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

DATE: April 24, 2017

TO: Janice M. Soreth, M.D.
Associate Commissioner for Special Medical Programs
Office of Medical Products and Tobacco
Office of the Commissioner, FDA

THROUGH: Jeffrey Anderson, MS, RAC
Director (Acting), Advisory Committee Oversight and Management Staff
Office of Special Medical Programs

FROM: Jayne E. Peterson, BS 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: Marvin Konstam, M.D.

Committee: Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

Meeting date: June 20, 2017

Description of the Particular Matter to Which the Waiver Applies:

The Endocrinologic and Metabolic Drugs Advisory Committee will meet on June 20, 2017, to discuss supplemental new drug application (sNDA) 022341 VICTOZA (liraglutide) injection, sponsored by Novo Nordisk, for the proposed additional indication as adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk. The topic of this meeting is a particular matter involving specific parties.

Dr. Konstam is serving as a temporary voting member of the Endocrinologic and Metabolic Drugs Advisory Committee. The Committee's function is to review and evaluate data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of endocrine and metabolic disorders, and to make appropriate recommendations to the Commissioner of Food and Drugs.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Konstam is Chief Physician Executive at the Cardiovascular Center and a Trustee/Board Member at Tufts Medical Center. He is Professor of Medicine at Tufts University School of Medicine. Tufts Medical Center is participating in a clinical study titled, "Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDENCE)". Janssen Pharmaceuticals' canagliflozin is a competing product to liraglutide, the product coming before this advisory committee meeting. The CREDENCE study began in 2014 and is expected to continue through 2020. The goal of this study is to assess whether canagliflozin has a renal and vascular protective effect, in reducing the progression of renal impairment relative to placebo, in participants with type 2 diabetes mellitus, Stage 2 or 3 chronic kidney disease and macroalbuminuria, and who are receiving standard of care including a maximum tolerated labeled daily dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Dr. Konstam is not an investigator for the study and he has no direct involvement or managerial oversight over the study.

The funding to Tufts Medical Center from Janssen Pharmaceuticals is anticipated to be between $0 – 50,000 per year for the period of October 1, 2014 – (b) (4). Dr. Konstam does not receive any salary support or personal remuneration from this study.

Additionally, Dr. Konstam is discussing with (b) (4) a possible Data Monitoring Committee (DMC) role for him for a trial of (b) (4). (b) (4) is also a competing product to liraglutide. (b) (4)

If he agrees to serve on the DMC, (b) (4) Dr. Konstam estimates that he will receive between $0 – 50,000 per year for two or three years.

Basis for Granting the Waiver:

At this meeting, the committee will discuss the findings from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, which investigated the cardiovascular safety of Victoza (liraglutide) compared to placebo, both in addition to standard of care in adults with type 2 diabetes at high risk for major adverse cardiovascular events. The results of this trial have been submitted to support the additional indication for liraglutide.

In December 2008, the FDA issued a Guidance for Industry requiring an assessment of cardiovascular risk for new antidiabetic therapies to treat type 2 diabetes; particularly, that the drug should rule out an unacceptable cardiovascular risk prior to approval and post approval. The Victoza marketing application was submitted to FDA before the December 2008 guidance issued; therefore, the manufacturer had not designed the later-recommended CV safety trials. FDA reviewed the available CV safety data, and determined there was no evidence of excess CV risk associated with Victoza. Additionally, FDA required a post-approval study to specifically evaluate the CV safety in a higher-risk population, as part of the Agency's commitment to post-marketing safety evaluation.

The study under review and before this committee was performed to satisfy the post-approval requirement. The LEADER trial was primarily designed to examine the long-term effects of liraglutide on CV outcomes in adults with type 2 diabetes and high CV risk, but the results suggest liraglutide has a beneficial effect in CV outcomes. According to the reported trial results, patients who received liraglutide (and standard of care) had lower rates of CV events and death from any cause compared to those on placebo (and standard of care). The new efficacy claim sought is related to CV disease and based on these findings.

The committee will discuss whether the primary endpoint of showing non-inferiority, as well as demonstrating superiority, with a statistically significant reduction in CV risk, was met. The committee will also discuss pancreatic and medullary thyroid cancer concerns from the LEADER trial, as well as other sources of data. Experts with various types of cardiology expertise, including heart failure expertise, are needed to opine on the trial findings, the level of evidence provided by the LEADER trial, and the clinical meaningfulness of the results.

The trial is not a "typical" diabetes or CV disease trial that would be conducted for an efficacy claim. The primary purpose of LEADER was to assess liraglutide's atherosclerotic CV safety. A secondary objective was to assess the effect of treatment with liraglutide compared to placebo on the incidence of CV events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) in patients with type 2 diabetes mellitus. Interpretation of the findings, for the purpose of reaching a regulatory decision, requires input from experts in cardiology, and in particular experts with CV clinical research and CV outcomes trial expertise.

The various cardiology experts who were invited to this meeting have different and varied expertise. Some experts are sub-specialized within the field of cardiology, in macrovascular disease (i.e., heart attack, etc.), and others are sub-specialized in heart failure. Some experts have conducted and analyzed large outcomes trials. These experts understand the issue of trial conduct and analysis which could impact interpretability of final results. Some other experts have extensive regulatory experience through their service on this and other committees; others are familiar with the Agency's current policy for CV safety for anti-diabetic drugs. A broad cardiology expertise is needed for this advisory committee meeting to ensure the committee's success.

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

Dr. Konstam is Chief Physician Executive at the Cardiovascular Center at Tufts Medical Center, and is Professor of Medicine at Tufts University School of Medicine. He received his medical degree from the College of Physicians and Surgeons, Columbia University, and did his post-graduate training at the Massachusetts General Hospital and Brigham and Women's Hospital. He is board certified in Cardiovascular Disease, Internal Medicine, and Radiology. He is an expert in cardiology with a subspecialty in advanced heart failure and transplant cardiology. It is important to have cardiologists at this meeting to provide input into the discussions concerning the indication to reduce the risk of all-cause mortality by reducing the incidence of CV death and to reduce the risk of CV death or hospitalization for heart failure in adults with type 2 diabetes mellitus and high CV risk. Dr. Konstam's clinical experience, clinical research and regulatory experience will help to ensure that the Agency can carry out a successful advisory committee meeting.

Dr. Konstam is a cardiology specialist with vast experience in academic medicine and research. He served as the Chief of Cardiology at Tufts-New England Medical Center from 1997 to 2007. In 2008, he served as Senior Advisor for Cardiovascular Diseases at the National Heart, Lung, and Blood Institute, providing direction to the NHLBI's extramural CV research programs. He has also served on FDA's Cardiovascular and Renal Drugs Advisory Committee and consulted for the Centers for Medicare and Medicaid Services with regard to their programs for improving quality of care in heart failure. He was lead author and committee chair for the Agency for Health Care Policy and Research (presently AHRQ) Clinical Practice Guideline on the care of patients with heart failure, and has served on the Heart Failure Guideline panels of the American Heart Association/American College of Cardiology and of the Heart Failure Society of America.

Dr. Konstam is an internationally-known expert on heart failure and cardiac care. His research has been published extensively in leading peer-reviewed medical journals, and he lectured throughout the world on such topics as ventricular remodeling in heart failure, drug treatment and strategies for improving the quality of care.

There is limited expertise available and it is difficult to locate similarly qualified individuals without a disqualifying financial interest.

Dr. Konstam is an expert in heart failure and in conducting clinical trials in heart failure; he is the only cardiologist attending this meeting with heart failure expertise. He is familiar with FDA's CV safety guidance for anti-diabetic products and with the regulatory requirements for demonstrating effectiveness of new products. His expertise in all these domains will be called upon at this advisory committee meeting, and it has been difficult to locate a similarly qualified individual without a disqualifying financial interest. Two other cardiologists were invited to the meeting but unable to attend. Dr. Konstam's participation will help ensure a successful and productive advisory committee meeting.

The sensitivity of the particular matter.

The discussion of liraglutide at this meeting is considered to be sensitive because it is likely to receive significant public interest due to the size of the patient population affected and the publicity surrounding publication of the study results. According to the Centers for Disease Control and Prevention, 29.1 million people in the U.S. have diabetes, and type 2 diabetes accounts for about 90 to 95 percent of all diagnosed cases of diabetes in adults. Cardiovascular disease is a highly prevalent complication and the major cause of premature death in type 2 diabetes patients. The study results suggest liraglutide had a beneficial effect in CV outcomes.

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

In the interest of public health it is critical for the Agency to review products that could potentially provide treatment to patients with diabetes who have an increased CV risk. A large percentage of older adults with diabetes die from some form of heart disease. Adults with diabetes are more likely to have heart disease than adults without diabetes. Dr. Konstam's knowledge in the area of cardiology and heart failure will provide the necessary expertise for this important discussion.

Accordingly, I recommend that you grant Dr. Marvin Konstam, a temporary voting member of the Endocrinologic and Metabolic Drugs Advisory Committee, a waiver from the conflict of interest prohibitions of 18 U.S.C. §208(a).

Certification:

X 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):

_____

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_____ Denied – The individual may not participate.

/s/ 5/30/2017

Janice M. Soreth, M.D. Date
Associate Commissioner for Special Medical Programs
Office of Medical Products and Tobacco
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