



GlaxoSmithKline responds to JAMA article on the ICES Thiazolidinediones and Cardiovascular Outcomes in Older Patients with Diabetes

11 December 2007 -- The following is GlaxoSmithKline's [NYSE: GSK] response to the retrospective analysis by the Institute for Clinical Evaluative Sciences (ICES) titled "Thiazolidinediones and Cardiovascular Outcomes in Older Patients with Diabetes".

GSK believes that the ICES retrospective analysis of the Ontario Drug Benefit (ODB) database has significant limitations and generates misleading conclusions regarding acute myocardial infarction and death. These conclusions are inconsistent with a more robust body of evidence from large, long-term, prospective, well-designed clinical studies, including ADOPT and RECORD.

- These long-term trials in diabetic patients comparing rosiglitazone to other oral anti-diabetic medicines show no increased risk for cardiovascular events compared to other commonly used medications, other than the well-known risk of congestive heart failure (CHF) with thiazolidinedione (TZDs).
- RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) was specifically designed to evaluate the cardiovascular safety of rosiglitazone, and is therefore the most robust data available. A recently published interim analysis for myocardial infarction and death from cardiovascular causes, or from any cause, showed no statistically significant difference between rosiglitazone in combination with either metformin or sulfonylurea vs. the active comparators of metformin plus sulfonylurea.

In addition, the RESULT clinical study specifically examined an elderly diabetic population, ages 59 to 89, in which 43 percent of the patients were greater than 70 years of age, and demonstrated the safety profile of rosiglitazone to be consistent with the control medicine (sulfonylurea).

Importantly, the results of this study do not reproduce what is already known about the risk of CHF in TZD users. TZDs can cause fluid retention which can lead to or exacerbate heart failure. TZDs also have a similar increased risk of CHF. Yet, in this analysis, pioglitazone is not associated with an increased risk of CHF (Adjusted RR of 0.91 (95% CI = 0.52-1.59) whereas rosiglitazone is associated with 2 fold-increased risk of CHF (Adjusted RR = 1.98

and 95% CI=1.44-2.72) compared to oral anti-diabetic combination therapy.

Moreover, the authors of this retrospective analysis fail to acknowledge the findings of large epidemiological studies, encompassing over 1.3 million patients with type 2 diabetes, as well as other similar studies presented during the recent FDA Advisory Committee meeting. These studies have investigated whether use of rosiglitazone in the real world setting is associated with an increase in myocardial infarction or coronary revascularization. The majority of these studies show that rosiglitazone is not associated with an increased risk of myocardial infarction compared to other anti-diabetic agents.

GSK cites the following as examples of the limitations of this retrospective analysis:

- As the authors state, patients on TZDs in their analysis may represent an older, select group of patients with advanced diabetes and therefore higher baseline risk for cardiovascular disease.
 - o The ODB database is composed of a select group of patients. Rosiglitazone is only prescribed for those patients who fail treatment on metformin and sulfonylurea, or for whom sulfonylurea or metformin are contraindicated. The rosiglitazone patients are therefore ones with higher baseline risk for cardiovascular disease.
 - o Patients prescribed rosiglitazone alone suffered from more chronic diseases compared with those prescribed pioglitazone alone; therefore they were sicker patients. However this difference is not corrected for in the analysis of the data and in the study conclusions
 - o The TZD monotherapy patient population in the ICES analysis had a 4-fold higher rate of kidney impairment, which is indicative of patients with more progressive type 2 diabetes.
- The authors state that the study may have been underpowered to detect adverse effects associated with pioglitazone because of the relatively small number of persons prescribed pioglitazone alone. It is stated that larger studies are needed to better determine the relative effect of each agent on cardiovascular outcomes.
- The ICES analysis included insulin therapy within the TZD combination group but excluded insulin combinations within the comparison group. Insulin is known to be associated with increased CHF and cardiovascular risk. Therefore, this biases the TZD combination group towards increased cardiovascular risk relative to the

comparison group. This also permits more advanced patients, with poor glycemic control and who are at greater risk of cardiovascular complications, to be included in the TZD population while excluding them from the control group.

Avandia[®] (rosiglitazone maleate) is a widely studied oral anti-diabetic medicine for the treatment of type 2 diabetes, and importantly, *Avandia* has been shown to control blood sugar for longer than the most commonly used oral anti-diabetic medicines – up to five years. When used in the appropriate patient, it is an important treatment option for health-care professionals managing the chronic and life threatening disease of diabetes. Across multiple sources of data, there is no consistent or systematic evidence that rosiglitazone increases the risk of myocardial ischemic events or death in comparison to other anti-diabetic agents.

About GlaxoSmithKline Inc.

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Important Safety Information for *Avandia*[®] (rosiglitazone maleate)

Avandia, along with diet and exercise, helps improve blood sugar control in patients with type 2 diabetes.

Avandia can cause or worsen heart failure. If you have severe heart failure (very poor pumping ability of the heart), you cannot be started on *Avandia*. *Avandia* is also not recommended if you have heart failure with symptoms (such as shortness of breath or swelling) even if these symptoms are not severe.

Avandia may increase your risk of other heart problems that occur when there is reduced blood flow to the heart, such as chest pain (angina) or heart attack (myocardial infarction). This risk appeared higher in patients taking medicines called nitrates or insulin. Taking *Avandia* with insulin or with nitrates is not recommended.

If you have chest pain or a feeling of chest pressure, you should seek immediate medical attention, regardless of what diabetes medicines you are taking.

If you take *Avandia*, tell your doctor right away if you:

- Have swollen legs or ankles, a rapid increase in weight or difficulty breathing, or unusual tiredness
- Experience changes in vision
- Become pregnant

Review your medical history and tell your doctor if you:

- Have heart failure or other heart problems
- Have liver problems or liver disease
- Are pregnant or are nursing

Women taking *Avandia* should know that *Avandia* may increase the risk of pregnancy.

More fractures have been observed in women taking *Avandia*.

For more information about *Avandia*, please see Patient Information. For further information on *Avandia*, please see full Prescribing Information.

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