

## Citizen Petition

July 15, 2022

On behalf of our one million consumer supporters, the Alliance for Natural Health USA submits this petition under 21 C.F.R. Section 10.20 and 10.30 to request the Commissioner of Food and Drugs issue a regulation that all makers of proton pump inhibitors (PPIs) add a black box warning to their product's labeling warning of the link between taking PPIs and the risk of developing dementia.

### **A. Action Requested**

This petition requests that the Commissioner of Food and Drugs issue a regulation that all makers of proton pump inhibitors (PPIs) add a black box warning to their product's labeling warning of the link between taking PPIs and the risk of developing dementia.

### **B. Statement of Grounds**

PPIs are among the most widely used drugs in the U.S. These medications are typically taken daily, often for many years, compounding the risk of side effects.

Many PPI users are not aware that studies have linked PPI use directly with dementia.<sup>1,2</sup> A large study published in *JAMA Neurology* found that regular use of PPIs increased the risk for dementia by as much as 52% compared with nonusers.<sup>3</sup>

In addition to these studies demonstrating a direct link, other side effects of PPI use are also connected with dementia and Alzheimer's. For example, PPI use is associated with higher risk of chronic kidney disease.<sup>4,5</sup> It has been accepted that

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<sup>1</sup> Torres-Bondia, F., Dakterzada, F., Galván, L. *et al.* Proton pump inhibitors and the risk of Alzheimer's

<sup>2</sup> Kumar, R, Kumar, A, Nordberg, A, Långström, B, Darreh-Shori, T. Proton pump inhibitors act with unprecedented potencies as inhibitors of the acetylcholine biosynthesizing enzyme—A plausible missing link for their association with incidence of dementia. *Alzheimer's Dement.* 2020; 16: 1031–1042. <https://doi.org/10.1002/alz.12113>

<sup>3</sup> Gomm W, von Holt K, Thomé F, et al. Association of Proton Pump Inhibitors With Risk of Dementia: A Pharmacoepidemiological Claims Data Analysis. *JAMA Neurol.* 2016;73(4):410–416. doi:10.1001/jamaneurol.2015.4791

<sup>4</sup> Lazarus B, Chen Y, Wilson FP, et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA Intern Med.* 2016;176(2):238–246. doi:10.1001/jamainternmed.2015.7193

<sup>5</sup> Arora, P., Gupta, A., Golzy, M. *et al.* Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. *BMC Nephrol* 17, 112 (2016). <https://doi.org/10.1186/s12882-016-0325-4>

kidney function is connected with brain activity,<sup>6</sup> and studies have linked kidney disease with dementia and Alzheimer's disease.<sup>7,8,9,10</sup>

PPI use also increases risk of heart disease<sup>11</sup> and heart attack.<sup>12,13</sup> Heart failure has been associated with a more than 80% increased risk of developing dementia and Alzheimer's disease.<sup>14</sup> Other studies have linked heart problems with cognitive impairment.<sup>15</sup>

In light of the evidence establishing the relationship between PPIs and dementia it is essential that the FDA update the existing black box warning on human drugs to include this effect. According to 21 CFR 201.57(c)(6)(i)

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<sup>6</sup> Zhang CY, He FF, Su H, Zhang C, Meng XF. Association between chronic kidney disease and Alzheimer's disease: an update. *Metab Brain Dis*. 2020 Aug;35(6):883-894. doi: 10.1007/s11011-020-00561-y. Epub 2020 Apr 3. PMID: 32246323.

<sup>7</sup> Basit, Saima, Damholt, Mette. Is kidney disease associated with both Alzheimer's disease and vascular dementia? *Journal of the Alzheimer's Association*. 2020 December 7; Volume 16, Issue S10. <https://doi.org/10.1002/alz.042527>

<sup>8</sup> Xu H, Garcia-Ptacek S, Trevisan M, Evans M, Lindholm B, Eriksdotter M, Carrero Pharm JJ. Kidney Function, Kidney Function Decline, and the Risk of Dementia in Older Adults: A Registry-Based Study. *Neurology*. 2021 May 5;96(24):e2956-65. doi: 10.1212/WNL.00000000000012113. Epub ahead of print. PMID: 33952656; PMCID: PMC8253567.

<sup>9</sup> Shi Y, Liu Z, Shen Y, Zhu H. A Novel Perspective Linkage Between Kidney Function and Alzheimer's Disease. *Front Cell Neurosci*. 2018 Oct 29;12:384. doi: 10.3389/fncel.2018.00384. PMID: 30429775; PMCID: PMC6220726.

<sup>10</sup> Kjaergaard AD, Johannesen BR, Sørensen HT, Henderson VW, Christiansen CF. Kidney disease and risk of dementia: a Danish nationwide cohort study. *BMJ Open*. 2021 Oct 22;11(10):e052652. doi: 10.1136/bmjopen-2021-052652. PMID: 34686557; PMCID: PMC8543681.

<sup>11</sup> Ariel H, Cooke JP. Cardiovascular Risk of Proton Pump Inhibitors. *Methodist DeBakey Cardiovasc J*. 2019 Jul-Sep;15(3):214-219. doi: 10.14797/mdcj-15-3-214. PMID: 31687101; PMCID: PMC6822659.

<sup>12</sup> The Pharmaceutical Journal, PJ, 20 June 2015, Vol 294, No 7867;294(7867):DOI:10.1211/PJ.2015.20068748

<sup>13</sup> Shah NH, LePendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J, Nead KT, Cooke JP, Leeper NJ. Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population. *PLoS One*. 2015 Jun 10;10(6):e0124653. doi: 10.1371/journal.pone.0124653. PMID: 26061035; PMCID: PMC4462578.

<sup>14</sup> Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart Failure and Risk of Dementia and Alzheimer Disease: A Population-Based Cohort Study. *Arch Intern Med*. 2006;166(9):1003-1008. doi:10.1001/archinte.166.9.1003

<sup>15</sup> Roberts RO, Geda YE, Knopman DS, et al. Cardiac Disease Associated With Increased Risk of Nonamnesic Cognitive Impairment: Stronger Effect on Women. *JAMA Neurol*. 2013;70(3):374-382. doi:10.1001/jamaneurol.2013.607



*In accordance with 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.*

## **Conclusion**

The risks of medications should be clearly indicated to consumers, and substantial evidence points to an increased risk of dementia associated with the use of PPIs. The Alliance for Natural Health USA urges the Commissioner of Food and Drugs to require PPIs include a clear black box warning to warn against the potential risk between taking proton pump inhibitors (PPIs) and developing dementia.

## **C. Environmental Impact**

Petitioner claims a categorical exclusion under 21 C.F.R. §25.30(h).

## **D. Economic Impact**

Pursuant to 21 C.F.R. §10.30(b), economic impact information will be submitted by the Petitioner upon the request of the Commissioner.

## **E. Certification**

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

Respectfully submitted,

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