CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

September 5, 2017

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

Re: Comments on Citizen's Petition #FDA-2016-P-4388

Herein, the Consumer Healthcare Products Association (CHPA), the 136-year-old trade association representing U.S. manufacturers and distributors of over-the-counter (OTC) medicines and dietary supplements (chpa.org), provides comments on Citizen Petition # FDA-2016-P-4388[1] which requests an amendment of the marketing status for loperamide (Imodium) from nonprescription (over-the-counter, OTC) to prescription.

Based on the available evidence demonstrating a long history of safe and effective use of loperamide when used according to labeled directions as well as a low rate of abuse/misuse of loperamide, we do not believe that changing the marketing status of loperamide from OTC to prescription is warranted. While published literature reports of serious cardiac adverse events and deaths in association with massive overdose of loperamide have increased in recent years, the number of such events is still extremely low.

We are currently working with member companies and the FDA to further assess reports of loperamide misuse/abuse and to develop additional strategies to mitigate this occurrence. This includes an analysis of loperamide adverse event reports contained in the National Poison Data Systems and the Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS) databases.

[1] Submitted by Sajoy P. Varghese, MD, FAPA, Jesse Brown VA Medical Center, 820 South Damen Avenue, Chicago, IL Network (dated December 21, 2016).

Loperamide is a peripherally acting μ opioid receptor agonist which acts by reducing peristalsis and increasing intestinal transit time. Initially approved as a prescription drug in 1976 to help control symptoms of diarrhea, loperamide was switched to OTC status in 1988. Near the time of the Rx to OTC switch, it was estimated that for a single year 99 million cases of gastroenteritis or acute diarrhea occurred among adults in the US. Half of the persons with gastroenteritis or diarrhea had restriction of their activities for more than a full day, a physician was consulted in 8.2 million of the cases, 250,000 persons were hospitalized, 7.9 million saw a physician but were not hospitalized, and more than 90 million experienced illness without seeking medical attention.[2] Thus, there was a clear benefit for an OTC loperamide product.

When taken as directed, loperamide has been shown to be both safe and effective.[3,4,5] The standard OTC dose of loperamide (IMODIUM® A-D; there are also store brands and generics) for adults and children 12 years and over is initially 4 mg, followed by 2 mg after each loose stool (up to a maximum of 8 mg/day). Loperamide is also still marketed as a prescription drug with a maximum labeled dose of 16 mg/day. Currently, the only other ingredient available OTC for the treatment of diarrhea is bismuth subsalicylate (Kaopectate®, Pepto Bismol®).

Central Nervous System (CNS) effects and psychotropic potential:

Loperamide has demonstrated an excellent safety and efficacy profile with an absence of CNS effects when taken according to dosage instructions provided on the label. As described in the medical literature, most misuse/abuse of loperamide involves intentional massive overdoses reportedly taken with the aim of avoiding opiate withdrawal or as an opiate substitute.

Administered as a prodrug (loperamide oxide), loperamide ($t_{½}$ 9-14 hours) is extensively first pass metabolized via cytochrome P-450 enzymes (CYP3A4 and CYP2C8) and, at labeled doses, has limited oral bioavailability due to negligible gastrointestinal absorption.[6] Loperamide entry into the CNS is also limited by p-glycoprotein,[7] a transporter expressed in a variety of human tissues including the intestine and blood brain barrier.

A clear dissociation between GI and CNS effects has been demonstrated in animals.[8] The lowest ED_{50} associated with inhibition of GI motility is 0.59 mg/kg, whereas toxic doses of 80 mg/kg (136 times the ED_{50} for inhibiting GI motility) of loperamide did not induce morphine-like behavior.[9]

---

[2] Garthright et al., 1988 Estimates of incidence and costs of intestinal infectious diseases in the United States, *Publ Health Rep* 103(2): 107-115

[3] Heel et al., 1978 Loperamide: a review of its pharmacological properties and therapeutic efficacy in diarrhea *Drugs* 15(1): 33-52

[4] Ericsson and Johnson, 1990 Safety and efficacy of loperamide *Am J Med* 88(6A): 10S-14S

[5] Laaveri et al., 2016 Systematic review of loperamide: No proof of antibiotics being superior to loperamide in treatment of mild/moderate travellers' diarrhea *Travel Med Infect Dis* 14(4): 299-312

[6] Lavrijsen et al., 1995 Reduction of the prodrug loperamide oxide to its active drug loperamide in the gut of rats, dogs, and humans, *Drug Metab Dispos* 23: 354–362

[7] Schinkel et al., 1996 P-glycoprotein in the blood-brain barrier of mice influences the brain penetration and pharmacological activity of many drugs, *J Clin Invest* 97(11): 2517-2524

[8] Niemegeers et al., 1979 Dissociation between opiate-like and antidiarrheal drugs *J Pharm Exp Ther* 210(3): 327-333

[9] McGuire et al., Interaction of loperamide and diphenoxylate with ethanol and methohexital *Arch Int Pharmacodyn Ther* 236(1): 51-59

1625 Eye Street, NW, Suite 600 | Washington, DC 20006 | T 202.429.9260 | F 202.223.6835 | chpa.org | @chpa

At recommended doses, loperamide does not significantly cross the blood-brain barrier [7,10,11] and is not associated with central opiate-like effects. In humans with a history of opioid addiction, loperamide (60 mg) did not produce subjective euphoria or objective opiate effects.[12] In addition, loperamide was associated with low liking scores, indicating little or no abuse potential. More recently, a review of post-marketing cases describing co-administration of loperamide with a P-glycoprotein substrate or inhibitor found insufficient evidence to demonstrate an interaction associated with CNS symptoms or opioid toxicity.[13]

Thus, evidence published to date demonstrates that when taken as directed, loperamide is safe and effective for the short-term treatment of diarrhea. While self-reported opiate-like effects of loperamide have been described following ingestion of massive overdoses, well-documented effects on the CNS have not been conclusively demonstrated. Further, these reports contrast with earlier clinical studies confirming an absence of CNS effects, even at high doses.[12]

[10] Heykants et al., 1974 Loperamide (R 18 553), a novel type of antidiarrheal agent. Part 5: the pharmacokinetics of loperamide in rats and man, *Arzneimittelforschung* 24(10): 1649-1653

[11] Wuster and Herz, 1978 Opiate agonist action of antidiarrheal agents in vitro and in vivo--findings in support for selective action, *Naunyn Schmiedebergs Arch Pharmacol* 301(3): 187-194

[12] Jaffe et al., 1981 Abuse potential of loperamide: adaptation of established evaluative methods to volunteer subjects *NIDA Res Monogr* 34: 232-240

[13] Vandenbossch et al., 2010 Loperamide and P-glycoprotein inhibition: assessment of the clinical relevance, *Pharmacy and Pharmacology*

1625 Eye Street, NW, Suite 600 | Washington, DC 20006 | T 202.429.9260 | F 202.223.6835 | chpa.org | @chpa

Cardiac effects:

Loperamide has been available as an OTC treatment for diarrhea for many years and has demonstrated an excellent safety profile when taken as directed.[5,14] More recently, a number of case reports of serious cardiac adverse events observed in association with loperamide have been published.[15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32] Several publications have described reports of these events contained in the FDA Adverse Event Database and/or from poison centers via National Poison Data System.[33,34,35,36,37]In the vast majority of cases, these were associated with massive overdoses of loperamide, often in a chronic dose setting. Online sources of information regarding illicit use of legally-marketed pharmaceuticals, including loperamide,[38] appear to have contributed to this rise in

---

[14] Wingate et al., 2001 Guidelines for adults on self-medication for the treatment of acute diarrhea *Aliment Pharmacol Ther* 15(6): 773-782

[15] MacDonald et al., 2015 Loperamide dependence and abuse, *BMJ Case Rep*

[16] Marzec et al., 2015 Torsade de Pointes Associated with High-dose Loperamide Ingestion, *J Innov Card Rhythym Manage* 6:1897-1899.

[17] Spinner et al., 2015 Ventricular tachycardia associated with high-dose chronic loperamide use, *Pharmacother* 35(2):234-238.

[18] Bishop-Freeman et al., 2016 Loperamide-Related Deaths in North Carolina, *J Anal Tox* 40(8):677-686.

[19] Lasoff and Schneir, 2016 Ventricular Dysrhythmias from Loperamide Misuse, *J Emerg Med* 50(3):508-509.

[20] Mukarram et al., 2016 Loperamide Induced Torsades de Pointes: A Case Report and Review of the Literature, *Case Rep Med* 2016:1-3

[21] O'Connell et al., 2016, High-dose loperamide abuse–associated ventricular arrhythmias, *Heart Rhythym Case Rep* 2:232-236.

[22] Quail, 2016 Loperamide Abuse to Decrease Opiate Withdrawal Symptoms - Emergency department nurses must be aware of the signs and dangers, *Adv Health Network Nurses* December 2016

[23] Upadhyay et al., 2016 Loperamide Induced Life Threatening Ventricular Arrhythmia, *Case Rep Cardiol* 2016:1-3

[24] Wightman et al., 2016 Not your regular high: cardiac dysrhythmias caused by loperamide, *Clin toxicol (Phila)* 54(5):454-458.

[25] Bhatti et al., 2017 Loperamide metabolite-induced cardiomyopathy and QTc prolongation, 1-3

[26] Caro et al., 2017 Loperamide Abuse and Life-Threatening Arrhythmias: A Case Report and Literature Review, *Psychosomatics* 58(4):441-445.

[27] Eggleston et al., 2017 Loperamide Abuse Associated With Cardiac Dysrhythmia and Death, *Ann Emerg Med* 69(1):83-86.

[28] Kozak et al., 2017 Torsades de pointes with high-dose loperamide, *J Electrocardiol* 50(3):355-357.

[29] Leo et al., 2017 Methadone Management of Withdrawal Associated With Loperamide-related Opioid Use Disorder, *J Addict Med*

[30] Patel et al., 2017 Takotsubo-Like Cardiomyopathy After Loperamide Overdose, *Am J Ther* doi: 10.1097/MJT.0000000000000595

[31] Rasla et al., 2017 Unexpected Serious Cardiac Arrhythmias in the Setting of Loperamide Abuse, *RI Med J* 100(4):33-36.

[32] Riaz et al., 2017 Cardiac Dysrhythmias Associated With Substitutive Use of Loperamide: A Systematic Review, *Am J Ther* doi: 10.1097/MJT.0000000000000585

[33] Eggleston et al., 2016 Notes from the Field: Cardiac Dysrhythmias After Loperamide Abuse - New York, 2008-2016, *MMWR Morb Mortal Wkly Rep* 65(45):1276-1277.

[34] Borron et al., 2017 Intentional Misuse and Abuse of Loperamide: A New Look at a Drug with "Low Abuse Potential", http://dx.doi.org/10.1016/j.jemermed.2017.03.018

[35] Miller et al., 2017 Loperamide misuse and abuse, *J Am Pharm Assoc* S45-S50.

[36] Swank et al., 2017 Adverse event detection using the FDA post-marketing drug safety surveillance system: Cardiotoxicity associated with loperamide abuse and misuse, 57(2S): S63-S67

[37] Lasoff et al., 2017 Loperamide Trends in Abuse and Misuse Over 13 Years: 2002–2015, *Pharmacotherapy* 37(2): 249-253

[38] Cameron et al., 2013 PREDOSE: a semantic web platform for drug abuse epidemiology using social media, *J Biomed Inform* 46(6): 985-997

1625 Eye Street, NW, Suite 600 | Washington, DC 20006 | T 202.429.9260 | F 202.223.6835 | chpa.org | @chpa

adverse event reports. A 2013 web-based study[39] described cases of illicit use of loperamide among opioid users to treat withdrawal symptoms.

In June 2016, FDA issued a drug safety communication (DSC)[40] noting serious heart problems reported in association with loperamide taken in doses higher than recommended. The majority of these cases involved individuals who were intentionally misusing/abusing high doses of loperamide. A total of 48 serious cases of heart problems associated with loperamide were reported to the FDA Adverse Event Database between 1976 and 2015. Of these reports, there were 31 hospitalizations and 10 deaths all of which involved either doses much higher than labeled dose or the labeled dose plus other concomitant medications which resulted in elevated loperamide levels. Patients were advised to follow the dosing recommendations on the label and to be aware that drug interactions with other medications could increase the risk of serious cardiac adverse events.

Issues described by the FDA in their June 2016 DSC were addressed in a product labeling update for loperamide products in August 2016 when FDA issued a supplement request to update labeling for loperamide NDA products. This included the addition of a "Heart Alert" warning and a revision of pediatric dosing instructions. Similar changes have also been enacted by other regulatory agencies including Health Canada[41] and the European Medicines Agency.[42]

CHPA and member companies marketing OTC loperamide are currently considering a broad range of actions aimed at developing a better understanding of the misuse and/or abuse of loperamide. This includes monitoring and assessment of cases of loperamide abuse on social media and those reported to databases such as the National Poison Data Systems and the Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS), which measures rates of abuse, misuse and diversion of prescription drugs throughout the U.S. Such efforts may contribute to the understanding of trends and aid the development of effective interventions.

We are also discussing ways to effectively communicate with a broad range of stakeholders in this effort as a means of enhancing understanding and awareness of this issue. Through cooperative efforts such as these, and ongoing monitoring, CHPA believes that loperamide can safely remain an over-the-counter product.

Changing loperamide from OTC to prescription is unlikely to meaningfully alter the already low numbers of misuse/abuse. Incidences of prescription drug overdose leading to serious adverse events or death have greatly increased in the U.S. in recent years. This has been in large part due to

---

[39] Daniulaityte et al., 2013 "I just wanted to tell you that loperamide WILL WORK": A web-based study of extra-medical use of loperamide, *Drug Alc Depend* 130: 241-244.

[40] FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse (June 7, 2016; updated November 2016).

[41] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database/label-safety-assessment-update/product-monograph-brand-safety-updates.html

[42] http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2017/03/WC500223722.pdf

1625 Eye Street, NW, Suite 600 | Washington, DC 20006 | T 202.429.9260 | F 202.223.6835 | chpa.org | @chpa

cases of prescription opioid abuse.[43,44] It is thus clear that prescription status does not prevent a pharmaceutical product from being abused.

CHPA advocates for the safe use of all OTC medicines by encouraging consumers to follow directions provided on the Drug Facts panel.

We appreciate the opportunity to comment on this Petition. Please feel free to contact me should you have any questions.

Regards,

Jay Sirois, Ph.D.
Senior Director, Regulatory & Scientific Affairs
Consumer Healthcare Products Association

[43] Faul et al., 2017 Methadone Prescribing and Overdose and the Association with Medicaid Preferred Drug List Policies — United States, 2007–2014, *MMWR* 66(12): 320-323
[44] Rudd et al., 2016 Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015, *MMWR Morb Mortal Wkly Rep* 65(5051): 1445-1452

1625 Eye Street, NW, Suite 600 | Washington, DC 20006 | T 202.429.9260 | F 202.223.6835 | chpa.org | @chpa