



**Summary Minutes of the Arthritis Advisory Committee (AAC) and the  
Drug Safety and Risk Management Advisory Committee (DSaRM) Joint Meeting  
January 11, 2019**

The joint meeting of the Arthritis Advisory Committee (AAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on January 11, 2019, at the College Park Marriott Hotel and Conference Center, General Vessey Ballroom, 3501 University Blvd. East, Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Takeda Pharmaceuticals. The meeting was called to order by Maria Suarez-Almazor, MD, PhD (Acting Chairperson). The conflict of interest statement was read into the record by Yinghua Wang, PharmD, MPH (Designated Federal Officer). There were approximately 110 people in attendance. There were two Open Public Hearing (OPH) presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

**Agenda:** The committees discussed supplemental new drug application (sNDA) 021-856, ULORIC (febuxostat) tablets, sponsored by Takeda Pharmaceuticals, which includes the results from the postmarketing safety trial required by FDA to evaluate the cardiovascular safety of febuxostat, entitled “Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES).” Febuxostat is a xanthine oxidase inhibitor indicated for the chronic management of hyperuricemia in patients with gout. The committee’s discussion included the results from the CARES trial, the benefit risk assessment of febuxostat, and potential regulatory actions.

**Attendance:**

**Arthritis Advisory Committee Members Present (Voting):** Jeffrey Curtis, MD, MS, MPH; Jennifer Horonjeff, PhD (Consumer Representative); Martha C. Nason, PhD; Alyce M. Oliver, MD, PhD; Veena K. Ranganath, MD, MS; Jose U. Scher, MD (via telephone)

**Arthritis Committee Member Present (Non-Voting):** James B. Chung, MD, PhD (Industry Representative)

**Arthritis Advisory Committee Members Not Present (Voting):** Mara L. Becker, MD, MSCE; John M. Davis III, MD, MS; Aryeh Fischer, MD; J. Steuart Richards, MD; Daniel H. Solomon, MD, MPH

**Drug Safety and Risk Management Advisory Committee Members Present (Voting):** Marie R. Griffin, MD, MPH; Laurel A. Habel, MPH, PhD; Martin Kulldorff, PhD; Steven B. Meisel, PharmD, CPPS; Anne-Michelle Ruha, MD, FACMT; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

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**Drug Safety and Risk Management Advisory Committee Members Not Present (Voting):**

Kelly Besco, PharmD, FISMP, CPPS; Denise M. Boudreau, PhD, RPh; Sonia Hernandez-Diaz, MD, MPH, DrPH; Suzanne B. Robotti; Soko Setoguchi, MD, DrPh

**Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting):** Linda Scarazzini, MD, RPh

**Temporary Members (Voting):** John Cush, MD; David T. Felson, MD, MPH; C. Michael Gibson, MS, MD; Matthew H. Liang, MD, MPH; Mara McAdams DeMarco, PhD; Donald R. Miller, PharmD; Steven E. Nissen, MD; Bruce M. Psaty, MD, PhD, MPH; Maria E. Suarez-Almazor, MD, PhD (Acting Chairperson); Gene H. Weiner (Patient Representative)

**FDA Participants (Non-Voting):** Sally Seymour, MD; Nikolay P. Nikolov, MD; Rosemarie Neuner, MD, MPH; Ya-Hui Hsueh, PhD

**Designated Federal Officer (Non-Voting):** Yinghua S. Wang, PharmD, MPH

**Open Public Hearing Speakers:** Herbert Baraf, MD; Michael Carome, MD (Public Citizen)

*The agenda was as follows:*

Call to Order and Introduction of Committee

**Maria Suarez-Almazor, MD, PhD**  
Acting Chairperson, AAC

Conflict of Interest Statement

**Yinghua Wang, PharmD, MPH**  
Designated Federal Officer, AAC

FDA Opening Remarks

**Nikolay P. Nikolov, MD**  
Associate Director for Rheumatology  
Division of Pulmonary, Allergy, and Rheumatology  
Products (DPARP)  
Office of Drug Evaluation II (ODE-II)  
Office of New Drugs (OND), CDER, FDA

**APPLICANT PRESENTATIONS**

**Takeda Pharmaceuticals**

Introduction and Regulatory History

**Beth-Anne Knapp**  
Vice President, Global Regulatory Affairs  
Takeda Development Centers America

Gout: Disease Burden, Background & Treatment Landscape

**Michael A. Becker, MD**  
Professor of Medicine Emeritus  
University of Chicago

CARES and Cardiovascular Safety of Febuxostat

**William B. White, MD**  
Professor of Medicine Cardiology Center  
University of Connecticut School of Medicine

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**APPLICANT PRESENTATIONS (CONT.)**

Efficacy of Febuxostat

**Lhanoo Gunawardhana, MD, PhD**  
Senior Medical Director  
Clinical Science, Marketed Products  
Takeda Development Centers America

Benefit/Risk Assessment

**John Affinito, MD**  
Executive Medical Director  
Global Patient Safety & Evaluation, Marketed Products  
Takeda Development Centers America

Clinical Perspectives

**N. Lawrence Edwards, MD, MACP, MACR**  
Professor and Vice Chairman  
Department of Medicine, University of Florida

Clarifying Questions

**BREAK**

**FDA PRESENTATIONS**

Introduction and Regulatory History

**Rosemarie Neuner, MD, MPH**  
Medical Officer  
DPARP, ODE-II, OND, CDER, FDA

Statistical Assessment of Cardiovascular Safety of CARES

**Ya-Hui Hsueh, PhD**  
Statistical Reviewer  
Division of Biometrics VII, Office of Biostatistics  
Office of Translational Sciences, CDER, FDA

Characteristics of Febuxostat and Allopurinol Users in Real World Settings and Utilization Patterns

**Marie Bradley, PhD, MScPH, MPharm**  
Epidemiology Reviewer  
Division of Epidemiology II  
Office of Pharmacovigilance and Epidemiology  
Office of Surveillance and Epidemiology  
CDER, FDA

Clinical Considerations and Benefit-Risk Assessment

**Rosemarie Neuner, MD, MPH**

Clarifying Questions

**LUNCH**

**OPEN PUBLIC HEARING**

Charge to the Committees

**Nikolay P. Nikolov, MD**

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Questions to the Committees/  
Committee Discussion

**BREAK**

Questions to the Committees/  
Committee Discussion (cont.)

**ADJOURNMENT**

***Questions to the Committees:***

1. **DISCUSSION:** Discuss the results of the “Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES)” study, particularly major adverse cardiovascular events (MACE) and cardiovascular (CV) mortality. Please consider the following in your discussion:
  - a. Biological plausibility of CV mortality
  - b. Strength of the findings for CV mortality, considering the totality of available data

*Committee Discussion:* The committee members agreed that the biological plausibility of CV mortality is unclear, with a couple of mechanisms suggested, such as platelet aggregation or quick drop of serum urate level. Despite the lack of biological plausibility, the committees agreed that there is a consistent signal of cardiovascular death associated with febuxostat based on the CARES data. Some members questioned the conduct of the CARES study, particularly missing data due to lost patient follow-up. Please see the transcript for details of the Committees’ discussion.

2. **DISCUSSION:** Discuss the benefits of febuxostat for the treatment of hyperuricemia in patients with gout.

*Committee Discussion:* The committee members agreed that febuxostat is an effective urate-lowering medication and an important alternative to allopurinol, given the limited treatment options for gout. Some committee members commented that compared to allopurinol, which may require frequent titration to optimal dosage, febuxostat dosage is simpler and therefore leads to favorable adherence. The committee members also noted that gout affects patient’s quality of life, and febuxostat will benefit gout patients who have failed allopurinol or are intolerant to allopurinol. On the other hand, some committee members noted that optimal allopurinol use should be addressed first before switching to febuxostat, in terms of dosing and in patients with renal impairment; and some questioned whether the benefit of febuxostat outweighs the cardiovascular risk. Please see the transcript for details of the Committees’ discussion.

3. **DISCUSSION:** Given the results of the CARES study, discuss whether the benefit-risk profile of febuxostat for the treatment of hyperuricemia in patients with gout has changed. Address the following in your discussion:

- a. Discuss any patient populations in which the benefits outweigh the risks of the use of febuxostat
- b. Discuss any patient populations in which the benefits do not outweigh the risks of the use of febuxostat

**Committee Discussion:** *Most committee members agreed that given the results of the CARES study, febuxostat should no longer be a first-line therapy. The committee members noted that febuxostat should be used in patients who have failed or couldn't tolerate allopurinol, as a second-line therapy, and should not be used in the general gout population, especially in patients with previous cardiovascular events or at high risk of cardiovascular events. The committee opined on how to define intolerance to allopurinol and noted that it was unclear whether there is cross hypersensitivity between allopurinol and febuxostat. One committee member suggested a randomized study to ascertain the benefit of febuxostat in gout patients who have failed or couldn't tolerate allopurinol. Please see the transcript for details of the Committees' discussion.*

4. **DISCUSSION:** Discuss the following potential regulatory activities in response to the results of the CARES study.
  - a. Update existing warning regarding Cardiovascular Events in the febuxostat product label
  - b. Addition of a boxed warning for cardiovascular death to the febuxostat product label
  - c. Modify labeling to limit use of febuxostat to second line therapy (e.g. 2<sup>nd</sup> line therapy in patients who have failed allopurinol)
  - d. Withdrawal of febuxostat from the market

**Committee Discussion:** *Most committee members favored options b and c (to add a boxed warning for cardiovascular death in the febuxostat product label and to modify the indication to emphasize it as second-line therapy in patients who have failed allopurinol). Some committee members suggested a Risk Evaluation and Mitigation Strategy (REMS) to either restrict access to specialty pharmacy or require a patient consent form to ensure the cardiovascular risk is well informed, while others questioned the barrier a REMS would create for patients in need. Some suggested a registry for gout patients on febuxostat, inclusion of the benefit of concomitant use of aspirin in the label, and patient education provided by the Sponsor (besides the patient label). The committee members noted that more data is needed to understand how a labeling change impacts the real-world drug utilization as a black box warning may have limited effects. Most committee members remarked that withdrawal of febuxostat from the market would limit treatment options for gout patients, especially those for whom the benefit may outweigh the risk. However, one committee member suggested withdrawal of febuxostat from the market in addition to studying it in patients intolerant to allopurinol. Please see the transcript for details of the Committees' discussion.*

5. **VOTE:** Based upon the available data, is there a patient population in which the benefit-risk profile for febuxostat is favorable for the treatment of hyperuricemia in patients with gout? (Y/N)

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- If you voted “Yes”, describe the patient population with a favorable benefit-risk profile for use of febuxostat. Also, describe any other recommendations (e.g. labeling changes) you may have for use of febuxostat in this population.
- If you voted “No”, discuss your rationale, the impact of this recommendation, and any other recommendations you may have.

**Vote Result:**      Yes: 19          No: 2          Abstain: 1

***Committee Discussion:** The majority of committee members voted “Yes”, that there is a patient population in which the benefit-risk profile for febuxostat is favorable for the treatment of hyperuricemia in patients with gout. These members noted that there is a subgroup of gout patients who have failed or could not tolerate allopurinol, in which the benefit outweighs the risk for febuxostat. The committee members suggested the following: stronger labels, boxed warning, second-line therapy in indication, update to the gout treatment guidelines by the American College of Rheumatology (ACR), and “Dear Healthcare Provider” letters to communicate the risk to patients and their providers so they can make an informed decision on the care plan. The committee members who voted “No” noted that there is clear evidence that febuxostat caused cardiovascular death, thus withdrawal is the next option in the absence of a REMS. The committee member who abstained noted that the question is ambiguous. Please see the transcript for details of the Committees’ discussion.*

The meeting was adjourned at approximately 5:14 p.m.