U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

FDA Drug Safety Communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil

Safety Announcement

[7-3-2013] The U.S. Food and Drug Administration (FDA) is warning that the blood pressure drug olmesartan medoxomil (marketed as Benicar, Benicar HCT, Azor, Tribenzor, and generics) can cause intestinal problems known as sprue-like enteropathy. FDA has approved changes to the labels of these drugs to include this concern.

Symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss. The enteropathy may develop months to years after starting olmesartan, and sometimes requires hospitalization (see Data Summary). If patients taking olmesartan develop these symptoms and no other cause is found, the drug should be discontinued, and therapy with another antihypertensive started. Discontinuation of olmesartan has resulted in clinical improvement of sprue-like enteropathy symptoms in all patients.

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) approved for the treatment of high blood pressure, alone or with other antihypertensive agents, and is one of eight marketed ARB drugs. Sprue-like enteropathy has not been detected with ARB drugs other than olmesartan.

FDA will continue to evaluate the safety of olmesartan-containing products and will communicate again if additional information becomes available.

FACTS about Olmesartan

- Olmesartan is an angiotensin II receptor blocker (ARB) approved for the treatment of hypertension, alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and heart attacks.
- In 2012, a total of approximately 10.6 million prescriptions were dispensed, and approximately 1.9 million patients received a dispensed prescription for olmesartan-containing products from U.S. outpatient retail pharmacies.[1] According to sales data, the majority of olmesartan-containing products were distributed to outpatient retail pharmacies (81.5% retail, 15% mail order/specialty pharmacies and 3.5% non-retail) during this time.[2]

Additional Information for Patients

- Contact your health care professional right away if you take an olmesartan-containing product and experience severe diarrhea, diarrhea that does not go away, or significant weight loss.
- Your health care professional may evaluate your symptoms to determine the cause. If no other cause is found, you may be asked to stop taking olmesartan and start taking a different high blood pressure medicine.
- Do not stop taking your high blood pressure medicine without first discussing it with your health care professional. When high blood pressure is not appropriately treated, strokes, heart attacks or kidney failure, or other serious harm can result.
- Discuss any questions or concerns about olmesartan with your health care professional.
- Report any side effects you experience to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Additional Information for Health Care Professionals

- Tell your patients to contact you if they develop severe, chronic diarrhea with substantial weight loss while taking an olmesartan-containing product, even if it takes months to years for symptoms to develop.
- If a patient develops these symptoms during treatment with olmesartan, other etiologies, such as celiac disease, should be investigated. If no other etiology is identified, olmesartan should be discontinued and another antihypertensive treatment started.
- Symptoms of sprue-like enteropathy may develop months to years after starting olmesartan.
- Report adverse events involving olmesartan-containing products to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Data Summary

Olmesartan medoxomil is an angiotensin II receptor blocker (ARB) that was approved on April 25, 2002, for the treatment of hypertension, alone or with other antihypertensive agents. The current olmesartan drug labels include diarrhea in the Adverse Reactions section.

FDA evaluated adverse event reports received by FDA's Adverse Event Reporting System (FAERS), published literature case series,[3-4] information from FDA's Mini-Sentinel pilot of the Sentinel Initiative, and information from the CMS Medicare database. FDA's evaluation found clear evidence of an association between olmesartan and sprue-like enteropathy.

FDA identified 23 serious cases in FAERS presenting as late-onset diarrhea with significant weight loss and, in some cases, with intestinal villous atrophy on biopsy. All patients improved clinically after discontinuation of olmesartan, and a positive rechallenge was seen in 10 of the cases.

In June 2012, Mayo Clinic researchers published a case series of sprue-like enteropathy associated with olmesartan in 22 patients whose clinical presentation was similar to that of the FAERS cases: Patients in the Mayo Clinic case series developed diarrhea, weight loss, and villous atrophy while on olmesartan, and drug discontinuation resulted in clinical improvement.[3] Eighteen patients had follow-up intestinal biopsies histologically demonstrating recovery or improvement of the duodenum after discontinuation of olmesartan.

In May 2013, an article describing patients with villous atrophy and negative serologies for celiac disease reported that some patients without definitive etiologies for villous atrophy were characterized as having unclassified sprue. Some of these patients were later found to have villous atrophy associated with olmesartan use.[4]

The signal of sprue-like enteropathy with olmesartan was further investigated for a possible ARB class effect using active surveillance data. Mini-Sentinel and CMS Medicare data were assessed for celiac disease (as a marker for enteropathy and other gastrointestinal symptoms) after exposure to ARBs. Mini-Sentinel and CMS Medicare assessments of ICD-9 codes for celiac disease showed that at a 2-year minimum exposure, which correlates with the long latency observed in literature and case reports, olmesartan users had a higher rate of celiac disease diagnoses in claims and administrative data than users of other ARBs. Interpretation is limited by the small number of events observed at longer exposure periods and the uncertainty about the validity of codes for celiac disease, but these results support other data in suggesting a lack of a class effect.

Although the mechanism for olmesartan-associated sprue-like enteropathy is uncertain, the long latency before onset of symptoms, findings of lymphocytic or collagenous colitis, and high association with HLA-DQ2/8 suggest a localized delayed hypersensitivity or cell-mediated immune response to the pro-drug olmesartan medoxomil. Rubio-Tapia et al., suggest that ARB-mediated inhibition of TGF-β, an important mediator of gut homeostasis, is a possible mechanism for olmesartan-associated sprue-like enteropathy, although it is unclear why this effect is not observed with other ARBs.[3]

References

1. IMS, Vector One: National (VONA) and Total Patient Tracker (TPT) Database. Year 2012. Extracted June 2013.
2. IMS Health, IMS National Sales Perspectives Database. MAT August 2012. Extracted June 2013.

3. Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. Mayo Clin Proc 2012;87:732-8.
4. DeGaetani M, Tennyson CA, Lebwohl B, et al. Villous atrophy and negative celiac serology: A diagnostic and therapeutic dilemma. Am J Gastroenterol 2013;108:647-53.