

**PUBLIC TESTIMONY SUBMITTED BY THE ENDOCRINE SOCIETY ON ROSIGLITAZONE
FOR THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE AND
THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE
DIRECTED AT THE FOOD AND DRUG ADMINISTRATION**

On May 21, 2007, the *New England Journal of Medicine* released a meta-analysis by Steven Nissen, M.D., and Kathy Wolski, M.P.H., examining the effects of rosiglitazone (Avandia) on cardiovascular morbidity and mortality. Since it was approved in 1999, rosiglitazone has been used by almost 6 million patients in the US for the treatment of type 2 diabetes. The findings of the NEJM article are based on 42 studies that met the inclusion criteria: duration of more than 24 weeks; use of a randomized control group not receiving rosiglitazone; and availability of outcome data for myocardial infarction and death from cardiovascular causes. The data analysis indicated that the use of rosiglitazone put patients at a statistically significant 43 percent higher risk of experiencing a heart attack ($p=0.03$) and a borderline significant 64 percent higher risk of cardiovascular death ($p=0.06$) compared to patients who took other drugs or a placebo. All-cause mortality was not different between the rosiglitazone and control groups.

The Endocrine Society shares the concerns of the article's authors and the FDA about the potential risk to patients using this drug. However, we also feel that no precipitous action should be taken by the FDA based solely on this meta-analysis, given the study's substantial limitations as pointed out by both the article's authors and by those writing the accompanying editorial (Bruce Psaty, M.D., Ph.D. and Curt Furberg, M.D., Ph.D.).

In particular, the Endocrine Society believes that a circumspect interpretation of the Nissen meta-analysis is warranted because of several worrisome characteristics of this study:

- the vast majority of the adverse events were not pre-defined nor subsequently validated/adjudicated; reclassification of such events could lead to substantial changes in the calculated odds ratios and consequently in the study's conclusions
- time-to-event and dose-response analysis could not be performed because of limited access to primary data
- the vast majority of the studies included were unpublished (only 11 of 42 studies used in the meta-analysis were peer-reviewed)
- most of the studies were very short in duration; for example, the PROACTIVE study of pioglitazone, which showed a cardioprotective effect of the drug after 36 months, had actually showed the opposite effect after 6 months
- most of the studies were quite small in size, and none were powered to evaluate the cardiovascular risks
- the appropriateness of the use of a fixed-effect model is questionable (use of a random-effect model leads to lower hazard ratios and loss of statistical significance)

- the use of the Peto method required exclusion of a number of trials from the calculation of odds-ratios
- the meta-analysis does not include all published studies that contained relevant data meeting the criteria for inclusion in the meta-analysis
- the meta-analysis's finding of a statistically significant 43% increase in risk of myocardial infarction in the rosiglitazone group seems puzzling when contrasted with the numerically lower aggregate incidence of myocardial infarction in that group (5.5 per 1000 patients for rosiglitazone vs 5.9 per 1000 patients for comparison groups).

The recently reported interim analysis of the large prospective RECORD trial showed no significant increase in myocardial infarction or cardiovascular death associated with rosiglitazone, similar to the findings in the two other large, longer-term studies (ADOPT and DREAM).

We believe that the RECORD study should be continued until its planned completion date in 2009 unless its Data Safety Monitoring Committee finds specific cause to stop it. If completed as planned, the RECORD study could provide the FDA with highly useful information. However, we are quite concerned that the low rates of adjudicated events and the high rate of dropouts in the RECORD trial will render it of insufficient statistical power to settle this issue. In addition, we understand that the flurry of publicity that has followed every action in this arena has the potential to accelerate dropouts from the RECORD study, an eventuality which may substantially impact the ability of the study to provide critically needed information.

Rosiglitazone has been useful in clinical practice, but alternatives are available if its use is restricted. However, switching patients from a drug on which they are well-controlled to an alternative medication always presents a degree of uncertainty.

We would urge that the FDA use the most rigorous scientific data in its evaluation of rosiglitazone. Given the technical defects of the Nissen meta-analysis, the FDA should consider performing or commissioning a repeat meta-analysis that avoids such problems. The FDA is undoubtedly aware that its actions in this case may well be interpreted as establishing a new evidentiary standard to be used henceforth in drug evaluation.

The recent controversy surrounding rosiglitazone highlights the need for strict and transparent post-marketing surveillance of all new drugs. Such an approach would complement the existing use of surrogate markers to gauge effectiveness when new drugs for the treatment of chronic illnesses are evaluated by the FDA and would facilitate continued innovation in pharmaceutical research.