MINUTES OF THE JOINT MEETING of the PEDIATRIC ADVISORY COMMITTEE (PAC) AND DRUG SAFETY AND RISK MANAGEMENT (DSaRM) ADVISORY COMMITTEE

The public meeting was convened from 1030 am to 12 pm September 27, 2019

Members Present (voting)	**Temporary Voting Members**
Kelly Wade, MD, PhD (*Chair)* Premchand Anne, MD, MBA, MPH, FACC David Callahan, MD Randall Flick, MD, MPH Peter Havens, MD, MS Sarah Hoehn, MD, MBe, FAAP Randi Oster, MBA Wael Sayej, MD Christy Turer, MD, MHS, FAAP, FTOS Benjamin Wilfond, MD Sonia Hernandez-Diaz, MD, MPH, DrPH Marie R. Griffin, MD, MPH Laurel A. Habel, MPH, PhD Steven B. Meisel, PharmD, CPPS Suzanne B. Robotti	Maryann Amirshahi, PharmD, MD, MPH Amy Celento, BS Angela Czaja, MD, MSc Richard Holubkov, PhD John Kelso, MD Edwin Kim, MD, MS Timothy Lesar, PharmD James McGough, MD Roberto Ortiz-Aguayo, MD, MMM Stephen Patrick, MD, MPH, MS Lynn Sleeper, ScD James Tracy, DO Terri Voepel-Lewis, RN, PhD **Non-Voting Members** Bridgette Jones, 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	**CDER Office of Surveillance and Epidemilogy**	**CDER Division of Pulmonary, Allergy and Rheumatology**
Susan McCune, MD **CDER Division of Pediatric and Maternal Health** Ethan D. Hausman, MD	Ann Biehl, PharmD, MS Veronica Sansing-Foster, PhD, MS Ibrahim T. Ibrahim, PharmD, MPH, BCPS	Sally Seymour, MD Katherine Clarridge, MD, MSc Stacy Chin, MD

Welcome and Introductory Remarks

- Kelly Wade, Chair, Pediatric Advisory Committee opened the meeting. Dr Wade directed those participating in the meeting and the audience to press representative Charlie Kohler, Press Officer, OC/OEA/OMA.
- Marieann Brill, Designated Federal Officer (DFO), read the usual, customary, and required disclosures and conflict of interest statement.
- Susan McCune, MD, Director of the Office of Pediatric Therapeutics gave opening remarks
    - Dr. McCune welcomed a new member to the PAC: Dr. Benjamin Wilfond, Professor and Chief, Division of Bioethics and Palliative Care, Professor, Division of Pulmonary and

Sleep Medicine, Department of Pediatrics, School of Medicine, University of Washington.

- Dr. McCune announced the general topic for discussion for the September 27th joint PAC and DSaRM Advisory Committee Meeting.

Discussion of Neuropsychiatric Events with Use of Singulair (Montelukast)

- Katharine Clarridge, MD, MSc, Clinical Reviewer, DPARP, ODEII, OSE, CDER "Neuropsychiatric Events with the Use of Montelukast in Pediatric Patients"
  - Dr. Clarridge presented the background regarding ongoing concerns regarding neuropsychiatric adverse events with montelukast, particularly in pediatric patients including a summary of the: (i) regulatory history related to neuropsychiatric findings; (ii) current review of montelukast and neuropsychiatric events; and (iii) regulatory considerations (including the general regulatory tools available to the FDA). Dr. Clarridge also presented the discussion topics for the September 27th Advisory Committee meeting.

- Ibrahim T. Ibrahim, PharmD, MPH, Drug Utilization Analyst, DEPI-II, OSE, CDER "Pediatric Utilization Patterns Montelukast, 2014-2018"
  - Dr. Ibrahim summarized the pediatric utilization patterns of montelukast between 2014-2018, including the (i) national sales distribution data; (ii) the outpatient retail pharmacy utilization data (including the prescription and patient level data and the top prescriber specialties); and (iii) office-based physician surveys. Dr. Ibrahim also described the limitations of the utilization data.

- Ann Biehl, PharmD, MS, Safety Evaluator, DPV-I, OSE, CDER "Neuropsychiatric Adverse Events and Montelukast: Postmarketing Experience"
  - Dr. Biehl described the FDA Adverse Event Reporting System (FAERS) and its strengths and limitations. Dr. Biehl summarized the postmarketing adverse event reports associated with montelukast to date, including fatal neuropsychiatric events, and select non-fatal neuropsychiatric events.

- Veronica Sansing-Foster, PhD, MS, Epidemiologist, DEPI-II, OSE, CDER "Neuropsychiatric Adverse Events and Montelukast: Observational Safety Analyses"
  - Dr. Sansing-Foster summarized findings from an observational literature review conducted December 2017, January 2018, and July 2019. Dr Sansing-Foster also summarized the findings of a Sentinel analysis conducted to investigate neuropsychiatric adverse events and montelukast use by determining if compared to inhaled corticosteroids (ICS), there is an increased risk of depressive disorders, self-harm, and completed suicides associated with montelukast use. The Sentinel study also examined the risk of neuropsychiatric adverse events with montelukast compared to ICS modified by the 2008 Drug Safety Communications (DSC) and montelukast labeling changes, age, sex, and psychiatric history.

- Stacy Chin, MD, Clinical Team Leader, DPARP, ODE-II, OND, CDER "FDA Summary and Discussion Topics"

- Dr. Chin provided a summary of the day's FDA presentations and of the regulatory considerations, including the general labeling tools and regulatory options available to the FDA (e.g. Warnings and Precautions, Medication Guide, Boxed Warning, PMR/PMC, REMS, Marked Withdrawal, Communications [DSC, DHCP]).

Open Public Hearing

- 15 speakers (see meeting transcript).

Committee Discussion

1. **DISCUSSION**: Discuss the neuropsychiatric safety findings presented for montelukast.
2. **DISCUSSION:** Discuss the current labeling for montelukast, including:
   - Current Warnings and Precautions
   - Request for Medication Guide and Boxed Warning
3. **DISCUSSION:** Discuss your recommendations for communication strategies:
   - Target audience
   - Target organizations
   - Modalities of communication

Committee Discussion (for Discussions #1 – 3): *Dr. Wade thanked the FDA, patients, families and advocacy groups for their attendance at the meeting. She summarized the committee's discussion. She noted that the stories that were told during the Open Public Hearing were very impactful and seemed consistent with what is already described in the warnings section of the montelukast label.*

The committee members discussed that the data from the Sentinel study seemed to suggest no association with montelukast and the neuropsychiatric adverse outcomes of interest; however, there was concern about the many anecdotal experiences that were shared by the open public hearing speakers and public comments submitted to the docket. In general, the Committee agreed that there is a disconnect in what the healthcare providers are communicating to parents/patients about the neuropsychiatric adverse effects associated with montelukast.

Several committee members expressed a desire for FDA to re-evaluate the risk/benefit ratio of the current indications of montelukast, and some committee members suggested removing the indication for allergic rhinitis. There was consistent support by the committee for the use of a medication guide to ensure better communication to patients and families. There were diverse opinions amongst the committee members on the utility of a boxed warning for montelukast, and some committee members expressed concerns that a boxed warning could result in some patients with uncontrolled asthma being scared to take their medication. There was a call for more research on possible pharmacogenomic and biological mechanisms related to the neuropsychiatric adverse effects associated with montelukast, as well as research on possible withdrawal effects from montelukast. The committee recommended better education/communications to healthcare providers, patients, and professional and advocacy organizations.

Adjournment

- Kelly Wade, Chair, PAC

The summary minutes for the September 27, 2019 joint meeting of the PAC and DSaRM Advisory Committee were approved on November 4, 2019.

I certify that I attended the September 27, 2019 joint meeting of the PAC and DSaRM Advisory Committee and that these minutes accurately reflect what transpired.

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

_____/s/_____
Kelly Wade, MD
Chair, PAC