Michael A. Carome, M.D., et al.
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Re: Docket No. FDA-2017-P-6513

OCT 09 2019

Dear Dr. Carome,

This letter responds to your citizen petition submitted on behalf of Public Citizen and Public Citizen's Health Research Group, which was received on November 15, 2017 (Petition). In your Petition, you request that the Food and Drug Administration (FDA or the Agency) immediately remove from the market all medications containing the angiotensin II receptor blocker (ARB) olmesartan medoxomil, including medications branded as Azor, Benicar, Benicar HCT, and Tribenzor, as well as all generic versions of these drugs. The Petition requests that these drug products be removed from the market 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.

(Petition at 1).

We have carefully considered your Petition, and for the reasons stated below, your Petition is denied.

I. BACKGROUND

A. Olmesartan Medoxomil

Olmesartan medoxomil is an orally absorbable pro-drug for olmesartan. It is an ARB that is approved for the treatment of high blood pressure, alone or with other antihypertensive agents. There are four new drug applications (NDAs) for drug products that contain olmesartan medoxomil: (1) Benicar (olmesartan medoxomil) (NDA 021286); (2) Benicar HCT (olmesartan medoxomil and hydrochlorothiazide) (NDA 021532); (3) Azor (olmesartan medoxomil and amlodipine besylate) (NDA 022100); and (4) Tribenzor (olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide) (NDA 200175). In addition, there are multiple abbreviated new drug applications (ANDAs) for olmesartan medoxomil; olmesartan medoxomil and

hydrochlorothiazide; olmesartan medoxomil and amlodipine besylate; and olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide.

B. 2013 FDA Drug Safety Communication and Labeling Changes

In 2013, FDA issued a Drug Safety Communication regarding olmesartan medoxomil.[1] The Drug Safety Communication announced that FDA had approved changes to the labeling of olmesartan medoxomil-containing drug products to include a warning regarding intestinal problems (sprue-like enteropathy).[2] The Prescribing Information for these drug products now states that severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation and that intestinal biopsies of patients often demonstrated villous atrophy. It also states that if a patient develops these symptoms while being treated with olmesartan medoxomil and other etiologies are excluded, providers should consider discontinuation. The 2013 Drug Safety Communication noted that discontinuation of olmesartan medoxomil has resulted in clinical improvement of sprue-like enteropathy symptoms in all patients.

FDA's decision to issue the 2013 Drug Safety Communication and to approve the addition of a warning about sprue-like enteropathy to olmesartan medoxomil labeling was based on an evaluation of data from the published medical literature, the Centers for Medicare and Medicaid Services (CMS) database, the FDA Adverse Event Reporting System (FAERS), and Mini-Sentinel. FDA's review included the 2012 case series by Rubio-Tapia et al.[3] FDA determined there was reasonable evidence of a causal association between olmesartan medoxomil and sprue-like enteropathy.

II. STATUTORY AND REGULATORY FRAMEWORK

A. NDA and ANDA Approval Standards

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations require that an applicant seeking to market a new drug submit an NDA or ANDA. NDAs are submitted under

---

[1] FDA, 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), available at https://www.fda.gov/downloads/Drugs/DrugSafety/UCM359496.pdf.

[2] See Prescriber Information for olmesartan medoxomil-containing drug products at Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

[3] Mini-Sentinel pilot of the Sentinel Initiative Angiotensin II receptor blockers and celiac disease available at https://www.sentinelsystem.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_Angiotensin-II-Receptor-Blockers-and-Celiac-Disease_0.pdf. The Mini-Sentinel pilot (2009 – 2016) was a collaborative effort between FDA and healthcare organizations for the development of the current Sentinel System. Mini-Sentinel was a national distributed electronic healthcare database network that provided an infrastructure for medical product safety surveillance queries and epidemiologic assessments. See Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe sprue-like enteropathy associated with olmesartan. *Mayo Clin Proc.* 2012;87(8):732-738.

section 505(b)(1) of the FD&C Act (21 U.S.C. 355(b)(1)) and approved under section 505(c) of the FD&C Act. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. NDA applicants must, among other things, describe the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions of use stated in the labeling.[4] Furthermore, applicants must not only provide substantial evidence of effectiveness for claimed indications in their applications, but also provide evidence to support the dosage and administration section of the labeling for the drug.[5] As stated in section 505(d) of the FD&C Act, "substantial evidence" means:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

An ANDA is an application submitted and approved under section 505(j) of the FD&C Act for a drug product that is a duplicate[6] of a previously approved drug product. An ANDA relies on FDA's finding that the previously approved drug product, i.e., the reference listed drug (RLD),[7] is safe and effective. An ANDA generally must contain information to show that the proposed generic product (1) is the same as the RLD with respect to the active ingredient(s), conditions of use, route of administration, dosage form, strength, and labeling (with certain permissible differences) and (2) is bioequivalent to the RLD. If in vivo bioequivalence studies are required for approval of the ANDA, the applicant must use the reference standard selected by FDA in such testing. A generic drug must meet the same high standards of quality and manufacturing as drug products approved under section 505(c) of the FD&C Act.[8]

B. Standard for Withdrawal of NDA or ANDA Approval

Section 505(e) of the FD&C Act establishes the circumstances under which the Agency shall, after due notice and opportunity for a hearing, withdraw approval of an NDA or ANDA. With respect to safety concerns, the Agency shall withdraw approval of an NDA or ANDA if it finds

---

[4] § 314.50(d)(5)(viii) (21 CFR 314.50(d)(5)(viii)).

[5] § 314.50(d)(5)(v).

[6] The term duplicate generally refers to a "drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug." See 54 FR 28872 at 28877 (July 10, 1989). However, the term duplicate, as used in this context, does not mean identical in all aspects to the listed drug.

[7] The RLD "is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA." 21 CFR 314.3(b). Because an ANDA applicant is relying upon FDA's finding that the RLD is safe and effective, FDA's practice is to designate as RLDs drug products that have been approved for safety and effectiveness.

[8] Section 505(j)(2)(A)(vi) of the FD&C Act.

either of the following:

> that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; [or] that new evidence of clinical experience, not contained in such application or not available to the [Agency] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [Agency] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved.[9]

With respect to effectiveness, the Agency shall withdraw approval of an NDA or ANDA if it finds "that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof."[10]

III. DISCUSSION

In your Petition, you request FDA to immediately require the removal from the market of all medications that contain olmesartan medoxomil, including Benicar, Benicar HCT, Azor, Tribenzor, and all generic versions of these drug products (Petition at 1). In support of your request, you: (1) describe new information, including cohort studies, a systematic review, and case series and case reports describing the link between sprue-like enteropathy and olmesartan medoxomil (Petition at 7-15, 17 & Petition Supp.); and (2) emphasize the availability of other ARBs and non-ARB medications that are approved for treating hypertension that you assert have a more favorable risk-benefit profile than medications that contain olmesartan medoxomil (Petition at 7, 14, 15, and 17).

FDA has reviewed the literature you cited[11] to support your request and the FAERS[12] data on adverse events associated with the use of drug products that contain olmesartan medoxomil. The results of our reviews are discussed below.

For the reasons discussed below, we have determined, based on the information currently available to us, that initiating the withdrawal of the marketing approval of drug products containing olmesartan medoxomil for reasons of safety is not warranted at this time. The safety

---

[9] Section 505(e)(1) and (2) of the FD&C Act; see also § 314.150(a)(2)(i) and (ii) (21 CFR 314.150(a)(2)(i) and (ii)).

[10] Section 505(e)(3) of the FD&C Act; see also § 314.150(a)(2)(iii). Additional circumstances under which FDA shall or may withdraw approval of an NDA or ANDA are identified in section 505(e) of the FD&C Act; see also § 314.150(a)(2)(iv) and (v).

[11] Although FDA reviewed and considered all literature provided, this response focuses on higher quality studies that: 1) used a cohort design to assess the specific association between ARB use and sprue-like enteropathy and 2) distinguished celiac disease from intestinal malabsorption.

[12] See FAERS, formerly AERS, available at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm.

concerns you raise in the Petition were appropriately and thoroughly considered in 2013 when the Drug Safety Communication was issued, and updated warnings were approved in the labeling of drug products that contain olmesartan medoxomil. Since then, there have been no new safety findings from FDA's ongoing surveillance, or raised in the Petition, that sufficiently alter the risk-benefit analysis of drug products containing olmesartan medoxomil to necessitate the removal of these products from the market under section 505(e) of the FD&C Act. FDA will continue to monitor and review available safety information related to drug products containing olmesartan medoxomil, taking any further action as appropriate.

A. FDA Review of Information Presented in the Petition Regarding Olmesartan Medoxomil and Sprue-like Enteropathy

We reviewed the information cited in your Petition, including cohort studies, a systematic review, and case series and case reports.

1. Cohort Studies

a. Basson et al. Article

In your Petition (Petition at 7-8), you cite an article by Basson et al.[13] to support your argument that medications containing olmesartan medoxomil should be removed from the market (Petition at 5-6). Basson et al. completed an observational cohort study using the French National Health Insurance claim database to assess the risk of hospitalization for intestinal malabsorption associated with olmesartan medoxomil compared with other ARBs and angiotensin-converting enzyme (ACE) inhibitors.[14] Because there is no validated algorithm for sprue-like enteropathy in claims data, the authors were not able to calculate an incidence rate for sprue-like enteropathy. Instead, the authors present results for the association between olmesartan [medoxomil] and severe forms of enteropathy and malabsorption.[15] The article concluded that olmesartan medoxomil is associated with an increased risk of hospitalization for intestinal malabsorption (adjusted rate ratio [adj. RR] = 2.49, 95% CI 1.73- 3.57) and celiac disease (adj. RR = 4.39, 95% CI 2.77 – 6.96) compared to ACE inhibitors.

Ultimately, Basson et al. concludes by recommending that:

> "[p]atients treated with olmesartan [medoxomil] should be informed about the risk of this complication [sprue-like enteropathy] and should be advised to seek medical attention if they experience [gastrointestinal] symptoms. This information should also be widely delivered to physicians of all disciplines, particularly to gastroenterologists who are faced with this new category of patients."[16]

---

[13] 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.

[14] Id. at 1.

[15] Id. at 5.

[16] Id. at 6.

The findings and recommendations in the Basson et al. article are consistent with the current labeling and with the 2013 Drug Safety Communication regarding the risk for sprue-like enteropathy for olmesartan medoxomil-containing products. Labeling of drug products that contain olmesartan medoxomil contains warnings regarding the risk of sprue-like enteropathy. The Highlights section of the Prescribing Information contains a warning about sprue-like enteropathy, and the Warnings and Precautions section contains a detailed warning about the risk of sprue-like enteropathy, which the Adverse Reactions section cross references. The 2013 Drug Safety Communication advised patients to contact a health care professional right away if they experience severe diarrhea, diarrhea that does not go away, or significant weight loss. This information was made available to physicians of all specialties through the 2013 Drug Safety Communication and the updated labeling. The safety concerns you raise based on the Basson et al. article have already been incorporated into currently approved labeling and were described in the 2013 Drug Safety Communication.

b. Dong et al. Article

In your Petition,[17] you cite an article by Dong et al.[18] to support your argument that medications containing olmesartan medoxomil should be removed from the market (Petition at 5-6). Dong et al. analyzed U.S. claims data covering years 2002 through 2015 from one commercial database, one Medicaid database, and three Medicare databases.[19] Dong et al. found olmesartan medoxomil was associated with an increased rate of celiac disease (hazard ratio [HR] after propensity score matching = 1.21; 95% CI 1.05 – 1.40), non-infectious enteropathy (adj. HR = 1.04; 95% CI 1.01 – 1.07), and concomitant diarrhea and weight loss (adj. HR =1.22; 95% CI 1.10 – 1.36), but not intestinal malabsorption (adj. HR = 1.00; 95% CI 0.88 – 1.13) as compared to other ARBs.[20] Because there is no validated algorithm for sprue-like enteropathy in claims data, Dong et al. used celiac disease as a primary surrogate outcome. FDA also evaluated celiac disease as an outcome in its analyses mentioned in the 2013 Drug Safety Communication.[21]

Dong et al. stated that "more than 90% of data included in [the Dong et al. article] covered the period before the [Rubio-Tapia] case series was published (June 2012)."[22] Thus, any publicity

---

[17] The Dong, et al. article was submitted in a supplement to the Petition on Feb. 1, 2018 (Docket No. FDA-2017-P-6513-0012) (Petition supp.).

[18] 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.

[19] Id. at 2.

[20] Id. 6-7.

[21] Id. at 2 (citing FDA's Mini-Sentinel pilot of the Sentinel Initiative Angiotensin II receptor blockers and celiac disease at https://www.sentinelsystem.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_Angiotensin-II-Receptor-Blockers-and-Celiac-Disease_0.pdf and FDA's Mini-Sentinel pilot of the Sentinel Initiative, ARBs, HCTZ, atenolol, amlodipine, and celiac disease at https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Mini-Sentinel_Modular-Program-Report_MSY3_MPR34_ARBs-HCTZ-Atenolol-Amlodipine-Celiac-Disease_0.pdf).

[22] Dong et al. at 8.

rising from the Rubio-Tapia case series that could have impacted subsequent physician attribution of enteropathy to olmesartan medoxomil would likely have been minimal.

Dong et al.'s study provides evidence of a higher rate of celiac disease and other outcomes with less than 1 year of exposure to olmesartan medoxomil as compared to other ARBs, while Mini-Sentinel and CMS Medicare data showed an increased rate of celiac disease with a minimum of 2 years of exposure.[23] The mean follow-up period in the Dong et al. study was relatively short (282 days). Dong et al. concluded that there is "a higher rate of enteropathy in olmesartan [medoxomil] initiators as compared to initiators of other ARBs, although the absolute incidence rate was low in both groups."[24] As stated in the 2013 Drug Safety Communication, FDA has determined that drugs containing olmesartan medoxomil can cause sprue-like enteropathy, and this condition has not been detected with ARB drugs other than olmesartan medoxomil.

The authors recommended that "the potential olmesartan [medoxomil]-associated enteropathy deserves attention in clinical practice. Until more evidence is available, clinicians should consider olmesartan [medoxomil] as a potential cause when evaluating patients with enteropathy and should consider alternative ARBs for these patients."[25] We agree with this assessment. This statement is consistent with the current labeling of drug products containing olmesartan medoxomil and the 2013 Drug Safety Communication.

In your Petition, you cite the article by Dong, et al. as support for the statement that "olmesartan [medoxomil] is associated with a higher rate of sprue-like enteropathy compared with the use of other ARBs."[26] The findings in this article are consistent with the current labeling regarding the risk for sprue-like enteropathy associated with olmesartan medoxomil-containing products. The safety concerns considered in the Dong et al. article were thoroughly considered in 2013 when the Drug Safety Communication was issued, and updated warnings were approved in the labeling of drug products that contain olmesartan medoxomil.

2. Systematic Review by Burbure et al.

In your Petition, you cite a systematic review by Burbure et al.[27] as support for the statement that there is "accumulating evidence of harm from olmesartan [medoxomil]-induced sprue-like enteropathy" (Petition at 7, 8-11). The Burbure et al. article reviewed:

> [t]he histopathologic changes and clinical observations described in recent reports of olmesartan [medoxomil]-associated sprue-like enteropathy comprising case series and

[23] FDA, 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), available at https://www.fda.gov/downloads/Drugs/DrugSafety/UCM359496.pdf.

[24] Dong et al. at 1.

[25] Id. at 8.

[26] Petition supp. at 1.

[27] 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.

> isolated reports, other relevant literature, and our experience at a referral center specializing in small intestinal disorders.[28]

Burbure et al. concluded that the mechanism of injury for olmesartan medoxomil-associated enteropathy is not well established, but there is evidence that "suggests an immune-mediated inflammatory disorder in susceptible individuals."[29] Consistent with the 2013 Drug Safety Communication, Burbure et al. found that "[c]essation of olmesartan [medoxomil] results in complete resolution of both clinical and histologic features."[30] Thus, Burbure et al. concluded that "it is important for pathologists, as well as other physicians, gastroenterologists cardiologists, and primary care, among others, to be aware of the histopathologic changes associated with ARB enteropathy."[31] As described above, these recommendations were addressed by the 2013 Drug Safety Communication and the updated warnings in the labeling of drug products that contain olmesartan medoxomil.

3. Case Series and Case Reports

In your Petition, you cite a French case series by Marthey et al.[32] and other smaller case series as support for the premise that patients were found to have olmesartan medoxomil-induced enteropathy that fully resolved or had improvement of symptoms after discontinuing olmesartan medoxomil (Petition at 11-14). You also cite several individual case reports to support the same premise (Petition at 14-15).

The case series by Marthey et al. concluded that this "study supports the causality of the association between olmesartan [medoxomil] and enteropathy."[33] In support of this conclusion, Marthey et al. states:

> "Firstly, our cases and those reported by *Rubio-Tapia et al.* were remarkably similar. Secondly, nondeliberate interruptions followed by reintroductions led to clinical remissions followed by clinical relapses respectively. Thirdly, as in the study by *Rubio-Tapia et al.*, duodenal mucosa returned to normal after olmesartan [medoxomil] withdrawal."[34]

As stated above, FDA based its decision to issue the 2013 Drug Safety Communication and approve a warning on the labeling of drug products that contain olmesartan medoxomil, in part, on published case series. The 2012 Rubio-Tapia et al. case series was included in FDA's review. Thus, because the case series in Marthey et al. are "remarkably similar" to those in the 2012

---

[28] Id. at 127.

[29] Id. at 133.

[30] Id.

[31] Id.

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

[33] Id. at 1107.

[34] Id. (citing Rubio-Tapia A, Herman ML, Ludvigsson JF, et al. Severe sprue-like enteropathy associated with Olmesartan. *Mayo Clin Proc* 2012; 87: 732).

Rubio-Tapia et al. case series, and because the ultimate conclusions of the Marthey et al. case series echo FDA's conclusions in its 2013 Drug Safety Communication, these concerns have been adequately addressed. Likewise, the additional case series and case reports you cite to support the premise that patients were found to have olmesartan medoxomil-induced enteropathy that fully resolved or had improvement of symptoms after discontinuing olmesartan medoxomil have been adequately addressed by the 2013 Drug Safety Communication and the updated warnings in the labeling of drug products that contain olmesartan medoxomil.

4. FAERS and Literature Cases

FDA conducted a review of FAERS cases and literature cases of enteropathy associated with olmesartan medoxomil between September 2011 and February 2018. This review did not indicate a new, worsened, or more prevalent enteropathy-related risk than already described in the olmesartan medoxomil labeling. Among the FAERS cases of enteropathy associated with olmesartan medoxomil, there were 15 cases with an outcome of death. Eleven of these cases reported the event of sprue-like enteropathy or malabsorption occurred prior to 2013 (FDA Drug Safety Communication issue date), three reported the events occurred after 2013, and one did not provide information on the time of event onset. Only one case with an outcome of death reported biopsy finding of villous atrophy in combination with negative celiac disease serology. This one case reported from France was a 74-year-old male with pre-existing hypercholesterolemia, tobacco use, and arteritis. Mesenteric ischemia and pulmonary embolus were listed as events related to the patient's death. The remaining 14 cases with outcome of death had insufficient information to determine whether alternative etiologies (such as celiac disease or other enteropathies potentially unrelated to olmesartan medoxomil) led to the reported adverse events. There was no conclusive evidence of olmesartan medoxomil-associated sprue-like enteropathy resulting in death among FAERS or literature cases.

The case series characteristics in FDA's review of FAERS cases and literature cases of enteropathy associated with olmesartan medoxomil between September 2011 and February 2018 were consistent with those described in our review that preceded the 2013 Drug Safety Communication and labeling changes and do not raise new safety concerns.

B. Risk-Benefit Profile of Olmesartan Medoxomil Relative to Other ARBs

In your Petition, you state that because multiple other ARBs do not appear to have the risk of sprue-like enteropathy, and because olmesartan medoxomil offers no unique clinical benefit, olmesartan medoxomil therefore has an unfavorable risk-benefit profile (Petition at 1, 15-17). As described above, our review of the new information presented is consistent with the current labeling warnings about the risk for sprue-like enteropathy for olmesartan medoxomil-containing products and the 2013 Drug Safety Communication.

Observational studies showed an increased risk of proxy outcomes for sprue-like enteropathy with olmesartan medoxomil as compared to non-olmesartan medoxomil ARBs, namely intestinal malabsorption, celiac disease, non-infectious enteropathy, and concomitant diarrhea and weight loss. The study results for the proxy outcomes are consistent with the current labeling and the 2013 Drug Safety Communication for olmesartan medoxomil-containing products regarding the

risk for sprue-like enteropathy.

Most patients taking drug products that contain olmesartan medoxomil do not develop sprue-like enteropathy. The incidence of various gastrointestinal events in olmesartan medoxomil users described in the studies reviewed by FDA range from 3 to 147 per 100,000 patient-years.[35] Removing from the market drug products that contain olmesartan medoxomil would unnecessarily disrupt blood pressure therapy for over 1 million hypertensive patients (most of whom are unlikely to develop sprue-like enteropathy) who would be required to seek medical care, obtain and fill a new prescription for a different antihypertensive, and make follow-up clinic visits to assess blood pressure control and titrate drug therapy, if appropriate. Some patients may not tolerate the new medication or achieve satisfactory blood pressure control, which would necessitate further medical follow-up.

The identification of a drug-specific risk does not necessarily warrant the withdrawal of a product from the market under section 505(e) of the FD&C Act. In this case, the risk is clearly labeled, identifiable, and reversible or able to be mitigated.

IV. CONCLUSION

FDA has determined, based on the information available to us at this time, that initiating the withdrawal of the marketing approval of NDAs and ANDAs for drugs containing olmesartan medoxomil is not warranted. The safety concerns you raise in the Petition were appropriately and thoroughly considered in 2013 when the Drug Safety Communication was issued, and updated warnings were approved in the labeling of drug products that contain olmesartan medoxomil. Since then, there have been no new safety findings from FDA's ongoing surveillance, or raised in the Petition, that sufficiently alter the risk-benefit analysis of drug products containing olmesartan medoxomil to necessitate the removal of these products from the market under section 505(e) of the FD&C Act.

Accordingly, for the reasons described above, your Petition is denied. FDA will continue to evaluate risks associated with drug products that contain olmesartan medoxomil and, if warranted, will take appropriate regulatory action to protect the public health.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[35] See 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; Malfertheiner P, Ripellino C, Cataldo N. Severe intestinal malabsorption associated with ACE inhibitor or angiotensin receptor blocker treatment. An observational cohort study in Germany and Italy. Pharmacoepidemiol Drug Saf. 2018; Dong et al. at 4.