



GlaxoSmithKline Responds to JAMA Articles

PHILADELPHIA, PA –September 11, 2007 - GlaxoSmithKline (NYSE: GSK) believes that conclusions drawn from the most recent meta-analyses published by Drs. Nissen et. al. and Furberg et. al. in the Journal of the American Medical Association (JAMA) do not confirm a difference in the safety profile of Avandia (rosiglitazone) and Actos (pioglitazone).^{1,2} These analyses reflect limitations that are common to all meta-analyses, by the authors' own admission. These analyses do not yield data robust enough to guide doctors in selecting appropriate diabetes treatments for their patients. Comparisons between different meta-analyses with different endpoints and patient populations are even more unreliable.

The pioglitazone meta-analysis is based on a small number of studies (19) provided directly by Takeda, and is heavily biased by data from the PROactive study (5,238 patients) which contributed 80 percent of the endpoint data. The patient population in the PROactive study was at high risk of cardiovascular disease.³

- PROactive compared diabetic patients on pioglitazone to those on placebo. Patients taking pioglitazone to control blood sugar might be expected to have fewer cardiovascular events than those who were not controlled on medication, consistent with the primary results of PROactive (Hazard Ratio 0.90 p=0.095).³ However, as described by FDA in the recent Advisory Committee, at six months PROactive actually showed an increased risk of heart attack (HR 1.2).⁴
- Applying the endpoint of CV death, myocardial infarction and stroke to the data on rosiglitazone across long-term clinical trials to enable a closer like-for-like comparison with the pioglitazone meta-analysis shows no statistical difference between rosiglitazone and comparators (a hazard ratio of 1.03).⁵ In RECORD, a study specifically designed to look at cardiovascular events, no real difference was seen between rosiglitazone and comparators (HR 0.96).⁶ In all of these analyses, the rosiglitazone and pioglitazone hazard ratios (HR 0.82 for pioglitazone in Nissen meta-analysis) do not suggest an increased risk versus the comparators.¹
- No long-term, head-to-head clinical trial data specifically evaluates cardiovascular risk between rosiglitazone and pioglitazone; however, the head-to-head data that does exist⁷, and the overwhelming majority of comparative observational data⁵ show no significant differences in CV events.

The JAMA article on rosiglitazone is yet another iteration of previously analyzed data, and offers no new information on the safety of rosiglitazone.² The suggested increase in heart attack cited comes from a selective re-analyses of previously published and highly selective data from only 4 of 116 available studies, and reflects a difference of only 11 events in 14,291 patients between rosiglitazone and control. In this limited meta-analysis, in the context of all the other evidence, we believe it is inappropriate for the author to advise doctors to disregard the FDA's advice which is to keep patients who are effectively controlling their diabetes on rosiglitazone. These data have been presented to an expert advisory panel of the FDA, which voted to keep rosiglitazone available to patients - a vote that reflects the role of this medicine as an important treatment option to help diabetes patients control their blood sugar.⁸

The conclusions of these meta-analyses conflict with the wealth of accumulated data on rosiglitazone - including 116 clinical trials in more than 52,000 patients and epidemiological studies of databases in over one million patients. Analyzed studies show no difference in the ischemic cardiovascular effects of rosiglitazone versus other oral anti-diabetic medicines, including pioglitazone.⁵

1. Across this extensive data set, the number of heart attacks is small, and rosiglitazone is shown to have a comparable cardiovascular profile to the two most prescribed oral anti-diabetic medicines — metformin and sulfonylurea — apart from the well characterized fluid-related events common to both rosiglitazone and pioglitazone.⁵
2. In three epidemiological studies of databases with more than one million diabetic patients, the risk of heart attack was similar for rosiglitazone compared to other anti-diabetic agents.⁵ A database study comparing rosiglitazone to pioglitazone showed no difference between the two.⁹
3. Two large epidemiology studies presented to the FDA Advisory Committee and conducted independently of GSK by WellPoint and by the Department of Defense/Tricare also showed no increased rates of heart attack between rosiglitazone and pioglitazone.⁸

Importantly, only rosiglitazone has been shown to control blood sugar for up to five years and to be 32% more effective than metformin and 63% more effective than glibenclamide in maintaining blood sugar control over the long-term.¹⁰ We know from clinical studies that effective treatment of diabetes requires intensive, long-term, day-to-day control of blood sugar levels to reduce the risk of serious complications (e.g., blindness, kidney failure, limb amputation, nerve injury) and ultimately save lives. Rosiglitazone is the most widely studied oral medication for type 2 diabetes, and is an important option for physicians who often need to prescribe several different diabetes medicines in combination to help their patients maintain blood sugar control.

The regulatory authorities are engaged in a full, objective analysis of the science, and will make their independent recommendations on the appropriate use of oral anti-diabetic medicines. GSK continues to support rosiglitazone as effective and well-tolerated when used according to the product label.

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Important Information for Avandia (rosiglitazone maleate) in Europe

Rosiglitazone helps improve blood sugar control in Type 2 diabetes. It may be taken alone by diabetic patients who cannot take metformin, in combination with metformin or a sulphonylurea, or with both metformin and a sulphonylurea. It is contraindicated for use in combination with insulin.

Rosiglitazone is also contraindicated for patients with cardiac failure and may cause fluid retention. Patients with sudden rapid increase in weight, increasing edema or shortness of breath should consult their doctor.

Patients with liver impairment should not take rosiglitazone. Blood tests should be used to check for liver problems before starting treatment, and periodically after that according to clinical appropriateness.

Caution is advised when using rosiglitazone in patients with significant renal impairment.

Rarely, some people have experienced vision changes due to swelling in the back of the eye while taking rosiglitazone

When used in combination therapy, particularly with sulphonylurea, hypoglycaemia may occur. Dose reduction of concomitant diabetes therapy may be required.

Rosiglitazone may increase the likelihood of pregnancy. Where appropriate, patients should seek contraceptive advice from their doctor prior to commencing therapy.

Rosiglitazone is contraindicated while breast feeding

Rosiglitazone contains lactose so should not be used by patients with rare hereditary problems associated with lactose intolerance.

For full prescribing information please consult the current rosiglitazone summary of product characteristics.

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¹ Lincoff A M, Wolski et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* Vol 208 (10); pp 1180-1189.

² Singh S, Loke Y, Furberg C. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* Vol 298 (10); pp 1189-1195

³ Dormandy et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive study: a randomised controlled trial. *Lancet*; 366; pp 1279-1289

⁴ Mahoney K. FDA briefing document for the thiazolidinedione/rosiglitazone public advisory committee meeting. P 94
<http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic>

⁵ GSK's analysis of 14,067 patients presented at the FDA Advisory Committee Meeting on July 30, 2007 (long- term clinical trials RECORD, ADOPT and DREAM)
<http://www.fda.gov/ohrms/dockets/ac/07/slides/2007-4308s1-03-gsk-steward.pdf>

⁶ Home P D, et al. Rosiglitazone Evaluated for Cardiovascular Outcomes – An Interim Analysis. *NEJM* 10.1056/NEJMMOa073394

⁷ Goldberg et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. *Diabetes Care*: 28: 1547-1554

⁸ <http://www.fda.gov/ohrms/dockets/ac/cder07.htm#EndocrinologicMetabolic>

⁹ Koro et al. Beneficial effect of thiazolidinediones on myocardial infarction risk in patients with type 2 diabetes. *Diabetes* 2004b; 53 (suppl 2); A247

¹⁰ Kahn S et al. Glycemic durability of rosiglitazone, metformin or glyburide monotherapy. *NEJM* 2006 355: 23; 2427-2443