

Testimony of Robert Vigersky, MD, FACP
Immediate-Past President, The Endocrine Society
To the
Food and Drug Administration Center for Drug Evaluation and Research
Endocrinologic and Metabolic Drugs Advisory Committee
July 14, 2010

Mr. Chairman and members of the Advisory Committee, thank you for the opportunity to testify today. My name is Robert Vigersky. I am an Endocrinologist, the Director of the Diabetes Institute at the Walter Reed Health Care System in Washington DC and Professor of Medicine at the Uniformed Services University of the Health Sciences in Bethesda MD. I am here today to present the views of the Endocrine Society, the world's largest professional organization of endocrinologists, representing over 14,000 members, of which I am the immediate Past President. As a matter of financial disclosure, the Endocrine Society receives unrestricted educational grants from both GSK and Takeda, along with many other pharmaceutical companies. The value of these grants represents an inconsequential fraction of the Endocrine Society's budget, and these companies have no influence over the decisions or views of the Endocrine Society.

The Endocrine Society would suggest four points to keep in mind during your deliberations.

First, the FDA decision on rosiglitazone will have broad implications on the entire process of drug development. For instance, will future new drug evaluations for safety and efficacy need to consider whether or not an alternative is available and how the new drug directly compares with alternatives? What will be the appropriate safety threshold when considering withdrawal of an approved drug? What is the level of post-marketing surveillance required to ensure that initially approved drugs remain below this safety threshold? The actions of the FDA in the case

of rosiglitazone will undoubtedly serve as precedent for answering these questions with regard to all other drugs.

Second, we ask the Advisory Committee to keep in mind how this drug is being used in the real world by clinicians and their patients. Consequently, we believe that the major focus of your deliberations should be based on Active Comparator studies rather than those with placebo control. The results of placebo-controlled studies have limited usefulness with regard to adverse effects in a clinical setting since placebo is not an acceptable alternative to rosiglitazone (or any other diabetes drug for that matter) in an individual diabetic patient. We, therefore, agree with the focus of the formal questions you have been charged with answering on the Active Comparator studies.

The process of drug selection is a routine part of the "practice of medicine" - doctors employ potentially dangerous drugs and evaluate alternatives to their use with regard to specific patients on a daily basis. By removing from the market a drug of proven efficacy in the context of conflicting and inconclusive safety data, the FDA is saying that the drug is so dangerous that the normal process of physicians' assessing risk/benefit on an individual basis must be superseded.

Third, there is a healthy heterogeneity in the types of clinical research studies – prospective controlled, cohort analysis, case-control, retrospective database analysis, and so forth - each of which has its own strengths and weaknesses. In general, greatest weight should be given to prospective, randomized-controlled trials of adequate power having pre-specified and adjudicated endpoints when such studies are available. However, all studies, regardless of type, inevitably have flaws in design and/or execution especially in patients with diabetes where multiple co-morbidities are present and may influence the outcomes. Having said this, the information from these imperfect studies can still be useful in determining whether or not a drug is both safe and effective, provided the limitations of each study are taken into account.

Finally, the Endocrine Society has extensively reviewed the published studies related to rosiglitazone safety as well as the data presentations for this meeting that were posted on-line in advance. In our view, there are real and significant discrepancies among these studies in patient

populations, study designs, analyses and interpretations of the data, and the conclusions drawn. In view of these differences, The Endocrine Society does not feel that it can make a clear-cut evidence-based recommendation for or against the retention of rosiglitazone on the market and/or the continuation of the TIDE trial. Ultimately, the FDA, with the Advisory Committee's input, has to be the final arbiter of the safety and efficacy of this and other pharmaceutical agents, particularly in situations like the present one where the various lines of evidence are conflicting or inadequate.

I would like to also state that this testimony has been endorsed by the American Association of Clinical Endocrinologists (AACE).

Thank you again, Mr. Chairman, for the opportunity to address the panel. I have a hard copy for your use and our statement can be found on our web site: www.endo-society.org.