signal posting. Ongoing and enhanced pharmacovigilance activities are continuing with expedited reporting of hypersensitivity reactions and root cause evaluation.

Voting

- Gamunex-C – FDA recommendations for Gamunex-C include routine safety monitoring, close monitoring of all reports of hypersensitivity, including lot-specific analyses, and continued discussion with the manufacturer to further investigate root cause. Does the Committee agree with FDA's conclusions and recommendations?

Vote Results: Yes: 21 No: 1 Abstain: 0

Center for Devices and Radiologic Health (CDRH) – Annual Update of Post-Market Humanitarian Device Exemption (HDE) Review

5. **"Flourish™ Pediatric Esophageal Atresia Device: H150003" – presented by Priya Venkataraman-Rao, MD, DCEAI, OCEA, CDRH**
   Dr. Venkataraman-Rao presented background data on the device and the granting of HDE, along with the post-approval study (PAS) enrollment and results to date. There have been 20 devices implanted after approval, and 6 patients enrolled in the PAS. Anastomosis rates post-marketing were 50%, which differed from the pre-approval rate of 100%.

   "Flourish™ Pediatric Esophageal Atresia Device" – sponsor presentation by Ted Heise, PhD, Mario Zaritzky, MD, and Bethany Slater, MD, MBA
   Dr. Heise provided a brief overview of Cook Medical and its commitment to unmet needs in pediatric device development. Drs. Zaritzky and Slater discussed the clinical need and the impact of open surgical repair of esophageal atresia. Dr. Heise provided a summary of post-approval experience with the Flourish™ device and challenges with their post-approval study.

Voting

- Flourish – The FDA will report on the following to the PAC in 2021: Annual distribution number, PAS follow-up results, revised PAS study (FDA working in collaboration with Cook), literature review, MDR review. Does the Committee agree with the FDA's plan for continued surveillance of the Flourish device?

  Vote Results: **Yes: 20** **No: 0 (*2 committee members were absent for the final vote*)**
  Abstain: 0

Votes were repeated into the record by Dr. McCune.

Adjournment

- Kelly Wade, Chair, PAC

The summary minutes for the September 15, 2020 meeting of the PAC were approved on December 30, 2020.

I certify that I attended the September 15, 2020 meeting of the PAC and that these minutes accurately reflect what transpired.

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Marieann Brill, MBA, RAC, MT(ASCP)
Designated Federal Officer, PAC

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Kelly Wade, MD
Chair, PAC