

## Drugs in the News 4/7/09 – Looking for Safer Type-2 Diabetes Drugs

In response to cardiovascular (CV) safety concerns with rosiglitazone (Avandia) and other drug used to treat type-2 diabetes the Food and Drug Administration (FDA) convened a public advisory committee meeting in early July 2008 to review the role of CV risk assessment in the pre-approval and post approval phases for new drugs and biologics being developed for the treatment of type-2 diabetes.

The advisory committee recommended by a vote of 14 to 2 that manufacturers should provide evidence to rule out unacceptable CV risk with new type-2 diabetes drugs.

In February 2008 the FDA issued a “*Guidance for Industry – Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention.*” A guidance is the FDA’s current thinking on a topic and does not carry the weight of a regulation.

In this guidance, FDA reaffirmed that HbA1c, a surrogate endpoint, remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication for glycemic control. However, FDA acknowledged that diabetes is associated with an elevated risk of CV disease that is the leading cause of morbidity and mortality in this patient population. The FDA stated that the absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term CV risk may not be practical.

However, for type 2 diabetes, the FDA noted that the wider range of treatments available before insulin therapy is considered for controlling hyperglycemia allows for an opportunity to evaluate the effect of these therapies on cardiovascular risk, enabling a more informed decision on the management of type-2 diabetes.

The guidance asks manufacturers to demonstrate that new treatments for type-2 diabetes do not result in an unacceptable increase in CV. The guidance does not address CV assessment of already-approved treatments for type-2 diabetes, which will be addressed in a future guidance.

Specifically, this guidance asks sponsors to do the following during the planning stage of their drug development programs for therapies for type 2 diabetes:

- Establish an independent CV endpoints committee to prospectively and blindly adjudicate major CV events, for example, CV death, myocardial infarction, and stroke) during phase 2 and 3 clinical trials.

- Ensure that the phase 2 and 3 clinical trials are appropriately designed so that a pre-specified meta-analysis of major CV events can reliably be performed. The manufacturer should provide a protocol describing the statistical methods for the proposed meta-analysis of all placebo-controlled trials, add-on trials, and active-comparator trials. The guidance states that it is likely that the controlled trials will need to last longer than the typical 3 to 6 months duration to obtain a sufficient number of events and to provide data on longer-term CV risk (e.g., minimum 2 years) for these chronically used therapies.
- To enroll patients at increased cardiovascular risk, such as elderly patients and those with renal impairment.

The guidance states that to support approvability from a CV standpoint, the manufacturer should compare the incidence of major CV events with the investigational drug to the incidence of the same types of events occurring with the control group and show that the upper bound of the two-sided 95 percent confidence interval (95% CI) for the estimated risk ratio is less than 1.8 with a reassuring point estimate. If this upper bound of this 95% CI is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval then a postmarketing CV trial generally will be needed to definitively show that this upper bound is less than 1.3. If the premarketing data show that this upper bound is less than 1.3 and the overall risk-benefit analysis supports approval then a postmarketing CV trial generally may not be necessary.

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