



May 24, 2007

FDA issues a safety alert on *Avandia*[®]

On Monday, May 21, 2007, the Food and Drug Administration (FDA) issued a safety alert on *Avandia*[®] (rosiglitazone), GlaxoSmithKline's treatment for type 2 diabetes, based on a meta-analysis of 42 controlled clinical trials that was published in the *New England Journal of Medicine*. This meta-analysis showed that rosiglitazone was associated with a very small, but significant increase in the risk of heart attack. There was a trend toward increased risk for death from cardiovascular causes, but this was not statistically significant. However, according to FDA, other published and unpublished data from long-term clinical trials of the drug provide contradictory evidence about the risks in patients treated with *Avandia*. Therefore, the agency has not been able to confirm the reported increased risk of ischemic cardiovascular events in the context of all the available data.

The FDA is advising patients who are taking *Avandia*, especially those who are known to have underlying heart disease or who are at high risk of heart attack, to talk to their doctor about this new information as they evaluate the available treatment options for their type 2 diabetes. However, the agency is advising patients not to stop their medication without talking to their doctor and is also not advising health care professionals to stop prescribing *Avandia*.

The FDA's analyses of all available data are ongoing. Pending questions include whether the other approved treatment from the same class of drugs – pioglitazone – has less, the same or greater risks. Furthermore, there is inherent risk associated with switching patients with diabetes from one treatment to another even in the absence of specific risks associated with particular treatments. For those reasons, the FDA is not asking GlaxoSmithKline, the drug's sponsor, to take any specific action at this time. The FDA said in a statement that it is providing this emerging information to prescribers so that they, and their patients, can make individualized treatment decisions. However, FDA has not concluded that there is a causal relationship between *Avandia* and the emerging safety concern.

Implications:

- Medco's position regarding *Avandia* is aligned with the FDA's statements and the joint statement from the American Heart Association (AHA), the American College of Cardiology (ACC) and the American Diabetes Association (ADA). Medco is educating patients who contact us about this trial so that they do not stop taking their medication. Patients are being urged to speak with their doctors if they have concerns. There are risks associated with switching patients with diabetes from one treatment to another. Those risks will need to be considered in the context of this emerging data.
- Medco programs, such as the patient safety system RationalMed[®], already include clinical alerts for patients with congestive heart failure or edema who receive glitazones. Patients with chronic heart failure (CHF) who receive glitazones are known to be among the high-risk population who may experience an increased rate of myocardial infarction (heart attack) when receiving *Avandia*. Expansion of those alerts to other high risk populations is also under consideration.
- Medco is speaking to its Pharmacy and Therapeutics (P&T) committee members for advice on those findings and how they should influence formulary and other clinical programs. For now, we are holding off any further action pending advice from our P&T Committee, and further investigation and analysis by the FDA.

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- As this situation unfolds and becomes more clear, Medco will consider the impact that these findings should have on formulary decision making, prior authorization for *Avandia* and other clinical programs and policies.
- The joint statement from AHA, ACC and ADA can be found on the ADA website at www.diabetes.org.

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Contact your Medco Account Management team.