FDA Drug Safety Communication: FDA review of cardiovascular risks for diabetics taking hypertension drug olmesartan not conclusive; label updates required

This information is in follow-up to the FDA Drug Safety Communication: Safety Review Update of Benicar (olmesartan) and cardiovascular events **[LINK TO http://www.fda.gov/Drugs/DrugSafety/ucm251268.htm]**

Safety Announcement

[6-24-2014] The U.S. Food and Drug Administration (FDA) has completed its safety review and has found no clear evidence of increased cardiovascular risks associated with use of the blood pressure medication olmesartan in diabetic patients. As a result, our recommendations for use of olmesartan (Benicar, Benicar HCT, Azor, Tribenzor, and generics) will remain the same, but we will require information about some of the studies to be included in the drug labels. Patients should discuss any questions they have with their health care professionals.

It is important to take olmesartan and other blood pressure medicines because uncontrolled high blood pressure increases the risks of cardiovascular problems such as heart disease and stroke, as well as kidney failure and other health problems. Do not stop taking olmesartan or any blood pressure medication without first discussing it with your health care professional.

Prompted by results from the ROADMAP (**R**andomized **O**lmesartan and **D**iabetes **M**icro**a**lbuminuria **P**revention)[1] trial, we reviewed several additional studies. ROADMAP examined the effects of olmesartan in patients with type 2 diabetes to see whether olmesartan could delay kidney damage. The trial unexpectedly found an increased risk of cardiovascular deaths in the olmesartan group compared to the group taking a placebo, or sugar pill. However, the risk of non-fatal heart attack was lower in the olmesartan-treated patients.

We also reviewed a large epidemiologic study in Medicare patients. While data from the ROADMAP trial and the Medicare study have suggested that high-dose olmesartan may increase CV risk in diabetic patients, when considering the data from all trials and studies, they are not conclusive. Overall, we determined these studies do not clearly show an increased cardiovascular risk. Thus, the collective evidence available at this time does not support changing our recommendations for olmesartan use and does not support recommending that its use be avoided in patients with diabetes.

Olmesartan is a type of blood pressure medicine called an angiotensin receptor blocker, or ARB. In 2013, there were approximately 1.8 million patients who received a dispensed prescription for olmesartan-containing products from U.S. outpatient retail pharmacies.[2]

FDA posted two previous Drug Safety Communications (DSCs) on this issue. The first, in June 2010, described the ongoing review of olmesartan and cardiovascular events **[link to http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm215222.htm].** The second was a DSC update in April 2011 **[link to http://www.fda.gov/Drugs/DrugSafety/ucm251268.htm]**

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

Additional Information for Patients

- FDA believes the benefits of olmesartan in patients with high blood pressure continue to outweigh the potential risks.
- Do not stop your treatment with olmesartan unless told to do so by your healthcare professional. Uncontrolled high blood pressure increases the risks of cardiovascular problems such as heart disease and stroke, as well as kidney failure and other health problems
- Talk to your healthcare professional if you have concerns about olmesartan.
- Report any side effects from the use of olmesartan products to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Data Summary

FDA has completed a safety review of olmesartan and cardiovascular risk that was prompted by results of the ROADMAP (**R**andomized **O**lmes**A**rtan and **D**iabetes **M**icro**A**lbuminuria **P**revention) trial and ORIENT (**O**lmesartan **R**educing **I**ncidence of **E**nd Stage Renal Disease in Diabetic **N**ephropathy **T**rial). These studies suggested that high-dose olmesartan may increase cardiovascular (CV) risk in diabetic patients.[1,3]

Diabetes causes kidney damage in some patients, and one of its manifestations can be microalbuminuria. The goal of ROADMAP was to show that olmesartan delayed the onset of microalbuminuria in patients with diabetes. The trial examined the use of olmesartan (40 mg daily) compared to placebo in patients with type 2 diabetes who did not have microalbuminuria. Patients had to have at least one risk factor for CV disease in addition to diabetes.[1] The trial met its primary endpoint, showing that olmesartan caused a delay in onset of microalbuminuria, but olmesartan had no beneficial effect on kidney function. The trial also found an increased number of CV deaths in the olmesartan group (15 in the olmesartan groups vs. 3 in the placebo group, hazard ratio [HR] 4.9, 95% confidence interval: 1.4 to 17), and a trend of increased strokes, both causes for concern. The CV deaths in the olmesartan-treated patients were primarily sudden cardiac deaths and fatal myocardial infarctions. Conversely, there was a trend towards a decreased number of non-fatal myocardial infarctions in the olmesartan group.

ORIENT was a much smaller trial than ROADMAP. It was conducted in a patient population with more advanced diabetes, and it also showed an increased risk of CV mortality for olmesartan.[3] After reviewing the results from ORIENT, however, we conclude that the evidence of cardiovascular risk was not strong. When the causes of death were carefully considered and deaths that occurred more than 30 days after the last dose of the drug were excluded from the analysis, there was no difference in mortality between the two groups.

The finding of increased risk of CV death in ROADMAP was unusual and surprising. Angiotensin receptor blockers (ARBs) such as olmesartan and other drugs that attenuate the effects of the renin-angiotensin system (RAS) have been found to have beneficial cardiovascular effects. In order to better understand the significance of the findings, we examined other studies, including observational studies using data from Medicare and the Clinical Practice Research Datalink (CPRD), a manufacturer-conducted patient-level meta-analysis, and an observational study conducted by the manufacturer. A summary of these studies and selected findings are discussed below.

A large (more than 300,000 patient-years) observational study of Medicare patients 65 years and older examined the rate of death in patients taking olmesartan compared to other ARBs.[4] In a selected group of diabetic patients—patients who received only the highest dose of olmesartan (40 mg daily) for longer than 6 months—olmesartan was associated with an increased risk of death (HR 2.0, 95% confidence interval: 1.1 to 3.8) compared to similar patients taking other angiotensin receptor blockers. In contrast, the same analysis in non-diabetic patients found that high-dose olmesartan was associated with a decreased risk of death (HR 0.46, 95% confidence interval: 0.24 to 0.86) compared to similar patients taking other ARBs. The conflicting results in diabetics and non-diabetics are difficult to reconcile and raise uncertainty about the credibility of the findings in either group. Moreover, no differences were found between the groups receiving lower doses of olmesartan and groups receiving other angiotensin blockers or in those receiving therapy for less than 6 months.

A study in CPRD, a database of anonymized, longitudinal primary care medical records in the United Kingdom, compared the outcomes of users of high-dose olmesartan to users of high doses of other ARBs (more than 58,000 patients) and found a numerically greater risk associated with high dose olmesartan for overall death and for acute myocardial infarction,[5] but the difference was not statistically significant. Cardiovascular death was not assessed specifically, and the numbers of patients in the diabetic subgroup treated with high-dose olmesartan were very small.

The manufacturer of Benicar, Daiichi-Sankyo, also conducted a patient-level meta-analysis that included studies of olmesartan compared to placebo or active comparator with a duration of at least 28 days (more than 7,500 patient-years of data; results not published), and FDA reviewed these results. When ROADMAP and ORIENT were not included in the analysis, there was no significant difference between the olmesartan and comparator groups for CV death or total mortality, although the meta-analysis was unable to assess patients with diabetes or patients receiving high-dose olmesartan.

Daiichi-Sankyo also conducted an observational study using a commercial insurance database that included two comparisons: olmesartan vs. other ARBs (more than 75,000 patient-years) and olmesartan vs. Angiotensin Converting Enzyme (ACE) inhibitors (more than 80,000 patient-years).[6] ACE inhibitors work through a mechanism that is similar but not identical to that of ARBs. For both the overall population and for the subgroup of patients with diabetes (defined by concomitant use of hypoglycemic medications), olmesartan was not associated with an increased risk of death. The effects in patients treated with high-dose olmesartan (diabetic or non-diabetic) were not assessed. Sudden cardiac death was increased in the diabetic subgroup taking olmesartan in both comparisons, but we cannot be certain of the finding because it was based on a very small number of events.

Overall, these data raise concern of possible increased cardiovascular risk associated with the use of high-dose olmesartan in diabetic patients. Of the studies reviewed to assess the finding observed in ROADMAP, the large Medicare study was the only study to analyze the subgroup of interest, i.e., diabetic patients taking high-dose olmesartan. The results seem to support the finding in ROADMAP; however, there are concerns regarding the credibility of the results of the Medicare study because of the discrepant findings in diabetics and non-diabetics. The observation of a large *decrease* in survival in patients with diabetes taking high doses of olmesartan, coupled with a large *increase* in survival in non-diabetic patients taking olmesartan—all relative to other drugs of the same class—is not a plausible finding.

References

1. Haller H, Ito S, Izzo JL, et al. Olmesartan for the delay or prevention of microalbuminuria in Type 2 Diabetes. N Engl J Med 2011; 364: 907-17.
2. IMS, Vector One®: Total Patient Tracker (TPT) Databases. Year 2013. Extracted May 2014.
3. Imai E, Chan JC, Ito S, et al. Effects of olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a multicentre, randomised, placebo-controlled study. Diabetologia 2011; 54: 2978-86.
4. Graham DJ, Zhou EH, McKean S, et al. Cardiovascular and mortality risk in elderly Medicare beneficiaries treated with olmesartan versus other angiotensin receptor blockers. Pharmacepidemiol Drug Saf 2014; 23: 331-9.
5. Zhou EH, Gelperin K, Levenson MS, et al. Risk of acute myocardial infarction, stroke, or death in patients initiating olmesartan or other angiotensin receptor blockers - a cohort study using the Clinical Practice Research Datalink. Pharmacepidemiol Drug Saf 2014; 23: 340-7.
6. Walker AM, Liand C, Clifford CR, et al. Cardiac mortality in users of olmesartan, other angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors. Pharmacoepidemiol Drug Saf 2014; 23: 348-56.