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Supplement to Citizen Petition - Docket Number FDA-2017-P-6513

Date: February 1, 2018

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 supplement to the November 15, 2017, citizen petition that was assigned docket number FDA-2017-P-6513. The petition requested that the Commissioner of Food and Drugs immediately require the removal from the market of all medications containing the widely prescribed angiotensin II receptor blocker (ARB) olmesartan medoxomil (hereafter referred to as "olmesartan") because (1) olmesartan 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 Food and Drug Administration (FDA) for the treatment of hypertension.[1]

Since the submission of our petition, a new large cohort study was published by Dong et al. that provides additional evidence showing that use of olmesartan is associated with a higher rate of sprue-like enteropathy compared with the use of other ARBs.[2] The findings from this study further confirm what the FDA already knew nearly five years ago: that olmesartan causes sprue-like enteropathy and olmesartan users experience a significantly higher rate of this adverse event than users of other ARBs.

Dong et al. conducted a large cohort study among ARB initiators using five U.S. administrative claims databases (the commercial health insurance database, Clinformatics Data Mart; one Medicaid database; and three Medicare databases) covering the years 2002 to 2015. The databases together covered approximately 100 million individuals and represented each of the three main insured segments of the U.S. population.

From each database, the researchers identified patients who initiated treatment with either olmesartan or other ARBs (candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan, and azilsartan, including single and combination products). They then used Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for enteropathy-related outcomes, including celiac disease — which was used as a primary surrogate outcome, as

[1] Public Citizen. Citizen petition regarding medications containing olmesartan medoxomil. https://www.citizen.org/sites/default/files/2390.pdf. Accessed February 1, 2018.
[2] Dong YH, Jin Y, Tsacogianis TN, et al. Use of olmesartan and enteropathy outcomes: a multi-database study. Aliment Pharmacol Ther. 2018 Jan 22. doi: 10.1111/apt.14518. [Epub ahead of print]

was done in prior analyses performed by the FDA[3,4] — as well as malabsorption, concomitant diagnoses of diarrhea and weight loss, and non-infectious enteropathy, comparing olmesartan initiators with initiators of other ARBs after propensity score (PS) matching. Key results were as follows:

- A total of 1,928,469 eligible patients were identified across the five databases; 350,790 (18%) initiated olmesartan and 1,577,679 (82%) initiated other ARBs.
- Among patients who initiated other ARBs, valsartan (n = 679,039) was the most common, followed by losartan (n = 543,797), irbesartan (n = 171,239), and telmisartan (n = 123,089).
- After PS matching, a total of 1,854,992 patients (350,430 olmesartan initiators and 1,504,562 other ARB initiators; 96% of the total study cohort) were included in the analysis.
- During a mean follow-up of 282 days of ARB exposure, the researchers observed 1,227 cases of celiac disease, 2,102 cases of malabsorption, 2,467 cases of concomitant diagnoses of diarrhea and weight loss, and 42,440 cases of non-infectious enteropathy (based on inpatient and outpatient diagnoses).
- After PS matching, use of olmesartan was associated with significantly increased rates of celiac disease, concomitant diagnoses of diarrhea and weight loss, and non-infectious enteropathy, with HRs of 1.21 (95% CI, 1.05-1.40), 1.22 (95% CI, 1.10-1.36) and 1.04 (95% CI, 1.01-1.07), respectively. Use of olmesartan was consistently associated with higher rates of each outcome in individual databases, although estimates tended to be less precise.
- In a sensitivity analysis in which the researchers restricted outcomes to only inpatient cases, the adjusted HRs were consistently higher, with significant findings for concomitant diagnoses of diarrhea and weight loss (2.84; 95% CI, 1.35-5.99) and for non-infectious enteropathy (1.17; 95% CI, 1.07-1.28).
- Among 1,227 patients who received a diagnosis of celiac disease during follow-up, 620 (51%) had at least one other enteropathy-related diagnosis code, 549 (45%) received gastrointestinal endoscopic examination, and 17 (1.4%) were hospitalized with acute kidney injury. In another sensitivity analysis in which the researchers restricted outcomes

[3] Sentinel. Mini-Sentinel Modular Program Report: Angiotensin II Receptor Blockers and Celiac Disease. January 16, 2012. https://www.sentinelinitiative.org/drugs/assessments/angiotensin-ii-receptor-blockers-and-celiac-disease and https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_Angiotensin-II-Receptor-Blockers-and-Celiac-Disease_0.pdf. Accessed February 1, 2018.

[4] Sentinel. Mini-Sentinel Modular Program Report: Angiotensin Receptor Blockers (ARBs), Hydrochlorothiazide, Atenolol, Amlodipine Use and Celiac Disease. June 7, 2013. https://www.sentinelinitiative.org/drugs/assessments/angiotensin-receptor-blockers-arbs-hydrochlorothiazide-atenolol-amlodipine-use-and and 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 February 1, 2018.

to these cases, the adjusted HRs for celiac disease were 1.49 (95% CI, 1.23-1.80), 1.45 (95% CI, 1.18-1.79), and 7.40 (95% CI, 3.63-15.11), respectively.

- A duration-response analysis showed treatment with olmesartan for longer than one year yielded higher adjusted HRs. Patients treated with high cumulative doses of olmesartan (greater than 365 defined daily doses, n = 48,316) also had a higher rate of celiac disease (adjusted HR, 1.78; 95% CI, 1.33-2.37). The researchers did not observe an increased rate of celiac disease (adjusted HR, 1.06; 95% CI, 0.62-1.79) for those treated with low cumulative doses of olmesartan (365 or fewer defined daily doses, n = 23,805) compared with those treated with other ARBs.

The Dong et al. study provides further evidence supporting our November 15, 2017, petition to 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, including medications branded as Azor, Benicar, Benicar HCT, and Tribenzor, and all generic versions of these drugs. Since olmesartan lacks any evidence of a unique benefit to patients but carries, in comparison with other ARBs, a significantly increased risk of serious sprue-like enteropathy, such an FDA ban clearly would result in a net benefit to public health.

Thank you for your consideration of this additional evidence.

Sincerely,

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