U.S. Food and Drug Administration
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Drug Safety Communications

FDA Drug Safety Communication: FDA review found no increased cardiovascular risks with Parkinson's disease drug entacapone

This is an update to the FDA Drug Safety Communication: Ongoing Safety Review of Stalevo and Possible Increased Cardiovascular Risk issued on August 20, 2010.

Safety Announcement

[10-26-2015] A Food and Drug Administration (FDA) safety review has found no clear evidence of an increased risk of heart attacks, stroke, or other cardiovascular events associated with the use of entacapone for the treatment of Parkinson's disease. As a result, our recommendations for using Comtan (entacapone) and Stalevo (a combination of entacapone, carbidopa, and levodopa) will remain the same in the drug labels. Patients should discuss any questions they have with their health care professionals.

Entacapone-containing products, Comtan and Stalevo, have been shown to be effective in treating symptoms of Parkinson's disease, such as muscle stiffness, tremors, spasms, and poor muscle control. The combination of entacapone with carbidopa and levodopa in Stalevo has been shown to reduce end-of-dose "wearing-off" in patients with Parkinson's disease to a greater degree than with entacapone alone or with the two-drug combination of carbidopa and levodopa.

We alerted patients and health care professionals about a possible increased risk for cardiovascular events and death with Stalevo in an August 2010 Drug Safety Communication. This possible safety issue was observed in a clinical trial called the Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD)[1] and in a meta-analysis that combined the cardiovascular-related findings from 15 clinical trials comparing Stalevo to carbidopa/levodopa. Carbidopa and levodopa have been used extensively and have not been shown to have an increased cardiovascular risk. We were concerned that the entacapone in Stalevo was responsible for these cardiovascular risks because the comparison drugs do not contain this ingredient.

To better understand the significance of these findings, we required the Stalevo manufacturer, Novartis, to study the potential for cardiovascular risk with the entacapone component of the drug. We examined the results from this required study and from one additional study[3] and concluded they do not show an increased risk of cardiovascular adverse events with entacapone. The results observed in the original meta-analysis were driven by results of a single study (STRIDE-PD), which was not designed to assess cardiovascular risks. We believe that the meta-analysis and STRIDE-PD results are chance findings and do not represent a true increase in risk due to entacapone.

Novartis's study assessed the potential for hearts attacks, also called myocardial infarction or MI, associated with entacapone in patients 18 to 64 years old with Parkinson's disease using data from an electronic commercial insurance database.[2] The risk for myocardial infarction that did not result in death was not significantly increased in patients treated with entacapone compared to the control group that received other Parkinson's disease drugs. No one in either group died from a myocardial infarction. This study had limitations, including that few patients had a myocardial infarction making it difficult to assess an association with the drug.

The second study by Graham et al.[3] assessed the risk of myocardial infarction, stroke, or death in Medicare patients at least 65 years old with Parkinson's disease treated with entacapone compared to those receiving other Parkinson's disease drugs. The study results did not support an association between entacapone use and increased cardiovascular risks.

In light of the results from these two additional studies, FDA finds no evidence of an increased risk of myocardial infarction, stroke, or other cardiovascular events associated with the use of entacapone, Comtan or Stalevo. As a result, the drug labels will remain unchanged.

We urge patients and health care professionals to report side effects involving entacapone, Comtan, or Stalevo to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

References

1. Stocchi F, Rascol O, Kieburtz K, Poewe W, Jankovic J, Tolosa E, Barone P, Lang AE, Olanow CW. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. Ann Neurol 2010 Jul; 68(1):18-27.
2. Final Study Report, "The risk of incident myocardial infarction in Parkinson's disease patients with add-on entacapone to levodopa/DDCI compared to other add-on Parkinson's disease therapy without entacapone". A retrospective cohort study using data from MarketScan™; February 2014.
3. Graham DJ, Williams JR, Hsueh YH, Calia K, Levenson M, Pinheiro SP, MaCurdy TE, Shih D, Worrall C, Kelman JA. Cardiovascular and mortality risks in Parkinson's disease patients treated with entacapone. Mov Disord 2013;28:490-497.