

**Summary Minutes of the
Arthritis Advisory Committee
November 24, 2008**

**Location: Hilton Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Road,
Silver Spring, Maryland.**

**All external requests for the meeting transcripts should be submitted to the CDER,
Freedom of Information office.**

**These summary minutes for the November 24, 2008 Meeting of the Arthritis Advisory
Committee of the Food and Drug Administration were approved on
December 4, 2008_____.**

**I certify that I attended the November 24, 2008 meeting of the Arthritis Advisory
Committee of the Food and Drug Administration and that these minutes accurately
reflect what transpired.**

/s/
Nicole Vesely, Pharm.D.
Designated Federal Official, AAC

/s/
Kathleen O'Neil, M.D.
Acting Committee Chair

The Arthritis Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 24, 2008 at the Hilton Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Kathleen O'Neil, M.D. (Acting Committee Chair); the conflict of interest statement was read into the record by Nicole Vesely, Pharm.D. (Designated Federal Official). There were approximately 150 persons in attendance. There were no speakers for the Open Public Hearing session.

Issue: The committee will discuss new drug application (NDA) 21856, ULORIC (febuxostat), Takeda Pharmaceuticals North America, Inc., for the proposed treatment of hyperuricemia in patients with gout.

Attendance:

Arthritis Advisory Committee Members Present (Voting):

Diane Aronson (Consumer Representative), Robert Stine, Ph.D., Nancy Olsen, M.D., Kathleen O'Neil, M.D. (Acting Chair)

Arthritis Advisory Committee Member Present (Non-Voting)

Mark Fletcher, M.D. (Industry Representative)

Special Government Employee Consultants (Temporary Voting Members):

Daniel Clegg, M.D., John Cush, M.D., Curt Furberg, M.D., Ph.D., Allan Gibofsky, M.D., J.D., Stephen Glasser, M.D., Robert Harrington, M.D., Sean Hennessy, Pharm.D., Ph.D., Suzanne Lindley (Patient Representative), Tuhina Neogi, M.D.

Special Government Employee Consultant (Non-Voting):

Milton Packer, M.D.

Arthritis Advisory Committee Members Not Present:

Gail Kerr, M.D.
Kenneth Saag, M.D.
Christy Sandborg, M.D.

FDA Participants (Non-Voting):

Curtis Rosebraugh, M.D., Bob Rappaport, M.D., Jeffrey Siegel, M.D., Jane Gilbert, M.D., Ph.D.

Designated Federal Official:

Nicole Vesely, Pharm.D.

Open Public Hearing Speakers: There were no registrants for the Open Public Hearing.

The agenda was as follows:

Call to Order and Introductions	Kathleen O'Neil, M.D. Acting Committee Chair Arthritis Advisory Committee
Conflict of Interest Statement	Nicole Vesely, Pharm.D. Designated Federal Official

Opening Remarks **Jeffrey Siegel, M.D.**
Clinical Team Leader, Division of Anesthesia, Analgesia and
Rheumatology Products, CDER/FDA

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Clinical Overview of Gout **John Cush, M.D.**
Director of Clinical Rheumatology
Baylor Research Institute
Baylor University Medical Center

Interpretation of Safety Data
In Clinical Trials **Milton Packer, M.D.**
The Gayle and Paul Stoffel Distinguished Chair in Cardiology
Department of Clinical Sciences
University of Texas Southwestern Medical School

Questions from the Committee to the Sponsor

Sponsor Presentation **Takeda Pharmaceuticals North America, Inc.**
Introduction **Nancy Joseph-Ridge, M.D.**
President
Takeda Global Research and Development Center, Inc (US)

Gout: Disease Burden and
Unmet Patient Needs **Michael A. Becker, M.D.**
Professor of Medicine Emeritus
The University of Chicago

Febuxostat Development
Program (Efficacy and Safety) **Nancy Joseph-Ridge, M.D.**
President
Takeda Global Research and Development Center, Inc (US)

Evaluation of Adjudicated
Cardiovascular Events in the
Febuxostat Program **William B. White, M.D.**
Professor of Medicine and Chief,
Division of Hypertension and Clinical Pharmacology
Pat and Jim Calhoun Cardiology Center
Director, Clinical Trials Unit
University of Connecticut School of Medicine – Farmington

Risk/Benefit and Conclusion **Nancy Joseph-Ridge, M.D.**
President
Takeda Global Research and Development Center, Inc (US)

Questions from the Committee to the Sponsor

FDA Presentation **NDA 21856**
Febuxostat (Uloric) for
Hyperuricemia in Gout **Jane Gilbert, M.D., Ph.D.**
Medical Officer, Division of Anesthesia, Analgesia and
Rheumatology Products, CDER/FDA

Questions from the Committee to the FDA

Open Public Hearing

Questions to the AAC and AAC Discussion

Adjourn

Questions to the committee:

1. Safety of febuxostat

In its review of the two initial Phase 3 trials (Studies 009 and 010) of febuxostat 80 mg and 120 mg, the FDA found a larger number of APTC-defined cardiovascular thromboembolic events in the febuxostat arms compared to the active control allopurinol arm. In the subsequent Phase 3 trial (Study F-153) of febuxostat 40 mg and 80 mg the event rate for cardiovascular thromboembolic events was not increased with either febuxostat dose compared to the allopurinol control; however, the event rate in the control group was low.

Please discuss:

- a) The strength of evidence suggesting a cardiovascular safety signal for the febuxostat 40 mg dose;
- b) The strength of evidence suggesting a cardiovascular safety signal for the febuxostat 80 mg dose

Committee members agreed that there is insufficient data to determine a dose-response relationship.

Committee members agreed that due to a low frequency of events, there was insufficient data to determine the presence of a cardiovascular safety signal or rule out the presence of a cardiovascular safety signal.

Committee members considered the possibility that allopurinol increases cardiovascular risk and noted that it is a question as to whether allopurinol would be considered neutral in regard to cardiovascular risk.

2. Appropriate dosing:

In the two Phase 3 trials of febuxostat 80 mg and 120 mg, the serum uric acid was decreased more in the febuxostat arms than in the control arm. In the subsequent Phase 3 trial, febuxostat 40 mg met the primary endpoint of non-inferiority to allopurinol. The Applicant has proposed a dose regimen of 40 or 80 mg. Please discuss the efficacy and clinical utility of each dose.

Committee members agreed with the dose regimen proposed by the Sponsor.

A few committee members noted that it was advantageous to have a higher dose available for those patients who did not respond to a lower dose.

3. Special populations:

For patients with renal impairment it is recommended that the dose of allopurinol be reduced to avoid accumulation of the drug and its metabolites. This practice often limits the ability to achieve target levels of uric acid with the use of allopurinol.

Please discuss:

- a) Whether patients with renal impairment represent an unmet medical need population for uric acid lowering therapies.
- b) The safety, efficacy and clinical utility of febuxostat in patients with renal impairment.

Committee members agreed that patients with renal impairment represent an unmet medical need population for uric acid lowering therapies.

One committee member questioned the Sponsor as to what doses were used during studies for those patients with renal impairment.

4. VOTE: Do you recommend approval of febuxostat for the treatment of chronic gout?

If the answer is yes:

Vote : **Yes=12** **No = 0** **Abstain = 1**

- a) What is the appropriate dose?
- b) What additional studies, if any, should be conducted postapproval to further assess the safety of the product?

Committee members agreed that further studies should be conducted postapproval to assess the safety of febuxostat. Committee members also agreed that a larger study would need to be done in which patients would need to be followed for a longer period of time.

Some members suggested conducting an observational trial which could allow for results quicker than a randomized control trial. However, members disagreed on how to interpret results of the observed trial versus the randomized control trial.

Committee members agreed that if febuxostat were approved, it will be difficult to conduct a randomized control trial that would have the appropriate number of patients and be completed in a timely fashion.

If the answer is no:

- a) What additional data are needed to gain approval?
- b) Is there an unmet medical need population for which febuxostat should be approved?
Specifically consider:

- (1) Patients who have inadequate response to or are intolerant of currently available therapies
- (2) Patients with renal impairment

The committee did not address this question as the majority voted yes to Question #4.

The meeting adjourned at approximately 3:55 p.m.