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Citizen Petition

Date: November 15, 2017

On behalf of Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, and Public Citizen's Health Research Group, the undersigned submit this petition under Section 355(e) of the Federal Food, Drug, and Cosmetic Act and under Food and Drug Administration (FDA) regulations at 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to immediately require the removal from the market of all medications containing the widely prescribed angiotensin II receptor blocker (ARB) olmesartan medoxomil because (1) olmesartan medoxomil is associated with a risk of sprue-like enteropathy (a disorder that mimics celiac disease but does not improve with a gluten-free diet), which can cause significant morbidity in patients and outweighs its benefits in treating hypertension and (2) multiple other ARBs that do not appear to have the same risk of sprue-like enteropathy have been approved by the FDA for treatment of hypertension. In summary, olmesartan medoxomil has unique serious risks but no unique benefit.

A. ACTION REQUESTED

Immediately require the removal from the market of all medications containing olmesartan medoxomil, including medications branded as Azor, Benicar, Benicar HCT, and Tribenzor, as well as all generic versions of these drugs.

B. STATEMENT OF GROUNDS

1. Background

Olmesartan medoxomil is one member of a class of medications called angiotensin II receptor blockers. It is a pro-drug that is metabolized in the gastrointestinal tract and liver to its active form: olmesartan.[1] The first olmesartan product[2] was approved by the FDA in 2002 for the treatment of hypertension.[3] Although serious gastrointestinal toxicity was not detected during preapproval clinical trials of olmesartan, the incidence of diarrhea, abdominal pain, and elevated

[1] Abraham HM, White CM, White WB. The comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases. *Drug Saf*. 2015;38(1): 33-54.
[2] For the remainder of this document, "olmesartan" and "olmesartan medoxomil" are used interchangeably.
[3] Daiichi Sankyo. Drug label: olmesartan medoxomil (BENICAR). November 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021286s036lbl.pdf. Accessed November 3, 2017.

liver enzymes was slightly higher in subjects receiving olmesartan than in those receiving a placebo in these trials.[4]

Seven other ARBs are marketed in the U.S., all of which are approved by the FDA for treatment of hypertension (see Table 1).

Table 1: List of angiotensin II receptor blockers

Generic Name	Brand Name Products
azilsartan medoxomil	Edarbi, Edarbyclor*
candesartan cilexetil	Atacand, Atacand HCT*
eprosartan mesylate	Teveten
irbesartan	Avalide,* Avapro
losartan	Cozaar, Hyzaar*
olmesartan medoxomil	Azor,* Benicar, Benicar HCT,* Tribenzor*
telmisartan	Micardis, Micardis HCT,* Twynsta*
valsartan	Byvalson,* Diovan, Diovan HCT,* Exforge,* Exforge HCT*

*Combination products

Olmesartan is marketed as a single agent under the brand name Benicar and in combination with hydrochlorothiazide (Benicar HCT), amlodipine (Azor), and both hydrochlorothiazide and amlodipine (Tribenzor). The FDA also has approved several generic formulations for each of these four brand-name products. All olmesartan-containing products are approved only for treatment of hypertension.

Certain other ARBs are approved by the FDA for the following additional indications:

- Treatment of diabetic nephropathy in hypertensive patients with type 2 diabetes, an elevated serum creatinine, and proteinuria (irbesartan,[5] losartan[6])
- Treatment of heart failure (candesartan,[7] valsartan[8])
- Reduction of the risk of stroke in patients with hypertension and left ventricular hypertrophy (losartan[9])

[4] Food and Drug Administration. Medical reviews for new drug application 21-286, olmesartan. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-286_Benicar_medr_P2.pdf. Accessed November 3, 2017. PDF pages 29-30, 31-32, 35-36, and 41.
[5] Sanofi-Aventis. Label: irbesartan (AVAPRO). February 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020757s059s067lbl.pdf. Accessed November 3, 2017.
[6] Merck & Co. Label: losartan (COZAAR). December 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020386s054lbl.pdf. Accessed November 3, 2017.
[7] AstraZeneca. Label: candesartan (ATACAND). February 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020838s039lbl.pdf. Accessed November 3, 2017.
[8] Novartis Pharmaceuticals. Label: valsartan (DIOVAN). January 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021283s50lbl.pdf. Accessed November 3, 2017.
[9] Merck & Co. Label: losartan (COZAAR). December 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020386s054lbl.pdf. Accessed November 3, 2017.

- Cardiovascular risk reduction in patients unable to take angiotensin-converting enzyme inhibitors (telmisartan[10])
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction (valsartan[11])

Randomized, double-blind clinical trials comparing olmesartan with other ARBs in general failed to demonstrate that olmesartan was consistently better than other ARBs at reducing blood pressure.[12,13,14,15,16,17,18] Depending on the drug doses tested and the duration of exposure, olmesartan had slightly greater, similar, or slightly less efficacy than the other ARBs in lowering blood pressure.

Olmesartan is widely prescribed. In 2011, 5.9 million prescriptions were filled for Benicar and 4.9 million prescriptions were filled for Benicar HCT.[19] In 2015, the number of filled prescriptions for Benicar and Benicar HCT decreased to 4.1 million and 3.0 million, respectively.[20] That same year, there were 1.5 million new prescriptions for Benicar and 1.1 million new prescriptions for Benicar HCT. In October 2016, the FDA approved the first generic version of olmesartan. In March 2017, the most recent date for which data are available, there were more than 400,000 total prescriptions for generic olmesartan.[21]

2. Initial published evidence linking olmesartan to sprue-like enteropathy

In August 2012, Rubio-Tapia et al. published a case series of 22 patients identified at the Mayo Clinic in Rochester, Minnesota over a 3-year period (August 1, 2008 to August 1, 2011) who had

[10] Boehringer Ingelheim Pharmaceuticals. Label: telmisartan (MICARDIS). December 2014. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020850s038lbl.pdf. Accessed November 3, 2017.
[11] Novartis Pharmaceuticals. Label: valsartan (DIOVAN). January 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021283s50lbl.pdf. Accessed November 3, 2017.
[12] Oparil S, Williams D, Chrysant SG, et al. Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. *J Clin Hypertens (Greenwich)*. 2001;3(5):283-291.
[13] Brunner HR, Stumpe KO, Januszewicz A. Antihypertensive efficacy of olmesartan medoxomil and candesartan cilexetil assessed by 24-hour ambulatory blood pressure monitoring in patients with essential hypertension. *Clin Drug Invest*. 2003;23(7):419-430.
[14] Smith DH, Dubiel R, Jones M. Use of 24-hours ambulatory blood pressure monitoring to assess antihypertensive efficacy: a comparison of olmesartan medoxomil, losartan potassium, valsartan, and irbesartan. *Am J Cardiovasc Drugs*. 2005;5(1):41-50.
[15] Giles TD, Oparil S, Silfani TN, et al. Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. *J Clin Hypertens (Greenwich)*. 2007;9(3):187-195.
[16] White WB, Weber MA, Sica D, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. *Hypertension*. 2011;57(3):413-420.
[17] Shiga Y, Miura S, Motozato K, et al. Comparison of efficacy and safety of azilsartan and olmesartan in patients with essential hypertension: A randomized and prospective study (CANZONE Study). *Int Heart J*. 2017;58(3):416-421.
[18] Kakio Y, Uchida HA, Umebayashi R, et al. Practical efficacy of olmesartan versus azilsartan in patients with hypertension: a multicenter randomized-controlled trial (MUSCAT-4 study). *Blood Press Monit*. 2017;22(2):59-67.
[19] IMS Health data. Obtained August 2, 2016.
[20] IMS Health data. Obtained August 2, 2016.
[21] IMS Health data. Obtained April 3, 2017.

been taking olmesartan and were hospitalized with chronic diarrhea (duration greater than 4 weeks) and weight loss without an identified cause.[22]

Rubio-Tapia et al. first suspected a linkage between olmesartan use and sprue-like enteropathy after two consecutive patients who were referred to the Mayo Clinic with presumed refractory celiac disease experienced symptom improvement during their hospital course (while antihypertensive treatment was withheld) followed by recurrence of symptoms after discharge (when medications were restarted). Also, in 2010, the researchers had reported that one-third of patients who were being followed and had a diagnosis of collagenous sprue were also found to be active users of olmesartan.[23]

Among the 22 patients in the 2012 cases series, 13 were female and nine were male, and they had a median age of 69.5 years (range 47 to 81 years). The patients reported having diarrhea for a median duration of 19 months (range three to 53 months) and had median weight loss of 18 kilograms (kg) (range 2.5 to 57 kg). Other commonly reported symptoms included nausea and vomiting, abdominal pain, bloating, and fatigue. Fourteen (64%) required hospitalization. Most of the patients had taken 40 milligrams (mg) of olmesartan per day (range 10 to 40 mg per day). Among the 14 patients for whom detailed information on the duration of exposure to the drug before onset of diarrhea was available in the medical record, the mean duration was 3.1 years (range 0.5 to 7 years). An additional five patients had taken the drug for at least one year before the onset of symptoms. The most frequent clinical diagnoses at time of referral to the Mayo Clinic were nonresponsive/refractory celiac disease (10 patients) and unexplained sprue (six patients).

In the Mayo Clinic researchers' analysis of olmesartan-treated patients with enteropathy, all were found to have negative serologic tests for IgA tissue transglutaminase antibody, a common antibody found in patients with celiac disease, and none of these patients saw improvement with introduction of a gluten-free diet, making celiac disease an unlikely cause of their disorder. A large number of patients in the cohort — 77 percent — tested positive for HLA DQ2, HLA DQ8, or both, which may increase the risk of immune-mediated damage in patients taking olmesartan. Intestinal biopsies revealed either total or partial villous atrophy with variable degrees of mucosal inflammation. Fifteen patients had active/acute mucosal inflammation, and increased intraepithelial lymphocytes were seen in 14 patients.

All 22 patients experienced a clinical response after discontinuing olmesartan, including 17 patients who had remission of symptoms. Of 18 patients who had follow-up duodenal biopsies after discontinuing the drug, 17 had normal histology, and one had improvement from total villous atrophy to partial focal villous atrophy. The Mayo Clinic researchers stated that no patients were deliberately rechallenged with olmesartan "because of the life-threatening nature of the syndrome,"[24] but four patients did experience a worsening of their symptoms when olmesartan use was resumed. Such positive rechallenges provide strong evidence for a causal

[22] Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*. 2012;87(8):732-738.
[23] Rubio-Tapia A, Talley NJ, Gurudu SR, et al. Gluten-free diet and steroid treatment are effective therapy for most patients with collagenous sprue. *Clin Gastroenterol Hepatol*. 2010;8(4):344-349.e3.
[24] *Ibid.*

relationship between exposure to a drug and an adverse reaction — in this case, olmesartan use and sprue-like enteropathy.

This 2012 Mayo Clinic case series study provided the first published evidence clearly linking olmesartan use with a risk of sprue-like enteropathy.

3. FDA assessments and actions

Before publishing their 2012 case series, Rubio-Tapia et al. reported to officials at the FDA their observations of patients with sprue-like enteropathy experiencing clinical and histologic recovery after discontinuing olmesartan. They also submitted MedWatch reports to the agency.[25]

In 2011, the FDA — presumably prompted by the reports from Rubio-Tapia et al. — observed an unexpectedly high number of reports in the FDA Adverse Event Reporting System (FAERS) of celiac disease in patients using olmesartan.[26] The agency subsequently requested a Mini-Sentinel rapid assessment that compared the incidence of celiac disease between users of olmesartan and users of other ARBs.[27] The Mini-Sentinel pilot program allowed the FDA to assess potential drug safety signals using electronic healthcare data from multiple sources for nearly 100 million individuals.[28] Results from the rapid assessment, which were released in January 2012, showed that, with limited adjustment for systematic errors, the risk of celiac disease with olmesartan use was not substantially higher than the risk with use of other ARBs.[29,30] Importantly, this Mini-Sentinel rapid assessment only analyzed the risk of celiac disease following exposure to an ARB for up to one year in new users of these drugs.[31] Following the release of these results, the FDA took no regulatory action regarding olmesartan.

However, in July 2013, the FDA issued a drug safety communication in which the agency concluded that "olmesartan medoxomil (marketed as Benicar, Benicar HCT, Azor, Tribenzor, and generics) **can cause intestinal problems known as sprue-like enteropathy**" [emphasis added].[32] The agency's conclusion was based on the following:

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[25] Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*. 2012;87(8):732-738.
[26] Toh S, Avorn J, D'Agostino RB Sr., et al. Re-using Mini-Sentinel data following rapid assessments of potential safety signals via modular analytic programs. *Pharmacoepidemiol Drug Saf*. 2013 Oct;22(10):1036-1045.
[27] *Ibid*.
[28] Food and Drug Administration. FDA's "Mini-Sentinel" safety pilot program is up and running, demonstrating rapid analysis of medical product safety questions. https://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM268035.pdf. Accessed November 3, 2017.
[29] Sentinel. Mini-Sentinel Modular Program Report: Angiotensin II Receptor Blockers and Celiac Disease. January 16, 2012. https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_Angiotensin-II-Receptor-Blockers-and-Celiac-Disease_0.pdf. Accessed November 3, 2017.
[30] Toh S, Avorn J, D'Agostino RB Sr., et al. Re-using Mini-Sentinel data following rapid assessments of potential safety signals via modular analytic programs. *Pharmacoepidemiol Drug Saf*. 2013 Oct;22(10):1036-1045.
[31] Sentinel. Mini-Sentinel Modular Program Report: Angiotensin II Receptor Blockers and Celiac Disease. January 16, 2012. https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_Angiotensin-II-Receptor-Blockers-and-Celiac-Disease_0.pdf. Accessed November 3, 2017.
[32] Food and Drug Administration. FDA drug safety communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil. July 3, 2013. https://www.fda.gov/Drugs/DrugSafety/ucm359477.htm. Accessed November 3, 2017.

(1) An analysis of FDA FAERS data: In reviewing the FAERS database, the FDA identified 23 cases of serious late-onset diarrhea with significant weight loss in patients taking olmesartan. In some of the cases, intestinal villous atrophy was seen on biopsy.[33] In each case, the patient improved clinically after discontinuing the medication. Notably, 10 of these patients had recurrence of their symptoms following rechallenge with olmesartan.

(2) A review of two case series published in the scientific medical literature:

(a) The Mayo Clinic case series published in August 2012 (see above);[34] and

(b) A case series from Columbia University Medical Center in New York, New York published in May 2013:[35] DaGaetani et al. identified 72 patients from 2001 to 2011 who were found to have villous atrophy on duodenal biopsies with no evidence of positive serologic tests for celiac disease. Nineteen (26%) of the patients had medication-related villous atrophy, the second-most common cause identified, and for sixteen of these patients (eight male, eight female; median age 66.5 years, range 52 to 83 years), the enteropathy was attributed to olmesartan use. Eleven of the 16 olmesartan-treated patients had intestinal biopsies consistent with collagenous celiac sprue. All 15 patients who had follow-up data available (out of the 16 identified with villous atrophy linked to olmesartan use) had clinical improvement after cessation of olmesartan. One patient had a recurrence of symptoms following rechallenge with olmesartan.

(3) An assessment of Mini-Sentinel and Centers for Medicare and Medicaid Services (CMS) data: Prompted by the link between sprue-like enteropathy and olmesartan use that was seen in FAERS reports and published case series, the FDA again queried the Mini-Sentinel database, as well as CMS Medicare data, for celiac disease (as a marker for enteropathy and other gastrointestinal symptoms) after exposure to ARBs.[36,37] The analysis included exposure to ARBs, as well as to three non-ARB hypertension drugs — hydrochlorothiazide, atenolol, and amlodipine — for a minimum of two years. The Mini-Sentinel and CMS Medicare analyses revealed that at a two-year minimum exposure, which correlated with the long latency observed in the published cases series and FAERS case reports, olmesartan users had a higher rate of celiac disease diagnoses in claims and

[33] *Ibid*.
[34] Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*. 2012;87(8):732-738.
[35] DaGaetani M, Tennyson CA, Lebwohl B, et al. Villous atrophy and negative celiac serology: A diagnostic and therapeutic dilemma. *Am J Gastroenterol*. 2013;108(5):647-653.
[36] Food and Drug Administration. FDA drug safety communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil. July 3, 2013. https://www.fda.gov/Drugs/DrugSafety/ucm359477.htm. Accessed November 3, 2017.
[37] Sentinel. Mini-Sentinel Modular Program Report: Angiotensin Receptor Blockers (ARBs), Hydrochlorothiazide, Atenolol, Amlodipine Use and Celiac Disease. June 7, 2013. https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_Modular-Program-Report_MSY3_MPR34_ARBs-HCTZ-Atenolol-Amlodipine-Celiac-Disease_0.pdf. Accessed November 3, 2017.

> administrative data than users of other ARBs and the three non-ARB hypertension drugs. These results supported other data that suggested a lack of a class effect.

In its July 2013 drug safety communication, the FDA noted that sprue-like enteropathy may develop months to years after starting olmesartan and sometimes requires hospitalization. The agency advised that if patients taking olmesartan develop symptoms of enteropathy and no other cause is found, the drug should be discontinued, and therapy with another antihypertensive should be started. The agency also required the addition of the following warning to the product labeling for olmesartan products:[38]

> **Sprue-like Enteropathy**
>
> Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, exclude other etiologies. Consider discontinuation of [olmesartan] in cases where no other etiology is identified.

However, given (a) the severity of olmesartan-induced sprue-like enteropathy and (b) the availability of multiple other ARBs and non-ARB medications approved for treating hypertension that have more favorable risk-benefit profiles, merely adding a weak warning to the labeling of olmesartan-containing products was seriously deficient from a public health perspective.

4. Accumulating evidence of harm from olmesartan-induced sprue-like enteropathy

Since 2013, additional evidence demonstrating that olmesartan causes sprue-like enteropathy has been published in the scientific medical literature, including a cohort study, a systematic review, case series, and case reports. Data from these publications are summarized below.

Cohort study

Basson et al. conducted a nationwide observational cohort study using the French National Health Insurance claim database to assess the risk of hospitalization for intestinal malabsorption associated with olmesartan compared with other ARBs and with angiotensin-converting enzyme (ACE) inhibitors.[39] They identified 4.5 million adult patients who had initiated an ARB or ACE inhibitor from January 2007 to December 2012 and who had no prior hospitalization for intestinal malabsorption, serologic testing for celiac disease, or a prescription for a gluten-free diet. The primary endpoint was the incidence of hospitalization with a discharge diagnosis of intestinal malabsorption, and the secondary outcome was hospitalization with a discharge diagnosis of celiac disease. Key results were as follows:

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[38] Daiichi Sankyo. Label: olmesartan medoxomil (BENICAR). July 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021286s027lbl.pdf. Accessed November 3, 2017.

[39] Basson M, Mezzarobba M, Weill A, et al. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. *Gut*. 2016;65(10):1664-1669.

- Olmesartan was associated with an adjusted rate ratio of 2.49 (95% confidence interval [CI] 1.73 to 3.57, p<0.0001) for hospitalization with a discharge diagnosis of intestinal malabsorption compared with ACE inhibitors and a rate ratio of 3.17 (95% CI 2.22 to 4.53, p<0.0001) compared with other ARBs.
- ARBs other than olmesartan were associated with a non-significant rate ratio of 0.78 (95% CI 0.58 to 1.07, p=0.12) for hospitalization with a discharge diagnosis of intestinal malabsorption compared with ACE inhibitors.
- Olmesartan was associated with an adjusted rate ratio 4.39 (95% CI 2.77 to 6.96, p<0.0001) for hospitalization with a discharge diagnosis of celiac disease compared with ACE inhibitors and an adjusted rate ratio of 4.82 (95% CI 3.12 to 7.45, p<0.0001) compared with other ARBs.
- ARBs other than olmesartan were associated with a non-significant rate ratio of 0.91 (95% CI 0.58 to 1.42, p=0.68) for hospitalization with a discharge diagnosis of celiac disease compared with ACE inhibitors.
- Compared with ACE inhibitors, the adjusted rate ratio of hospitalization with a discharge diagnosis of intestinal malabsorption associated with olmesartan exposure was 0.76 (95% CI 0.39 to 1.49, p=0.43) for treatment duration shorter than 1 year, 3.66 (95% CI 1.84 to 7.29, p<0.001) for treatment duration between 1 and 2 years, and 10.65 (95% CI 5.05 to 22.46, p<0.0001) for treatment duration beyond 2 years.

Basson et al. estimated that the number needed to harm beyond two years of olmesartan exposure was one additional case of enteropathy per 12,500 patient-years. However, they cautioned that their study underestimated the true incidence of olmesartan-related enteropathy and only provided the incidence of the most severe forms of enteropathy associated with olmesartan use.[40]

Systematic review

In 2016, Burbure et al. published the largest relevant systematic review analyzing data from seven published case series (including the initial case series at the Mayo Clinic by Rubio-Tapia et al. and at Columbia University Medical Center by DaGaetani at al. described above) and eight published single-patient case reports of olmesartan-associated sprue-like enteropathy.[41] The review included a total of 104 patients who had received olmesartan for durations ranging from less than one month to more than 11 years prior to onset of symptoms. Ninety-five percent of the patients had resolution of symptoms or clinical improvement after discontinuing olmesartan.

Burbure et al. focused on the histopathology of olmesartan-associated sprue-like enteropathy. Total or subtotal small bowel villous atrophy was seen in 68 percent of the patients, partial villous atrophy in 24 percent, and nonspecified villous atrophy in 3 percent. Also, a substantial proportion of patients had findings of small bowel intraepithelial lymphocytosis (70% of 96 patients evaluated) and collagenous sprue (30% of 73 patients evaluated), as well as microscopic colitis (32% of 73 patients evaluated). Descriptions of the case series and selected case reports not previously discussed are presented below and summarized in Table 2.

[40] *Ibid*.
[41] Burbure N, Lebwohl B, Arguelles-Grande C, et al. Olmesartan-associated sprue-like enteropathy: a systematic review with emphasis on histopathology. *Human Path*. 2016; 50:127-134.

Table 2: Summary of case series and selected case reports (adapted from Burbure et al.)[42]

Source	N	Length of olmesartan use before symptoms	HLA DQ2 and/or DQ8 positive	Small bowel villous atrophy	IEL	Collagenous sprue	Microscopic colitis	Lymphocytic or collagenous gastritis	Clinical response to drug cessation
Rubio-Tapia et al., 2012[43]	22	0.5-7 years (14)†	81% (21)	68% TVA 32% PVA	64%	32%	38% (13)	50% (14)	100%
DeGaetani et al., 2013[44]	16	N/A	92% (13)	50% TVA 12% STVA 19% PVA 19% NSVA	69%	69%	N/A	N/A	100% (15)
Marthey et al., 2014[45]	36	<1 month-11.6 years	63% (19)	72% TVA/STVA 17% PVA 11% No VA	68% (28)	8% (26)	19%	N/A	92%
Theophile et al., 2014[46]	5	N/A	N/A	40% STVA 40% PVA 20% No VA	40%	N/A	0%	0% (1)	100%
Bhat et al., 2014[47]	7	0.5-5 years	N/A	43% TVA 57% PVA	100%	N/A	100% (1)	N/A	100%
Ianiro et al., 2014[48]	3	3 years (1)	0%	67% TVA 33% PVA	0%	N/A	N/A	N/A	100%
Scialom et al., 2015[49]	7	2-10 years	67% (6)	57% TVA 43% STVA	100%	14%	0%	14%	67% (6)
Marco-Marqués et al., 2015[50]	11	1 month-10 years	100% (9)	N/A	N/A	N/A	N/A	N/A	100%
Sáez-González et al., 2016.[51]	12	1-5 years	42%	33% SVA 8% PVA 58% MVA	58%	N/A	100% (9)	N/A	100%
Adike et al., 2016[52]††	3	6 months-10 years	DQ2 positive (1)	100% NSVA	100%	N/A	50% (2)	N/A	100%
Ebrahim et al., 2017[53]††	3	2-2.5 years (2)	N/A	100% NSVA	100% (2)	N/A	100% (2)	100% (2)	100%

[42] *Ibid.*

[43] Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*. 2012;87(8):732-738.

[44] DaGaetani M, Tennyson CA, Lebwohl B, et al. Villous atrophy and negative celiac serology: A diagnostic and therapeutic dilemma. *Am J Gastroenterol*. 2013;108(5):647-653.

[45] Marthey L, Cadiot G, Seksik P, et al. Olmesartan-associated enteropathy: results of a national survey. *Aliment Pharmacol Ther* 2014;40(9):1103-1109.

[46] Theophile H, David XR, Miremont-Salame G, Haramburu F. Five cases of sprue-like enteropathy in patients treated by olmesartan. *Dig Liver Dis*. 2014;46(5):465-469.

[47] Bhat N, Anupama NK, Yelsangikar A, Vizhi K. Olmesartan-related sprue-like enteropathy. *Indian J Gastroenterol.* 2014;33(6):564-567.

[48] Ianiro G, Bibbo S, Montalto M, et al. Systematic review: sprue-like enteropathy associated by with olmesartan. *Aliment Pharmacol Ther*. 2014; 40(1):16-23.

[49] Scialom S, Malamut G, Meresse B, et al. Gastrointestinal disorder associated with olmesartan mimics autoimmune enteropathy. *PLoS One*. 2015;10(6):e0125024.

[50] Marco-Marqués A, Sanahuja-Martinez A, Bosca-Watts MM, et al. Could HLA-DQ suggest why some patients have olmesartan-related diarrhea and others don't? *Am J Gastroenterol*. 2015;110(10):1507-1508.

[51] Sáez-González E, Díaz Jaime FC, Del Val Antoñana A. Clinical, laboratory, serological, and histological profile of sprue-like enteropathy associated with olmesartan use. *Rev Esp Enferm Dig*. 2016;108(10):685-686.

[52] Adike A, Corral J, Rybnicek D, et al. Olmesartan-induced enteropathy. *Methodist Debakey Cardiovasc J*. 2016;12(4):230-232.

[53] Ebrahim VS, Martin J, Murthy S, et al. Olmesartan-associated enteropathy. *Proc (Bayl Univ Med Cent)*. 2017;30(3):348-350.

Source	N	Length of olmesartan use before symptoms	HLA DQ2 and/or DQ8 positive	Small bowel villous atrophy	IEL	Collagenous sprue	Microscopic colitis	Lymphocytic or collagenous gastritis	Clinical response to drug cessation
Roca-Argente et al., 2017[54]††	19	9 months-7 years	N/A	N/A	N/A	N/A	N/A	N/A	100%
de Fonseka et al., 2012[55]	1	6.5 years	No	TVA	Yes	N/A	Yes	N/A	Yes
Nielsen et al., 2013[56]	1	N/A	DQ2 positive	TVA	Yes	Yes	N/A	N/A	Yes
Stanich et al., 2013[57]	1	N/A	No	TVA	Yes	N/A	Yes	N/A	Yes
Dreifuss et al., 2013[58]	1	N/A	No	PVA	Yes	No	No	N/A	Yes
Khan et al., 2014[59]	1	2 years	No	TVA	No	N/A	N/A	N/A	Yes
Fiorucci et al., 2014[60]	1	4 years	DQ2 positive	TVA	Yes	N/A	Yes	Yes	Yes
Gaur et al, 2014[61]	1	1 year	N/A	PVA	Yes	N/A	Yes	Yes	Yes
Heerasing et al., 2015[62]	1	6 months	DQ2 positive	TVA	Yes	N/A	N/A	N/A	Yes
Talbot, 2012[63]††	1	No symptoms	DQ2 positive	NSVA	Yes	N/A	No	N/A	N/A
Tran and Li, 2014[64]††	1	N/A	No	NSVA	Yes	N/A	No	N/A	Yes
Martins et al., 2016[65]††	2	4-5.5 years	N/A	100% PVA	100%	N/A	0%	N/A	100%
Machado et al., 2016[66]††	1	5.5 years	DQ2 positive	TVA	Yes	N/A	N/A	N/A	Yes (post steroids)
Uehara et al., 2016[67]††	1	3 years	N/A	NSVA	Yes	N/A	N/A	Atrophic gastritis	Yes

[54] Roca-Argente L, Diaz-Jaime FC, López-Romero LC, et al. Acute kidney injury secondary to diarrhea caused by "sprue-like" enteropathy associated with olmesartan. *Nefrologia*. 2017;37(5):548-550.
[55] deFonseka A, Tuskey A, Moskaluk C. A case of olmesartan induced enteropathy. *Inflamm Bowel Dis*. 2012;18(Supl 1):S17.
[56] Nielsen JA, Steephen A, Lewin M. Angiotensin-II inhibitor (olmesartan)–induced collagenous sprue with resolution following discontinuation of drug. *World J Gastroenterol*. 2013;19(40):6928-6930.
[57] Stanich PP, Yearsley M, Meyer MM. Olmesartan-associated sprue-like enteropathy. *J Clin Gastroenterol*. 2013;47(10):894-895.
[58] Dreifuss SE, Tomizawa Y, Farber NJ, et al. Spruelike enteropathy associated with olmesartan: An unusual case of severe diarrhea. *Case Rep Gastrointest Med*. 2013;2013:618071.
[59] Khan AS, Peter S, Wilcox CM. Olmesartan-induced enteropathy resembling celiac disease. *Endoscopy*. 2014;46(Suppl. 1 UCTN):E97-98.
[60] Fiorucci G, Puxeddu E, Colella R, et al. Severe spruelike enteropathy due to olmesartan. *Rev Esp Enferm Dig*. 2014;106(2):142-144.
[61] Gaur V, Albeldawi M, Weber L. Chronic diarrhea and weight loss. *Gastroenterology*. 2014;146(2):347, 591.
[62] Heerasing N, Hair C, Wallace S. Olmesartan-induced enteropathy. *Intern Med J*. 2015;45(1):117-118.
[63] Talbot GH. Small bowel histopathologic findings suggestive of celiac disease in an asymptomatic patient receiving olmesartan. *Mayo Clin Proc*. 2012;87(12):1231-1232.
[64] Tran TH, Li H. Olmesartan and drug-induced enteropathy. *PT*. 2014;39(1):47-50.
[65] Martins C, Teixeira C, Ribeiro S, et al. Seronegative intestinal villous atrophy: A diagnostic challenge. *Case Rep Gastrointest Med*. 2016;2016:6392028.
[66] Machado I, Reolid M, Martinez de Juan F, et al. Sprue-like enteropathy associated with olmesartan in a patient with villous atrophy, HLA-DQ2 genotype and antinuclear antibodies. *Rev Esp Enferm Dig*. 2016 Nov;108(11):732-733.
[67] Uehara T, Ikusaka M, Ohira Y, et al. Olmesartan-induced Enteropathy Manifesting as Wernicke-Korsakoff Syndrome. *Intern Med*. 2016;55(24):3675-3678.

Source	N	Length of olmesartan use before symptoms	HLA DQ2 and/or DQ8 positive	Small bowel villous atrophy	IEL	Collagenous sprue	Microscopic colitis	Lymphocytic or collagenous gastritis	Clinical response to drug cessation
Galanopoulos et al., 2017[68††]	2	1 year	0% (1)	100% NSVA	0% (1)	0% (1)	0% (1)	N/A	100%

Abbreviations: IEL, intraepithelial lymphocytosis; MVA, mild villous atrophy; N/A, not available; NSVA, nonspecified villous atrophy; PVA, partial villous atrophy; STVA, subtotal villous atrophy; SVA, severe villous atrophy; TVA, total villous atrophy; VA, villous atrophy.
[†]Values in parentheses indicate number of patients evaluated for a given characteristic.
[††]Additional case series and case reports not included in systematic review by Burbure et al.

Additional case series

In 2014, Marthey et al. published the largest case series of patients with olmesartan-associated sprue-like enteropathy, which was based on a national survey of French gastroenterologists.[69] The survey identified 36 patients in France who were found to have olmesartan-associated enteropathy with abnormal duodenal biopsies, including 32 patients with villous atrophy and four with no villous atrophy. The following demographic and clinical features were reported for the patients in the Marthey et al. case series:

- Twenty patients (56%) were women.
- The median age was 70 years (range 46 to 91 years) for those patients with villous atrophy; for patients without villous atrophy, the age range was 55 to 74 years (median was not reported).
- Patients with villous atrophy took olmesartan for a median duration of 28 months (range 2 to 139 months) before symptoms began; patients without villous atrophy took olmesartan for a median duration of 49 months (range 0 to 114 months) before symptom onset.
- All patients reported diarrhea, 75 percent reported abdominal pain, and 53 percent had vomiting. Weight loss was common and ranged as high as 48 percent of body weight. The median duration of symptoms was 10 months.
- Thirty-one patients (86%) had hypokalemia and 25 (69%) had acute renal failure, including one who required dialysis.
- Nearly all patients had negative serologic tests for celiac disease, and 12 of 19 tested (63%) were HLA DQ2 or DQ8 positive.
- Thirty-four patients (94%) were hospitalized, and six (17%) required intensive care.
- Thirty-three patients (92%) had clinical remission following discontinuation of olmesartan (some also received steroids or other immunosuppressants).
- Thirteen of 14 patients who did not receive steroids or other immunosuppressants had clinical remission following discontinuation of olmesartan, and nine of 10 patients who were rechallenged with olmesartan had clinical relapse.

[68] Galanopoulos M, Varytimiadis L, Tsigaridas A, et al. Small bowel enteropathy associated with olmesartan medoxomil treatment. *Ann Gastroenterol*. 2017;30(1):131-133.
[69] Marthey L, Cadiot G, Seksik P, et al. Olmesartan-associated enteropathy: results of a national survey. *Aliment Pharmacol Ther* 2014;40(9):1103-1109.

- Fifteen patients who had duodenal villous atrophy on initial evaluation had follow-up duodenal biopsies a median of 9 months (range 2 to 39 months) after olmesartan cessation. In all cases, the repeat biopsy results were normal.

The following additional smaller case series involving three or more patients have been published since 2014:

- A French case series by Theophile et al. discussed five patients (three men, two women) diagnosed with sprue-like enteropathy associated with olmesartan use from 2010 to 2013.[70] All were elderly (age range 79 to 87 years) and were hospitalized for severe diarrhea and significant weight loss or dehydration. Two patients had renal failure. Villous atrophy was seen on intestinal biopsies in four of the patients. Olmesartan was discontinued and symptoms fully resolved in all patients; two patients who restarted olmesartan had recurrence of symptoms requiring re-hospitalization, after which symptoms again resolved once the medication was stopped.

- In 2013, Bhat et al. reported seven patients (three male, four female) in India with median age 63 years (range 48 to 83 years) who were found to have sprue-like enteropathy caused by olmesartan use.[71] Patients had taken olmesartan for a period of 6 months to 5 years before symptoms began. All patients had diarrhea, bloating, nausea, abdominal discomfort, and weight loss. All had evidence of villous atrophy and increased intraepithelial lymphocytes on duodenal biopsies. All patients had improvement of symptoms after discontinuing olmesartan, and the two patients who had follow-up duodenal biopsy were found to have improved villous morphology and decreased lymphocytic infiltration on histopathology.

- A systematic review published by Ianiro et al. that included significantly fewer patients than the systematic review by Burbure et al. described a case series of three additional patients (two male, one female) who presented with olmesartan-related sprue-like enteropathy.[72] The patients' ages ranged from 59 to 78 years. Symptoms reported among the three patients included severe diarrhea, weight loss, fatigue, and dyspnea. Serologic testing for celiac disease was negative in all three patients, and duodenal histopathology revealed partial or complete villous atrophy in all three patients. All three patients had clinical resolution following cessation of olmesartan use.

- Seven patients (three male, four female) with olmesartan-associated enteropathy were identified by Scialom et al. in another French case series.[73] The median age of the patients, who were referred to a single medical center between 2000 and 2014, was 72

[70] Theophile H, David XR, Miremont-Salame G, Haramburu F. Five cases of sprue-like enteropathy in patients treated by olmesartan. *Dig Liver Dis*. 2014;46(5):465-469.
[71] Bhat N, Anupama NK, Yelsangikar A, Vizhi K. Olmesartan-related sprue-like enteropathy. *Indian J Gastroenterol.* 2014;33(6):564-567.
[72] Ianiro G, Bibbo S, Montalto M, et al. Systematic review: sprue-like enteropathy associated by with olmesartan. *Aliment Pharmacol Ther*. 2014; 40(1):16-23.
[73] Scialom S, Malamut G, Meresse B, et al. Gastrointestinal disorder associated with olmesartan mimics autoimmune enteropathy. *PLoS One*. 2015;10(6):e0125024.

years (range 60 to 79 years), and their symptoms began 2 to 10 years after beginning treatment with olmesartan. All had chronic diarrhea with malnutrition and were unresponsive to a gluten-free diet. Duodenal biopsies from all patients showed total or subtotal villous atrophy and epithelial lymphocyte infiltration. All patients received steroids and other immunosuppressants (including anti-TNF-α antibodies in six patients), which in all but one patient were started while they were still taking olmesartan. One patient refused to discontinue olmesartan and required immunosuppressive therapy to control diarrhea. Four patients who had achieved remission with immunosuppression treatment while still taking olmesartan sustained their remission following withdrawal of immunosuppressive therapy and cessation of olmesartan. One patient had already stopped taking olmesartan prior to starting immunosuppressive therapy, but diarrhea persisted; this patient achieved remission following treatment with anti-TNF-α antibodies. The seventh patient who began immunosuppressive therapy while using olmesartan relapsed after the immunosuppressive therapy was discontinued despite cessation of olmesartan. This patient achieved remission following another course of immunosuppressive therapy.

- Marco-Marqués et al. described 11 patients (four male, seven female) with olmesartan-induced enteropathy who were evaluated at a single medical center in Spain from April 2014 to April 2015.[74] The patients had a median age of 72 years (range 58 to 79 years). The most common symptom was diarrhea lasting one to 16 months. Other symptoms included weight loss, abdominal pain, nausea, and vomiting. Patients had been taking olmesartan for a median of 36 months (range 1 to 119 months) prior to onset of symptoms. Nine patients were hospitalized, and 6 had acute renal failure. Celiac serology tests were negative in 10 patients and positive in one, and nine patients tested positive for HLA DQ2 or DQ8. Ten of the patients had duodenal mucosal changes including villous atrophy. All patients experienced clinical improvement after discontinuation of olmesartan. Some patients required corticosteroid treatment (four out of 11 patients) or a gluten-free diet (three out of 11 patients) but maintained their clinical responses after discontinuation of steroids or resumption of a gluten-containing diet.

- Sáez-González et al. published an observation study of 12 patients who presented with olmesartan-associated sprue-like enteropathy at a single hospital in Spain from 2013 to 2015.[75] The patients (three male, nine female) had a mean age of 67 years (range 47 to 87 years). The patients had diarrhea and weight loss, and all were hospitalized with severe illness, including prerenal kidney failure electrolyte imbalance and malnutrition. The patients had been taking olmesartan for one to five years. Serologic testing for celiac disease was negative. Five patients (42%) tested positive for HLA DQ2 or DQ8. All patients had villous atrophy on duodenal biopsies. All patients showed clinical and pathohistological improvement after olmesartan was discontinued.

[74] Marco-Marqués A, Sanahuja-Martinez A, Bosca-Watts MM, et al. Could HLA-DQ suggest why some patients have olmesartan-related diarrhea and others don't? *Am J Gastroenterol*. 2015;110(10):1507-1508.
[75] Sáez González E, Díaz Jaime FC, Del Val Antoñana A. Clinical, laboratory, serological, and histological profile of sprue-like enteropathy associated with olmesartan use. *Rev Esp Enferm Dig*. 2016;108(10):685-686.

- Adike et al. reported three female patients (ages 66 to 69 years) who had symptoms of chronic diarrhea, weight loss, or both while being treated with olmesartan.[76] Time of exposure to olmesartan prior to symptom onset ranged from six months to 10 years. All patients had negative serologic tests for celiac disease. Duodenal biopsies revealed villous atrophy and increased lymphocytes in all three patients. One patient had microscopic colitis. Two patients received immunosuppressive therapy with glucocorticoids, azathioprine, or both. All patients improved with cessation of olmesartan, and two patients remained in clinical remission after switching to losartan.

- A case series of three patients with olmesartan-related enteropathy was reported by Ebrahim et al.[77] The patients, ranging in age from 57 to 72 years, presented with chronic diarrhea and other symptoms, such as abdominal pain, bloating, and weight loss. Symptoms began after 2 to 2.5 years of olmesartan use in two patients (exposure duration was not explicitly reported for the third patient). All patients had duodenal villous atrophy, and two were reported to have intraepithelial lymphocytosis. Colon biopsies from two patients revealed lymphocytic and collagenous colitis. Symptoms resolved in all three patients following cessation of olmesartan, with evidence of histologic recovery on follow-up biopsies with two patients. One patient had immediate return of diarrhea after a single dose of olmesartan but full resolution after olmesartan was again discontinued.

- A case series of 19 patients focusing on acute kidney injury in olmesartan-related enteropathy was published by Roca-Argente et al. in 2017.[78] In this case series, 10 male and nine female patients, with a median age of 70 years (range 56 to 88 years), were identified with chronic diarrhea while taking olmesartan. The patients, who were treated at a single hospital in Spain from 2012 to 2016, had taken olmesartan for a mean period of 30 months (range 9 to 84 months). Serologic testing for celiac disease was negative in all patients. Fourteen of the 19 patients had evidence of acute kidney injury — including 9 patients who had stage 3 acute kidney injury, the most severe stage — caused by dehydration secondary to diarrhea from the enteropathy. In all cases, cessation of olmesartan resulted in symptomatic improvement. Though initial histopathology findings were not reported for patients, it was noted by the authors that 12 patients who underwent follow-up histopathologic assessments had evidence of full tissue recovery. (This case series may have included the 12 patients in the Sáez-González et al. case series.)

Individual Case reports

Numerous reports of one or two individual cases of olmesartan-induced sprue-like enteropathy also have been published since the initial 2012 case series by Rubio-Tapia et al. Table 2 provides a summary of a selected sample of 16 of these cases (see Appendix for additional case reports).

[76] Adike A, Corral J, Rybnicek D, et al. Olmesartan-induced enteropathy. *Methodist Debakey Cardiovasc J*. 2016;12(4):230-232.
[77] Ebrahim VS, Martin J, Murthy S, et al. Olmesartan-associated enteropathy. *Proc (Bayl Univ Med Cent)*. 2017;30(3):348-350.
[78] Roca-Argente L, Diaz-Jaime FC, López-Romero LC, et al. Acute kidney injury secondary to diarrhea caused by "sprue-like" enteropathy associated with olmesartan. *Nefrologia*. 2017;37(5):548-550.

The clinical features of these cases generally were very similar to those reported in the case series summarized above. Of note, in nearly all cases in which olmesartan was discontinued, the patients' symptoms improved or resolved. In at least one case, the patient's symptoms relapsed upon rechallenge with olmesartan.[79]

In one unusual published case report, a patient being evaluated for symptoms of gastroesophageal reflux who had been treated with olmesartan for three years for hypertension was found to have villous atrophy and intraepithelial lymphocytosis on duodenal biopsy.[80] The patient did not have symptoms of sprue-like enteropathy, such as diarrhea and weight loss, as was seen in all other reported cases. This case demonstrates that the spectrum for the clinical presentation of olmesartan-induced sprue-like enteropathy can range from asymptomatic to severe and life-threatening.

5. Cases of non-olmesartan angiotensin II receptor blockers associated with sprue-like enteropathy

There have been a very small number of case reports of patients developing sprue-like enteropathy while taking ARBs other than olmesartan. Zanelli et al. recently published a summary of seven previously published case reports of such patients[81,82,83,84,85,86,87] and presented five additional cases that they had observed.[88] The implicated ARBs included eprosartan, irbesartan, losartan, telmisartan, and valsartan.

Although these case reports describe clinical presentations of enteropathy with non-olmesartan ARBs that are very similar to olmesartan-induced enteropathy, the available epidemiologic

[79] Uehara T, Ikusaka M, Ohira Y, et al. Olmesartan-induced enteropathy manifesting as Wernicke-Korsakoff Syndrome. *Intern Med*. 2016;55(24):3675–3678.
[80] Talbot GH. Small bowel histopathologic findings suggestive of celiac disease in an asymptomatic patient receiving olmesartan. *Mayo Clin Proc*. 2012;87(12):1231-1232.
[81] Marthey L, Cadiot G, Seksik P, et al. Olmesartan-associated enteropathy: results of a national survey. *Aliment Pharmacol Ther*. 2014;40:1103-1109.
[82] Cyrany J, Vasatko T, Machac J, et al. Letter: telmisartan-associated enteropathy – is there any class effect? *Aliment Pharmacol Ther.* 2014;40(5):569-570.
[83] Cammarota G, Ianiro G, Bibbo S, Gasbarrini A. Letter: telmisartan-associated enteropathy – is there any class effect? Authors' reply. *Aliment Pharmacol Ther*. 2014;40(5):570.
[84] Herman ML, Rubio-Tapia A, Wu TT, Murray JA. A case of severe sprue-like enteropathy associated with valsartan. *ACG Case Rep J*. 2015;2(2):92-94.
[85] Maier I, Hehemann K, Vieth M. Celiac disease-like enteropathy due to antihypertensive therapy with the angiotensin-II receptor Type 1inhibitor eprosartan. *Cesk Patol*. 2015;51(2):87-88.
[86] Negro A, Rossi GM, Santi R, et al. A case of severe sprue-like enteropathy associated with losartan. *J Clin Gastroenterol*. 2015;49(9):794
[87] Mandavdhare HS, Sharma V, Prasad KK, et al. Telmisartan-induced sprue-like enteropathy: a case report and a review of patients using non-olmesartan angiotensin receptor blockers. *Intest Res*. 2017;15(3):419-421.
[88] Zanelli M, Negro A, Santi R, et al. Letter: sprue-like enteropathy associated with angiotensin II receptor blockers other than olmesartan. *Aliment Pharmacol Ther*. 2017;46(4):471-473.

evidence indicates that risk of sprue-like enteropathy is significantly higher with olmesartan than with all other ARBs.[89,90,91]

It is also quite notable that for some reported cases of olmesartan-induced sprue-like enteropathy, symptoms of enteropathy remained in remission after the patients were switched to another ARB.[92]

6. Potential mechanism of action causing olmesartan-related enteropathy

The pathophysiology of sprue-like enteropathy seen in patients taking olmesartan is not known. However, a review of common laboratory and histopathologic findings among the aforementioned studies may provide initial insight into this potential mechanism. In many of the studies, symptom onset occurred many years after initiation of olmesartan. It is suspected that the substantial delay in symptoms after medication initiation may indicate a process in which cell-mediated immunity causes damage.[93]

Some observers have speculated that olmesartan may trigger an immune-mediated enteropathy through its inhibitory effects on transforming growth factor-β, a major cytokine that plays a role in gut immune homeostasis.[94]

An immunohistochemistry analysis was performed by Marietta et al. using duodenal biopsy samples from patients with olmesartan-related enteropathy to evaluate the pathogenesis of enteropathy in these patients.[95] Biopsy samples were collected before and after discontinuation of olmesartan. Duodenal samples taken from patients taking olmesartan were noted to have increases in CD8+ cells and cells positive for FoxP3, a regulatory T-cell marker, in the duodenum compared with samples taken from patients who had discontinued the drug. Samples collected from patients taking olmesartan also had higher levels of expression of the interleukin-15 (IL-15) receptor, which suggests that the inflammatory cytokine IL-15 may play a role in the pathogenesis of the enteropathy.

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[89] Food and Drug Administration. FDA drug safety communication: FDA approves label changes to include intestinal problems (sprue-like enteropathy) linked to blood pressure medicine olmesartan medoxomil. July 3, 2013. https://www.fda.gov/Drugs/DrugSafety/ucm359477.htm. Accessed November 3, 2017.

[90] Sentinel. Mini-Sentinel Modular Program Report: Angiotensin Receptor Blockers (ARBs), Hydrochlorothiazide, Atenolol, Amlodipine Use and Celiac Disease. June 7, 2013. https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_Modular-Program-Report_MSY3_MPR34_ARBs-HCTZ-Atenolol-Amlodipine-Celiac-Disease_0.pdf. Accessed November 3, 2017.

[91] Basson M, Mezzarobba M, Weill A, et al. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. *Gut*. 2016;65(10):1664-1669.

[92] Adike A, Corral J, Rybnicek D, et al. Olmesartan-Induced Enteropathy. Methodist Debakey Cardiovasc J. 2016 Oct-Dec;12(4):230-232.

[93] Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe spruelike enteropathy associated with olmesartan. *Mayo Clin Proc*. 2012;87(8):732-738.

[94] Scialom S, Malamut G, Meresse B, et al. Gastrointestinal disorder associated with olmesartan mimics autoimmune enteropathy. *PLoS One*. 2015;10(6):e0125024.

[95] Marietta EV, Nadeau AM, Cartee AK, et al. Immunopathogenesis of olmesartan-associated enteropathy. *Aliment Pharmacol Ther*. 2015;42(11-12):1303-1314.

7. Conclusions

There is now overwhelming evidence that olmesartan causes sprue-like enteropathy and that the risk of this life-threatening complication is far greater with olmesartan than with all other ARBs.

Since 2012, case series and case reports published in the scientific medical literature have documented more than 150 patients worldwide with sprue-like enteropathy linked to olmesartan use. Numerous cases involving remission of enteropathy symptoms after discontinuation of olmesartan followed by rapid relapse of symptoms upon rechallenge with the drug provide the strongest evidence for a causal link between the drug and enteropathy. Indeed, the FDA itself concluded in 2013 that olmesartan causes sprue-like enteropathy based on a review of 23 cases of olmesartan-associated enteropathy reported to the FAERS database, including 10 cases that had a positive rechallenge; two published case series; and an assessment of Mini-Sentinel and CMS data.

Although there have been a handful of reported cases of sprue-like enteropathy associated with other ARBs, the best available evidence — including the FDA's 2013 analyses of Mini-Sentinel and CMS Medicare data and the French nationwide observational cohort study conducted by Basson et al. — demonstrate that the risk of enteropathy seen with olmesartan exceeds the risk for all other ARBs.

Importantly, olmesartan-induced enteropathy causes serious morbidity. For many of the cases reported in the scientific medical literature, the patients had severe weight loss and malnutrition. Most required hospitalization, with some needing intensive care. Severe serum electrolyte abnormalities and acute kidney injury were among the complications of the enteropathy experienced by patients.

The vast majority of cases of olmesartan-induced enteropathy undoubtedly are never reported in the scientific medical literature or to the FDA. It is also certain that there are many patients with milder forms of enteropathy caused by olmesartan, as well as patients with this condition who are misdiagnosed and inappropriately treated for celiac sprue or other inflammatory gastrointestinal disorders.

In addition, olmesartan offers no unique clinical benefits compared with other ARBs. It is only approved by the FDA for treatment of hypertension. Seven other ARBs also are approved for hypertension, as are multiple ACE inhibitors that also work through the same renin-angiotensin-aldosterone axis. Unlike some other ARBs, olmesartan is not approved by the FDA for any other uses.

In summary, compared with other ARBs, olmesartan has an unfavorable risk-benefit profile, given that it causes serious sprue-like enteropathy and has no unique benefits.
With millions of prescriptions for olmesartan-containing drugs filled each year, immediately banning this drug is essential to prevent avoidable serious harm to thousands of patients.

For the reasons stated above, we hereby petition the FDA, pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355(e), and 21 C.F.R. §§ 10.30, to immediately ban all

medications containing olmesartan medoxomil, including medications branded as Azor, Benicar, Benicar HCT, and Tribenzor, and all generic versions of these drugs.

C. ENVIRONMENTAL IMPACT STATEMENT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

D. ECONOMIC IMPACT

Will be submitted upon request.

E. CERTIFICATION

We certify that, to the best of the knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

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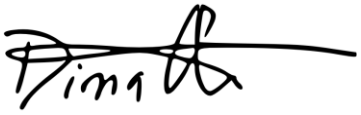

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Appendix
Additional Published Case Reports

1. Abdelghany M, Gonzalez L, Slater J, Begley C. Olmesartan Associated Sprue-Like Enteropathy and Colon Perforation. *Case Rep Gastrointest Med*. 2014;2014:494098.
2. Campos-Ruiz A, Urtasun-Arlegui L, Marra-López-Valenciano C. Sprue-like enteropathy linked to olmesartan. *Rev Esp Engerm Dig*. 2016;108(5):292-293.
3. Carneiro L, Moreira A, Pereira A, et al. Olmesartan-Induced Sprue Like Enteropathy. *GE Port J Gastroenterol*. 2016;23(2):101-105.
4. Desruisseaux C, Bensoussan M, Desilets E, et al. Adding water to the mill: olmesartan-induced collagenous sprue – A case report and brief literature review. *Can J Gastroenterol Hepatol*. 2016;2016:4837270.
5. Eusébio M, Caldeira P, Gião Antunes A, et al. Olmesartan-induced enteropathy: an unusual cause of villous atrophy. *GE Port J Gastroenterol*. 2016;23(2):91-95.
6. Fabian E, Schiller D, Wenzl H, et al. Case No 156: 82-year-old woman with chronic diarrhea and weight loss of 20 kilograms. *Wein Klin Wochenschr*. 2015;127(23-24):974-980.
7. Fukushima M, Kitamoto H, Inokuma T, Imai Y. Severe spruelike enteropathy associated with olmesartan observed by double-balloon enteroscopy. *Gastrointest Endosc*. 2016;83(1):269-270.
8. Gallivan C, Brown I. Olmesartan induced enterocolitis. *Pathology*. 2014;46(4):360-361.
9. Halevy D, Teeuwen U, Kohlhof P. A new spruelike disease as a cause of severe diarrhea. *Dtsch Med Wochenschr*. 2014;139(45):2290-2293.
10. Hammoudi N, Dior M, Giraud V, Coffin B. Olmesartan-induced enteropathy associated with cutaneous lesions. *Clin Case Rep*. 2016;4(4):379-382.
11. Hartranft ME, Regal RE. "Triple phase" budesonide capsules for the treatment of olmesartan-induced enteropathy. *Ann Pharmacother*. 2014;48(9):1234-1237.
12. Imperatore N, Tortora R, Capone P, et al. An emerging issue in differential diagnosis of diarrhea: sprue-like enteropathy associated with olmesartan. *Scand J Gastroenterol*. 2016;51(3):378-380.
13. Kulai R, Arnason T, MacIntosh D, Igoe J. Duodenal villous atrophy in a TTG-negative patient taking olmesartan: a case report and review of the literature. *Can J Gastroenterol Hepatol*. 2016;2016:6091571.
14. Muñoz-Muñoz C, López-Vivancos J, Huaman W, García-Cors M. Sprue-like enteropathy due to olmesartan. *Rev Esp Enferm Dig*. 2015 Oct;107(10):647-648.
15. Naik DK, Martelli MG, Gonzalo DH, et al. An atypical case of chronic diarrhea: olmesartan-induced sprue-like enteropathy. *BMJ Case Rep*. 2015 Sep 14;2015.
16. Non-Alcoholic Fatty Liver Disease Study Group, Dolci, M., Nascimbeni F, Romagnoli D, et al. Nonalcoholic steatohepatitis heralding olmesartan-induced sprue-like enteropathy. *Dig Liver Dis*. 2016;48(11):1399-1401.
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