Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Antimicrobial Drugs Advisory Committee and the Drug Risk and Safety Management Advisory Committee
November 5, 2015

Location: FDA White Oak Campus ,10903 New Hampshire Avenue, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland

Topic: The committees will discuss the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, and uncomplicated urinary tract infections in the context of available safety information and the treatment effect of antibacterial drugs in these clinical conditions. These summary minutes for the November 5, 2015 joint meeting of the Antimicrobial Drugs Advisory Committee and the Drug Risk and Safety Management Advisory Committee of the Food and Drug Administration were approved on November 30, 2015.

I certify that I attended the November 5, 2015 joint meeting of the Antimicrobial Drugs Advisory Committee and the Drug Risk and Safety Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/

Jennifer A. Shepherd, RPh
Designated Federal Officer, AMDAC

/s/

CAPT Monica Parise, MD
Chairperson, AMDAC

Summary Minutes
Joint Meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
November 5, 2015

The following is the final report of the joint meeting of the Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on November 5, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anti-Infective Products and the Office of Surveillance and Epidemiology, and posted on the FDA website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm424449.htm and
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm433818.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Antimicrobial Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met jointly on November 5, 2015, at the FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA, Janssen Research & Development, LLC, and Bayer Healthcare Pharmaceuticals, Inc. The meeting was called to order by CAPT Monica Parise, MD (Chairperson). The conflict of interest statement was read into the record by Jennifer Shepherd, RPh (Designated Federal Officer). There were approximately 200 people in attendance for the meeting. There were thirty-one Open Public Hearing speakers.

Issue: The committees discussed the risks and benefits of the systemic fluoroquinolone antibacterial drugs for the treatment of acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease, and uncomplicated urinary tract infections in the context of available safety information and the treatment effect of antibacterial drugs in these clinical conditions.

Attendance:

Antimicrobial Drugs Advisory Committee Members Present (Voting): Ellen M. Andrews, PhD (Consumer Representative); Antonio Carlos Arrieta, MD; Lindsey R. Baden, MD; Amanda H. Corbett, PharmD, BCPS, FCCP; Demetre C. Daskalakis, MD, MPH; Jonathan Honegger, MD; Vincent Lo Re, MD, MSCE; CAPT Monica E. Parise, MD (Chairperson); Marc H. Scheetz, PharmD, MSc

Antimicrobial Drugs Advisory Committee Members Not Present (Voting):
Luis Z. Ostrosky, MD; Yu Shyr, PhD

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Kelly Besco, PharmD, FISMP, CPPS; Niteesh K. Choudhry, MD, PhD; Tobias Gerhard, PhD, RPh; Marjorie Shaw Phillips, MS, RPh, FASHP; Christopher H. Schmid, PhD; Almut Winterstein, RPh, PhD, FISPE

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Karen M. Hopkins, MD (Consumer Representative); Jeanmarie Perrone, MD, FACMT; Andy S. Stergachis, PhD, RPh; Til Stürmer, MD, MPH, PhD; Linda Tyler, PharmD, FASHP

Temporary Members (Voting): James S. Floyd, MD, MS; Beth B. Hogans, MS (Biomath), MD, PhD; I. Jon Russell, MD, PhD, ACR Master; Jennifer A. Schwartzott, MS (Patient Representative); Roland Staud, MD; Benedetto Vitiello, MD

Acting Industry Representative to the Committees (Non-Voting): Nicholas Kartsonis, MD

FDA Participants (Non-Voting): Robert Ball, MD, MPH, ScM; Edward M. Cox, MD, MPH; Sumati Nambiar, MD, MPH; Scott Proestel, MD; Judy Staffa, PhD, RPh; Joseph Toerner, MD, MPH

Open Public Hearing Speakers: Tim Rhudy on behalf of Gail Orth Aikmus; Charles Bennett, MD, PhD, MPP; Teresa King; Sidney Wolfe, MD (Public Citizen); Daniel Miller; Lisa Bloomquist on behalf of Linda Livingston; Kimberly Bryant; Christopher Jones; Heather McCarthy; Andrea Siana; Nic Delaine; Terry Aston; Jonathan Furman; Linda Landmon; Michael Christian Kaferly; Laura LaLone; Tracy Rupp, PharmD, MPH, RD (National Center for Health Research); Nicholas Newell; Joseph Brodine (National Physician's Alliance); Rachel Brummer (Quinolone Vigilance Foundation); Shan Harly; Sherry Reiver; Virginia Kaplan; Timothy David Averch, MD (American Urological Association); Christabelle Chajon (Fluoroquinolone Toxicity Group); John Fratti, MBA; Lisa Bloomquist on behalf of Suzanne Higley; Lisa Bloomquist (Floxie Hope, LLC); Stephanie Heller; Zoe Chapman; Mark Girard

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The agenda was as follows:

Call to Order and Introduction of Committee	**CAPT Monica Parise, MD** Chairperson, AMDAC
Conflict of Interest Statement	**Jennifer Shepherd, RPh.** Designated Federal Officer, AMDAC
FDA Introductory Remarks	**Sumati Nambiar, MD, MPH** Division Director Division of Anti-Infective Products (DAIP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA

FDA PRESENTATIONS

ABS, ABECB-COPD, and uUTI Antibacterial Drug Treatment Effects	**Joseph Toerner, MD, MPH** Deputy Director for Safety DAIP, OAP, OND, CDER, FDA
Oral Fluoroquinolone Utilization Patterns	**LT Travis Ready, PharmD** Drug Use Analyst Division of Epidemiology II (DEPI-II), Office of Pharmacovigilance and Epidemiology (OPE) Office of Surveillance and Epidemiology (OSE) CDER, FDA
Epidemiology of Selected Fluoroquinolone-Associated Adverse Reactions – A Literature Review	**LCDR James Phillip Trinidad, MPH, MS** Epidemiologist DEPI-II, OPE, OSE, CDER, FDA
"Fluoroquinolone-Associated Disability" (FQAD) Cases in Patients Being Treated for Uncomplicated Sinusitis, Bronchitis, and/or Urinary Tract Infections	**Debra Boxwell, PharmD** Safety Evaluator Division of Pharmacovigilance II OPE, OSE, CDER, FDA
Clarifying Questions to the Presenters	

BREAK

INDUSTRY PRESENTATIONS

Introduction	**Melissa Tokosh** Director, Global Regulatory Affairs Established Products Janssen Research & Development, LLC
Medical Need for Fluoroquinolones	**Lionel A. Mandell, MD, FRCPC, FRCP [LOND]** Professor Emeritus Department of Medicine, McMaster University Hamilton, Ontario, Canada
Appropriate Role for Fluoroquinolones	**Jeff Alder, PhD** Senior Director, Global Clinical Development Anti-Infectives/Primary Care Bayer HealthCare Pharmaceuticals Inc.
Safety of Fluoroquinolones	**Susan C. Nicholson, MD, FIDSA** Vice President Safety Surveillance and Risk Management Johnson and Johnson Family of Companies

INDUSTRY PRESENTATIONS (CONT.)

Benefits/Risk Conclusions	**Stephen H. Zinner, MD** Charles S. Davidson Distinguished Professor of Medicine Harvard Medical School Past Chair, Department of Medicine Mount Auburn Hospital Cambridge, Massachusetts
Conclusions	**Jeff Alder, PhD**

Clarifying Questions to the Presenters

LUNCH

OPEN PUBLIC HEARING

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **VOTE**: Do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of acute bacterial sinusitis (ABS)?

   Vote: YES: 0 NO: 21 Abstain: 0

   a. Following your vote, provide specific recommendations, if any, concerning the indications for treatment of ABS and safety information, including the constellation of adverse reactions that were characterized as a fluoroquinolone associated disability (FQAD)

   Committee Discussion: *The committee voted unanimously that the benefits and risks of the systemic fluoroquinolone antibacterial drugs do not support the current labeled indication for the treatment of acute bacterial sinusitis (ABS). The committee provided a wide range of recommendations regarding labeling, such as more specific language indicating use as second line therapy, incorporation of treatment guidelines put forth by professional societies, and including language that describes the constellation of adverse effects identified as Fluoroquinolone Associated Disability (FQAD). The committee also made recommendations about adding a REMS program to the fluoroquinolones ranging from a Medication Guide to required education for prescribers and patients. Many committee members recommended further study of FQAD, peripheral neuropathy, and psychiatric adverse effects. One committee member recommended requiring a post-marketing study to evaluate the benefits*

and risks of the fluoroquinolones. Please see the transcript for details of the committee discussion.

2. **VOTE:** Do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease (ABECB-COPD)?

   Vote: YES: 2 NO: 18 Abstain: 1

   a. Following your vote, provide specific recommendations, if any, concerning the indications for treatment of ABECB and safety information, including the constellation of adverse reactions that were characterized as a fluoroquinolone associated disability (FQAD)

      Committee Discussion:
      The majority of the committee members voted that the benefits and risks of the systemic fluoroquinolone antibacterial drugs do not support the current labeled indication for the treatment of acute bacterial exacerbation of chronic bronchitis in patients who have chronic obstructive pulmonary disease (ABECB-COPD). The majority of the committee members stated that their comments regarding safety and risk for the ABS indication also apply to ABECB-COPD since the committee was asked not to repeat duplicative recommendations due to time constraints. The committee members made several recommendations to change the drug labeling such as removing language identifying susceptible microorganisms and adding language stating that a positive culture should be obtained prior to initiating treatment with a fluoroquinolone. One committee member suggested adding a patient registry to a REMS requirement for study of FQAD. Another committee member cautioned that removing the indication from the label could affect patients' ability to obtain the medication due to non-payment by third party payers. One of the committee members who voted "Yes" indicated that there was evidence of efficacy in treatment of ABECB-COPD and that fluoroquinolones would be appropriate as second line therapy. Please see the transcript for details of the committee discussion.

3. **VOTE:** Do the benefits and risks of the systemic fluoroquinolone antibacterial drugs support the current labeled indication for the treatment of uncomplicated urinary tract infection (uUTI)?

   Vote: YES: 1 NO: 20 Abstain: 0

   a. Following your vote, provide specific recommendations, if any, concerning the indications for treatment of uUTI and safety information, including the constellation of adverse reactions that were characterized as a fluoroquinolone associated disability (FQAD)

      Committee Discussion: *The majority of the committee members voted that the benefits and risks of the systemic fluoroquinolone antibacterial drugs do not support the current labeled indication for the treatment of uncomplicated urinary tract infection (uUTI). The majority of the committee members stated that their recommendations regarding safety and risk for the ABS and ABECB-COPD indications also apply to this indication since the committee was*

asked not to repeat duplicative recommendations due to time constraints. Several committee members re-stated the need for second line therapy language in the drug label and that urine culture may be an important consideration for future guidelines in treating adult patients. One committee member stated that the box warning should include language about patient with existing tendon disorders and those who exercise strenuously. The committee member who voted "Yes" stated that there is some efficacy in uUTI. Please see the transcript for details of the committee discussion.

The meeting was adjourned at 6:05 pm.