



Philadelphia July 16, 2007

GlaxoSmithKline Responds to Reviews of Oral Diabetes Medications

On July 16, The Agency for Healthcare Research and Quality released an Executive Summary of a report entitled *Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes*. This report is cited as the foundation for the Consumer Reports paper, *Treating Type 2 Diabetes: The Oral Diabetes Drugs*, as well as for the Annals of Internal Medicine article entitled *Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus*. The following response from GSK therefore responds to points raised in all three publications based on the same data:

This review contains no new data, but is an analysis of a selection of older, short term studies of oral anti-diabetes treatments, none of which were conclusive.

The authors call for large, long-term clinical studies to be conducted that compare medicines directly against endpoints such as heart attack, chronic kidney disease and cardiovascular (CV) death. Yet, their analysis does not include, for example, results from ADOPT, a long-term clinical study (4-6 years) that directly compares Avandia (a thiazolidinedione or TZD) with metformin and glyburide (a sulfonylurea), which was published in December 2006. The authors' conclusions therefore do not consider all of the relevant information currently available.

One of the largest, long-term clinical studies ever conducted, ADOPT has shown that Avandia has greater long-term effectiveness and a safety profile comparable to the most commonly prescribed diabetes medicines (metformin and sulfonylureas).

Data from ADOPT showed that the overall risk of serious, cardiovascular events (CV death, heart attack, and stroke - or MACE endpoint) for patients on Avandia was comparable to metformin and glyburide – two of the most commonly used medicines to treat type 2 diabetes. Importantly, ADOPT also demonstrated that Avandia was superior to metformin and glyburide regarding long-term control of blood sugar over five years, (a 32% risk reduction of monotherapy failure compared to metformin and 63% compared to glyburide). Long-term control of blood sugar is a key goal in managing diabetes to avoid the long-term complications of the disease.

With regard to specific Adverse Events:

Congestive heart failure (CHF)

More than 4.5 million Americans suffer from CHF, which also is one of the most common complications of type 2 diabetes. CHF is a condition in which the heart can't pump enough blood to the body's other organs, which can result in fluid retention, or edema. It is also well known that TZDs can cause edema, which can lead to or worsen CHF. Information about CHF has been included in the label for TZDs – in the case of Avandia since 1999, when the medicine was approved by the US Food and Drug Administration.

Lipids

As noted by the authors, TZDs (Avandia and Actos) modify the lipids profile of people with type 2 diabetes. Randomized clinical trials have documented the following positive effects of Avandia:

- Sustained increases in HDL cholesterol over time: 20 percent after two years. (According to the American Diabetes Association (ADA), HDL may be the most consistent predictor of coronary heart disease in patients with type 2 diabetes.)
- The total cholesterol to HDL (TC/HDL) ratio remains unchanged over time. In patients with small dense LDL particle types, AVANDIA helps promote a shift toward larger, more buoyant particles. Larger, more buoyant particles are potentially less likely to form lipid deposits in the arteries.

However, in terms of lipids, any differences among TZDs, or between TZDs and other classes of oral antidiabetic medication, aren't clinically meaningful considering the standard of care for diabetes patients today. As recommended by numerous treatment guidelines — including those of the National Cholesterol Education Program (NCEP III) and the International Diabetes Federation (IDF) — all people with type 2 diabetes should receive cholesterol-lowering medications (statins) to correct lipid abnormalities common in these patients. Published clinical studies have shown similar lipid-lowering effects in patients with type 2 diabetes and diabetic lipid abnormalities when a statin was added to TZD therapy regardless of which TZD was used (either Avandia or Actos).

Bone fracture

GSK elected to evaluate the rates of bone fractures in a post hoc analysis of the ADOPT data as part of its continuing commitment to patient safety. In ADOPT, more women with bone fractures were observed in the rosiglitazone group versus those in the metformin or glyburide groups. Prior to this post hoc analysis of the ADOPT data, there were no findings in the rosiglitazone clinical trial database to suggest that people with type 2 diabetes taking rosiglitazone were at increased risk for fractures.

An observational study of TZDs in people with type 2 diabetes reported similar effects on bone mineral density for three TZDs (pioglitazone, rosiglitazone and troglitazone). There is a precaution for fracture on the labels of both Avandia and Actos.

The risk of fracture should be considered in the care of patients with type 2 diabetes mellitus who are currently being treated with rosiglitazone or when initiation of rosiglitazone treatment is being considered, and attention should be given to assessing and maintaining bone health according to current standards of care.

Cost

The authors say that metformin and second-generation SUs share three advantages over other agents: longer use in practice, more intensive scrutiny in long-term trials with “clinically relevant endpoints”, and lower cost. However, Avandia has initiated the most comprehensive and rigorous program of scientific analysis for any oral anti-diabetic medicine on the market today, with experience in over 52,000 patients, including long-term clinical trials.

Avandia has been used since 1999 and data show Avandia is superior in long-term control of blood sugar over five years compared to metformin and sulfonylurea. In addition, new findings from a retrospective cohort study using real-world claims data of more than 15,000 drug naïve patients with type 2 diabetes showed that initial therapy with Avandia was associated with significantly fewer healthcare visits and lower total medical costs when compared to patients initiating therapy with a sulfonylurea. These data were presented Sunday, June 24, 2007 at the American Diabetes Association 67th Scientific Sessions. Key findings:

- Total direct medical costs were significantly lower in the group taking Avandia when compared to the sulfonylurea group (\$1,065 vs. \$1,315 per patient per month (PPPM), including lower in-patient and out-patient costs (\$718 vs. \$1,046 PPPM).
- Total medical costs, which included indirect costs due to work loss and direct medical costs, were also lower in patients taking Avandia (\$1,221 vs. \$1,512 PPPM).

GlaxoSmithKline - one of the world's leading research-based pharmaceutical and healthcare companies - is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For company information, visit GlaxoSmithKline on the World Wide Web at www.gsk.com.

Inquiries

US Media inquiries:	Nancy Pekarek	(215) 751 7709
	Mary Anne Rhyne	(919) 483 2839
	Alice Hunt	(215) 751 7709
UK Media inquiries:	Phil Thomson	(020) 8047 5502
	Joss Mathieson	(020) 8047 5502
US Analyst/ Investor inquiries:	Frank Murdolo	(215) 751 7002
	Tom Curry	(215) 751 5419

European Analyst/Investor inquiries:

David Mawdsley

(020) 8047 5564

Sally Ferguson

(020) 8047 5543