

Testimony of Sidney M. Wolfe, M.D.
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Before House Agriculture-FDA Appropriations Subcommittee Hearing on Avandia
April 28, 2010

Congresswoman DeLauro and members of the subcommittee, thank you for the opportunity to testify on the serious dangers of the diabetes drug, rosiglitazone (Avandia). I will present arguments, strengthened by new information since we originally petitioned the FDA to ban the drug in October, 2008, as to why an unethical international experiment in 14 countries involving the drug, called TIDE, requested by the FDA, must be stopped immediately and, simultaneously, why rosiglitazone must be removed from the market.

Almost simultaneously with our petition to ban rosiglitazone, an expert committee representing the two largest organizations of diabetes experts in the world, the American Diabetes Association and the European Association for the Study of Diabetes, issued a consensus statement, based on a careful safety review, that: “given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone.”¹

Since then considerably more evidence concerning the unique risks and any lack of a unique benefit of rosiglitazone have been published, but, starting in May, 2009, the manufacturer, GlaxoSmithKline (GSK), as ordered by the FDA, started to recruit for a large, 16,000 person randomized trial to evaluate the cardiac safety of rosiglitazone in comparison to standard treatment and in comparison to another drug in the same family, pioglitazone. Thus in the face of recommendations not to use the drug by the leading diabetes organizations, a large human experiment to further establish the dangers of rosiglitazone, under the urging of the FDA, has begun.

Newer Evidence of Cardiac Risks of Rosiglitazone

1/ GSK Study, RECORD, published online January 29th, 2010

This randomized controlled trial involved 4447 people inadequately controlled on metformin or an older sulfonylurea diabetes drug. Half of them were given rosiglitazone and the other half were given, in addition to what they had previously taken, either metformin or a sulfonylurea. In addition to a significant doubling of heart failure deaths or hospitalizations in the group given rosiglitazone, among those admitted to the hospital with heart failure, there was a significant, more than four-fold increase in all subsequent cardiovascular deaths in the rosiglitazone group.² This study is extremely relevant for the TIDE study since it answers one of the research questions of that study: how does rosiglitazone compare to standard diabetes treatment: The answer is very poorly.

¹ Diabetologia. 2009 Jan;52(1):17-30. Epub 2008 Oct 22

² European Heart Journal, published online January 29, 2010.

2/ Canadian Population-Based Study comparing rosiglitazone with pioglitazone

This observational study, published in August 2009, evaluated cardiovascular outcomes in 39,736 people who were started either on rosiglitazone or pioglitazone from 2002 through 2008. The authors found major differences in the risk of congestive heart failure and death from any cause in patients taking rosiglitazone as compared to those taking pioglitazone. They estimated that one additional hospitalization for heart failure would occur annually for every 120 patients prescribed rosiglitazone rather than pioglitazone, and that one additional death would occur each year for every 269 patients treated with rosiglitazone rather than pioglitazone.³ At the population level, this translates into many thousands of additional adverse outcomes resulting from the use of rosiglitazone rather than pioglitazone. This study strongly answers the other part of the research question in TIDE: how do the cardiac risks of rosiglitazone compare to those of pioglitazone.

3/ Johns Hopkins study reviewing 40 randomized, controlled trials involving cardiac risks of older diabetes drugs

Of all the drugs evaluated, metformin hydrochloride was the only drug associated with a decreased risk of cardiovascular mortality compared with any other oral diabetes agent or placebo; The only diabetes drug with increased cardiovascular risk was rosiglitazone, for which the increased risk was 1.68, falling just short of statistical significance. Pioglitazone had neither increased nor decreased cardiovascular risk in the six randomized trials that comprised the study.⁴

Older evidence of differential risk of rosiglitazone and pioglitazone on blood lipids

One plausible biological hypothesis to explain the relatively recent findings of increased risk of heart attacks for patients using rosiglitazone in some studies is that rosiglitazone has much more deleterious effects on serum cholesterol and triglycerides than pioglitazone. Eight hundred patients were randomized to get either rosiglitazone or pioglitazone. Those who took pioglitazone had significantly greater decreases in their triglycerides, much lower increases in total cholesterol and significantly smaller increases in LDL cholesterol.⁵

Summary of relative risks of rosiglitazone and pioglitazone

Whereas there are many studies showing increased cardiovascular risk for rosiglitazone compared with pioglitazone, there are no studies showing the opposite: increased risk of pioglitazone compared with rosiglitazone. There was a 20 to 3 vote by an FDA advisory committee in July 2007 that there were data from randomized trials suggesting that rosiglitazone increased the risk of ischemic events (such as heart attacks). The FDA, later

³ BMJ 2009;339:b2942

⁴ Arch Intern Med. 2008;168(19):2070-2080

⁵ Diabetes Care, Volume 28, Number 7, July 2005.

that year, ordered a black box warning on the drug stating that one study “showed AVANDIA to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction.” It pointed out that other studies had not confirmed this but such a warning about possible heart attacks has never been placed on pioglitazone.

Why the TIDE trial is unethical and must be stopped before additional preventable injuries and deaths occur from exposure to rosiglitazone

(This portion of the testimony greatly benefited from the input from David N. Juurlink MD, PhD, FRCPC, FACMT, FAACT Attending Physician, Division of General Internal Medicine, Head, Division of Clinical Pharmacology and Toxicology, Sunnybrook Health Sciences Centre Scientist, Institute for Clinical Evaluative Sciences and the principal investigator for the Canadian study comparing rosiglitazone with pioglitazone (see reference 3 above.)

In light of the growing evidence that rosiglitazone imparts greater cardiac risk than pioglitazone yet offers no particular advantage, the Saudi Arabian drug regulatory agency has recently removed rosiglitazone from the market.

The trial is unethical for several reasons:

1. Misplaced scientific objectives

A primary purpose of the TIDE trial is to establish with certainty whether or not rosiglitazone is indeed more dangerous than pioglitazone. However, there are now well-documented differences in cardiovascular risks between rosiglitazone and pioglitazone, demonstrated in several studies conducted in the United States, Canada and the UK. The TIDE trial defies a basic tenet of clinical trial design – that trials should be conducted to determine the balance of risk and benefit and not simply to provide absolute proof on harm. Because rosiglitazone has no safety or efficacy advantage – not even a theoretical one – over pioglitazone, and because a wealth of data now suggests rosiglitazone carries greater risks than pioglitazone, it is not possible to advance a cogent argument that this trial is ethical given the present state of evidence.

2. Absence of clinical equipoise

Clinical equipoise requires that no subject receive an intervention known to be inferior to current standards of care. RCTs are justified in cases in which the expert scientific community is unsure about the comparative merits of interventions, and there should be equivalent evidence for the two interventions. This is clearly not the case in the context of rosiglitazone and pioglitazone. Several guidelines and systematic reviews (the highest level of evidence) have all demonstrated that rosiglitazone has an inferior safety profile relative to pioglitazone, and the positions of the ADA and EASD support this.

3. Unfavorable balance of risks and benefits of rosiglitazone

The balance of risks and benefits on rosiglitazone is clearly unfavorable. *A priori* the risks of harm with rosiglitazone are substantial, and it is highly unlikely and statistically improbable that patients in the rosiglitazone arm will derive any additional clinical benefit beyond that provided by pioglitazone. There are several different classes of drugs available to treat patients with type 2 diabetes that do not carry these risks.

Current Status of TIDE Clinical Trial Sites

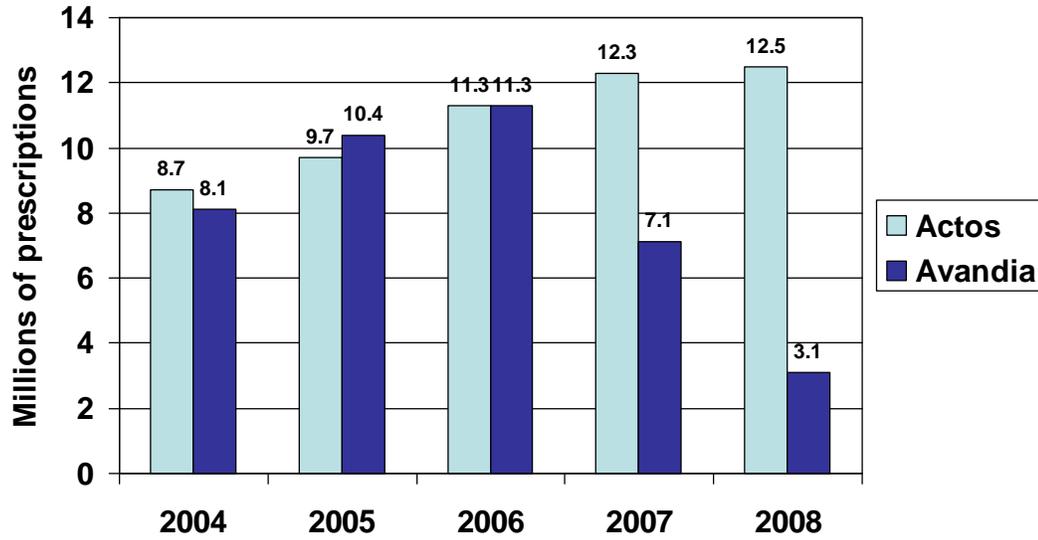
This trial now involves 137 sites in 14 countries (see below), including 19 sites in the U.S and 34 in Canada. Presently, 83 of these sites are recruiting subjects for the trial, which has an anticipated sample size of 16,000 subjects and a targeted completion date in 2015. In an apparent attempt to increase enrollment, 53 new sites were added between the previous posting on March 31, 2010 and the updated posting on April 23rd.⁶

Summary

The TIDE trial continues to recruit patients despite a lack of clinical equipoise, exposing thousands of high-risk patients with diabetes to a drug with an unfavorable safety profile and no clinical advantage over its comparator. It is almost certain that prospective study subjects are deprived of the opportunity to make a fully informed decision because the consent form does not present an accurate portrayal of existing safety concerns. It is difficult to imagine that a patient would willingly participate in a trial involving a drug that, according to the American Diabetes Association and its European equivalent, has safety concerns that leave it with no present-day role in the management of type 2 diabetes. The TIDE trial can only continue with the misplaced objective of proving definitive proof of what many studies have already suggested – that rosiglitazone is indeed more dangerous than pioglitazone. The price of such definitive proof will almost certainly be measured in the lives of study subjects who have been incompletely informed about the available evidence regarding the risks and benefits of participation.

⁶ Clinicaltrials.gov, accessed 4/22/10 (3/31 posting) and 4/26/10 (4/23 posting). Other countries include Chile, Colombia, the Czech Republic, Denmark, Germany, India, Latvia, Mexico, Pakistan, Netherlands, South Africa and Sweden.

Decrease in Avandia Prescribing after Publication of Studies About Cardiac Risks



Prescription Data from Drug Topics Magazine