



Waiver to Allow Participation in a Food and Drug Administration Advisory Committee

DATE: November 29, 2018

TO: Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs

FROM: Jayne E. Peterson, B.S. Pharm., J.D.
Director, Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research

Name of Advisory Committee Member: **Jeffrey R. Curtis, M.D., M.S., M.P.H.**

Committees: Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee (AAC/DSaRM)

Meeting date: January 11, 2019

Description of the Particular Matter to Which the Waiver Applies:

Dr. Curtis is a standing voting member of the Arthritis Advisory Committee. The Committee's function is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of arthritis, rheumatism, and related diseases and make appropriate recommendations to the Commissioner of Food and Drugs.

On January 11, 2019, the committee will meet, along with the Drug Safety and Risk Management Advisory Committee, to discuss supplemental new drug application (sNDA) 021856 Uloric (febuxostat), sponsored by Takeda Pharmaceuticals, which includes the results from the post-marketing safety trial required by FDA to evaluate the cardiovascular safety of febuxostat - the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities [CARES] trial. Febuxostat is a xanthine oxidase inhibitor indicated for the chronic management of hyperuricemia in patients with gout. The discussion will include the results from the CARES trial, the benefit risk assessment of febuxostat, and potential regulatory actions.

Type, Nature, and Magnitude of the Financial Interest(s):

Dr. Curtis reported a financial interest in [REDACTED] (b) (6), a healthcare sector mutual fund. The value of his holding in this fund is between \$50,001-\$100,000. At the writing of this waiver, this fund contained assets in three competing/affected firms – [REDACTED] (b) (6) – representing approximately [REDACTED] (b) (6) respectively, of the underlying value of the fund.

Under a regulatory exemption issued by the Office of Government Ethics, an employee may participate in any particular matter affecting one or more holdings of a sector mutual fund where the disqualifying financial interest in the matter arises because of ownership of an interest in the fund and the aggregate market value of interests in all funds in which there is a disqualifying financial interest and which concentrate in the same sector does not exceed \$50,000. Because Dr. Curtis's financial interest in the [REDACTED] (b) (6) exceeds that amount, he has disqualifying financial interests based on the fund's holding of the above-listed companies.

Basis for Granting the Waiver:

The primary issue for discussion at this AAC/DSaRM meeting will be the results from the CARES (Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities) trial and the benefit risk assessment of febuxostat, and potential regulatory actions.

Gout is a chronic illness characterized by an abnormally high level of uric acid in the blood (hyperuricemia), joint disease (arthropathy), deposit of uric acid crystals development, called tophus, and urolithiasis (stones in the kidney, bladder, and/or urinary tract) and is associated with an increased risk of cardiovascular and chronic kidney disease. The risk of cardiovascular events, including death, is substantially higher in people with gout than in those without gout. Xanthine oxidase inhibitors, such as allopurinol and febuxostat, are the mainstay of urate-lowering treatment for gout and may have different effects on cardiovascular risk in patients with gout.

A productive discussion of these matters depends upon having strong expertise in this area and hearing many perspectives. It will be critical to have Dr. Curtis's expertise in rheumatology included in the discussion on the risk/benefit profile of febuxostat to ensure the success of this advisory committee meeting.

Dr. Curtis has unique qualifications and specialized expertise needed for this particular matter.

Jeffrey R. Curtis, M.D., M.S., M.P.H., is a standing, voting member of the Arthritis Advisory Committee. He is Professor of Medicine in the Division of Clinical Immunology and Rheumatology at the University of Alabama at Birmingham (UAB). He received a Medical Degree (MD) and a Master of Public Health (MPH) degree from Oregon Health & Sciences University in Portland, OR. He subsequently completed a residency in internal medicine at Oregon Health & Science University and a fellowship in rheumatology at UAB. He completed a graduate program in Clinical Informatics at Stanford University and received his Master of

Science (MS) degree in epidemiology at the Harvard School of Public Health. He is board certified in both rheumatology and clinical informatics.

Dr. Curtis is also the Co-Director of the UAB Center for Education and Research on Therapeutics (CERTs) of Musculoskeletal Disorders, which has a major emphasis on evaluating the safety and comparative effectiveness of medications for rheumatic diseases. Additionally, as the Director of the UAB Arthritis Clinical Intervention Program, he leads the clinical trials unit for the rheumatology division at UAB, with a particular focus on rheumatoid arthritis (RA) and psoriatic arthritis. He is the Co-Director of the UAB Pharmacoepidemiology and Pharmacoeconomics Research (PEER) Unit. PEER uses multiple large data sources to study comparative effectiveness questions across multiple chronic diseases. These data sources include national administrative data from Medicare and commercial health plans, electronic health record data, and large registries. He has been awarded the William J. Koopman Endowed Professorship in Rheumatology and Immunology. The evaluation of the efficacy, comparative effectiveness, and safety of the medications used to treat RA and spondyloarthritis are among Dr. Curtis's research interests. He also studies risk factors for and outcomes of osteoporosis.

A key topic of discussion at this advisory committee meeting is going to be the interpretation of CARES study data on the potential for increased cardiovascular (CV) adverse events related to febuxostat and the current CV warning in the drug's label. It is particularly important to include Dr. Curtis in the upcoming AAC/DSaRM meeting given his experience in rheumatology as well as his background in epidemiology and pharmacoeconomic research of large data sources. The combination of this background and experiences will be invaluable to the discussion centering on the risk/benefit profile of febuxostat and the results of the CARES trial. Further, as an experienced member of the AAC, it will be essential to have his perspective, complementary to other members who may be participating for the first time in a AAC/DSaRM meeting.

Multiple experts are needed.

From the rheumatologists considered and invited to participate in the meeting, six were unable to attend due to schedule conflicts, five were recused due to conflicts of interest or appearance issues, and six were not invited due to known conflicts of interest. It is important that we have a sufficient number of rheumatologists on the panel to discuss the results of CARES, the benefit/risk assessment of febuxostat and potential regulatory actions. Dr. Curtis is one of the key opinion leaders in rheumatology and his expertise and experience as an AC member will be invaluable to the discussion at hand.

The particular matter is sensitive.

On November 15, 2017, the Agency issued a drug safety communication alerting the public to the increased risk for CV-related death and all-cause death associated with febuxostat versus allopurinol. After the safety alert was distributed by the Agency, results from the CARES study were published in New England Journal of Medicine in March 2018, which generated significant interest in the community.

The meeting topic is considered to be sensitive. The FDA Division responsible for the review of this product expects that the meeting may receive significant public interest, (non-trade) press interest and Congressional interest.

Dr. Curtis' expertise in this particular matter is necessary in the interest of public health.

Gout, one of the most common forms of inflammatory arthritis, is caused by accumulation of excess urate crystals (monosodium urate) in joint fluid, cartilage, bones, tendons, bursas, and other sites.

In the American College of Rheumatology Guidelines for Management of Gout, xanthine oxidase inhibitor (XOI) therapy with either allopurinol or febuxostat was recommended as the first-line pharmacologic urate-lowering therapy (ULT) approach in gout. In clinical practice, allopurinol is generally used as the first-line XOI in gout. The XOI febuxostat is commonly used in ULT when allopurinol is not tolerated, or when the maximum allopurinol dose chosen has not achieved lowering of the urate level to the selected target.

Risk factors and manifestations of cardiovascular disease (CV) are particularly common in patients with gout. When febuxostat was approved in 2009 for the management of hyperuricemia in gout, the FDA required that the drug manufacturer, Takeda, perform a postmarketing randomized controlled trial (RCT) to compare febuxostat and allopurinol for the risk of serious adverse CV events, which lead to the CARES trial: Cardiovascular Safety of Febuxostat and Allopurinol in Participants with Gout and Cardiovascular Comorbidities. The purpose of this study is to determine whether subjects with gout who receive febuxostat or allopurinol for up to 9 years have a higher rate of serious heart and blood vessel complications (major cardiovascular events). The CARES trial showed no significant difference between allopurinol and febuxostat in the primary composite end point of CV events in subjects with gout and established CV comorbidities at baseline. However, there was a significantly increased risk of CV and all-cause mortality with febuxostat. As a result, the FDA issued a public safety alert, responding to the results of the CARES trial. The FDA safety alert highlights the need for shared ULT medical decision-making with gout patients, including discussion of the CV safety of febuxostat. Dr. Curtis' vast experiences in rheumatology and pharmacoconomics coupled with his background in epidemiology and clinical informatics will ensure a fruitful discussion and a more broad consideration of the public health.

Accordingly, I recommend that you grant a waiver for Dr. Jeffrey Curtis, a standing voting member of the AAC, participating in the AAC/DSaRM meeting to be held on January 11, 2019, from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

 The individual may participate, pursuant to 18 U.S.C. 208(b)(3) – The need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved.

Limitations on the Regular Government Employee's or Special Government Employee's Ability to Act:

_____ Non-voting

_____ Other (specify):

_____ Denied – The individual may not participate.

Russell Fortney -S
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Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs

December 18, 2018
Date