April 22, 2016

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Woodcock,

On behalf of the 89 million Americans with prediabetes, diabetes experts, and health professionals, we respectfully request a meeting to seek your guidance for how stakeholders can best work with FDA to update the approved labeling for metformin to guide its use for diabetes prevention in appropriately selected populations.

Since your involvement in its approval in 1995, metformin has become the first line therapy for treatment of type 2 diabetes across the world. Metformin has a well characterized safety profile and established effectiveness in people with type 2 diabetes. Without any patent protection, the original sponsor has had no incentive to amend the metformin label, so it has remained largely unchanged despite an expanding body of evidence that has further supported metformin's safety and effectiveness for diagnosed type 2 diabetes, and more recently, for reducing progression to type 2 diabetes in people with prediabetes.

We are very pleased the FDA has recently announced it will require manufacturers to revise the labeling of metformin-containing drugs to indicate these products may be safely used in patients with mild to moderate renal impairment. This clearly demonstrates the broad safety profile of metformin. As a next step, we want to support the expansion of the metformin label to indicate use in appropriate populations with prediabetes who were shown to benefit from the drug in the Diabetes Prevention Program (DPP)[1] and other trials.[2] Overall, study participants in the metformin arm reduced their risk of developing type 2 diabetes by 31%. Metformin was most effective in people 25 – 44 years old, those with a BMI of 35 or more, and women with a history of gestational diabetes. In the 10-

year follow-up of the DPP, metformin continued to reduce the development of type 2 diabetes by 18%, and was found to be cost-saving. Despite recommendations by the American Diabetes Association and the American Association of Clinical Endocrinologists for physicians to consider metformin in the management of prediabetes, this approach is highly underutilized.[3] We believe this is largely explained by the lack of an indication for prevention of type 2 diabetes in the metformin labeling.

More than 1 in 10 health care dollars in the U.S. are spent directly on diabetes and its complications, and more than 1 in 5 health care dollars in the U.S. goes to the care of people with diagnosed diabetes. In the Medicare program, one out of every three dollars is spent on diabetes. Nearly 30 million Americans have diabetes, and at least one of three people will develop diabetes in their lifetime. It is of utmost importance to the health of our nation to ensure we are fully utilizing all tools available to help the 89 million individuals with prediabetes delay or prevent the onset of type 2 diabetes. We strongly advocate that diabetes prevention starts with promoting physical activity and a healthy diet. When these measures are not fully successful, available evidence supports the selected use of metformin.

It is our understanding that a number of potential options are available in this unusual situation for amending the class metformin label to reflect its appropriate use in delaying the progression of prediabetes. Choosing the most suitable option involves both scientific and policy deliberations, which we believe will require your leadership. We seek your engagement along with the Division of Metabolic and Endocrine Products to ensure the metformin labeling reflects the evidence from the diabetes prevention trials, and we wish to meet with you to understand the most suitable process to achieve this goal. We look forward to finding a time when we can all meet, ideally by the end of June 2016, so we can move forward with this effort that is so important to millions of Americans with prediabetes. Please contact Dr. Robert Ratner, American Diabetes Association Chief Scientific and Medical Officer, at RRatner@diabetes.org, or 703-299-2069 so we can collaborate on the best time for our discussion.

We appreciate your consideration.

Sincerely,

George Grunberger, MD, FACP, FACE
President, American Association of Clinical Endocrinologists

Desmond Schatz, MD
President of Medicine and Science, American Diabetes Association

Henry M. Kronenberg, MD
President, Endocrine Society

Cc: John Jenkins, MD, Director, Office of New Drugs, CDER
Robert Temple, MD, Deputy Director for Clinical Science, CDER
Douglas Throckmorton, MD, Deputy Director for Regulatory Programs, CDER
Jane Axelrad, JD, Associate Director for Policy, CDER
Grail Sipes, JD, Director, Office of Regulatory Policy, CDER
Heidi Marchand, PharmD, Assistant Commissioner, Office of Health and Constituent Affairs
Helene Clayton-Jeter, OD, Director, Cardiovascular & Endocrine Liaison Program

[1] Group TDPPR; Diabetes Prevention Program Research Group, Long-Term Safety, Tolerability, and Weight Loss Associated with Metformin in the Diabetes Prevention Program Outcomes Study, Diabetes Care, 2012.
[2] Ramachandran A, Snehalatha C, Mary S, et al., The Indian Diabetes Prevention Programme Shows that Lifestyle Modification and Metformin Prevent Type 2 Diabetes in Asian Indian Subjects with Impaired Glucose Tolerance (IDPP-1), Diabetologia, 2006.
[3] Moin T, Li J, Duru OK, et al., Metformin Prescription for Insured Adults with Prediabetes From 2010 to 2012, Annals of Internal Medicine, 2015.