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DEC 2 0 2017

RE: Docket No. FDA-2015-P-0633

Dear Petitioners,

This letter responds to your citizen petition received on February 27, 2015 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or the Agency) require that over-the-counter (OTC) combination analgesic headache (migraine) products include specific warning language in the drug facts label (DFL) informing patients about the potential for medication overuse headaches (MOH).

We have carefully considered your Petition, related evidence, and material submitted by interested parties to the public docket. For the reasons described below, your request is granted in part, insofar as the Agency is requesting that sponsors of OTC migraine headache products include a specific warning informing patients about the potential for MOH.

I. BACKGROUND

A. Medication Overuse Headache

Migraine sufferers are at risk of developing a condition called MOH. MOH is a migraine-like daily headache or a marked increase in frequency of migraine attacks caused by the overuse of acute migraine drugs, including OTC drug products indicated for migraine. MOH is characterized by the International Headache Society (IHS) as "an interaction between a therapeutic agent used excessively and a susceptible patient."[1] The criteria for MOH from the 2013 International Classification of Headache Disorders 3rd Beta edition (ICHD-III ß) are:

[1] Medication-overuse headache (MOH) [Internet]. London, U.K.: International Headache Society; c2013. Available from: http://ihs-klassifikation.de/en/02_klassifikation/03_teil2/08.02.00_substance.html.

- Headache occurring on 15 days per month in a patient with a pre-existing headache disorder;

- Regular overuse of one or more drugs that can be taken for acute and/or symptomatic treatment of headache for more than 3 months; and

- Not better accounted for by another ICHD-III ß diagnosis.[2]

Most MOH patients have underlying primary headache disorders, including migraines, tension-type headaches, and, rarely, cluster headaches.[3] Those with migraine and tension-type headaches have a higher potential to develop MOH,[4] though most MOH sufferers have migraine headaches.

Migraine is a chronic neurovascular disorder characterized by recurrent attacks of often severe headaches, typically presenting with nausea and sensitivity to light or sound. Migraine headache is typically throbbing, unilateral, and aggravated by physical activity. In adults, migraine attacks usually last from 4 to 72 hours.[5]

To establish a diagnosis of migraine, criteria proposed by the IHS require a combination of some of the aforementioned characteristics and associated symptoms in at least five attacks.[6] Migraine impacts about 12% of the population worldwide,[7] while tension-type headache is "very common[,] with life-time prevalence in the general population between 30% and 78% in different studies."[8]

Migraine headache products are available OTC and by prescription. There are currently two approved new drug applications (NDAs) for OTC products indicated for the treatment of migraine—Excedrin Migraine (acetaminophen 250 mg, aspirin 250 mg, caffeine 65 mg) tablets, caplets and geltabs and Advil Migraine (ibuprofen 200 mg) capsules.[9] The Agency has

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[2] The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia [Internet]. 2013;33(9):650. Available from: http://www.ihs-klassifikation.de/_downloads/mixed/International-Headache-Classification-III-ICHD-III-2013-Beta.pdf.

[3] Munksgaard SB, Jensen RH. Medication Overuse Headache. *Headache.* 2014 Jul-Aug;54(7):1251-1257.

[4] Kristoffersen ES, Lundqvist C. Medication-overuse headache: epidemiology, diagnosis and treatment. *Ther Adv Drug Saf.* 2014 Apr;5(2):87-99.

[5] The International Classification of Headache Disorders, 3rd edition (beta version), supra note 2.

[6] Id.

[7] Episodic Acute Migraine Treatment. Headache: The Journal of Head and Face Pain. The American Headache Society. 2014:1681-1682.

[8] Id.

[9] There are seven currently marketed abbreviated new drug application (ANDA) OTC migraine products (ANDA referencing Excedrin Migraine – 075794 (Perrigo), ANDAs referencing Advil Migraine - 202300 (Amneal Pharms), 078682 (Bionpharma Inc.), 206568 (Humanwell Puracap), 079205 (Marksans Pharma), 077338 (P and L Dev LLC), 203599 (Sofgen Pharms)). Under section 505(j)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21

published draft guidance for industry recommending all new prescription drugs indicated for the acute treatment of migraine include a description of MOH in the "Warning and Precautions" section of the labeling.[10]

B. Legal Background

FDA regulations at 21 CFR 201.66 establish standardized content and format requirements for labeling for all OTC drug products (drug facts labeling or DFL). The DFL for OTC drug products is intended to make it easier for consumers to read and understand OTC drug product labeling, and to use OTC drug products safely and effectively. All OTC DFLs must contain the drug product's active ingredient(s), purpose(s), indication(s), warning(s), contraindication(s), directions for use, and other information, as applicable.

II. DISCUSSION

In your Petition, you claim MOH is a significant health concern and that, as a result, FDA should require OTC migraine headache products to include MOH warning language on the labeling[11] (Petition at 1-2). You specifically request FDA require the DFL for OTC migraine headache products to include a specific statement under "Warnings" informing patients about the potential for MOH (Petition at 1). Additionally, you state the current language—"Stop use and ask a doctor if your migraine is not relieved or worsens after first dose"—is insufficient to alert patients of the potential for MOH (Petition at 1).

A. Evidence of a Safety Risk

FDA reviewed the information and arguments discussed in your Petition, analyzed post-marketing data, and conducted a literature review to assess the evidence of MOH in patients who use acute medications for frequent and routine treatment of recurrent migraines. FDA also established a Tracked Safety Issue (TSI) to identify significant safety issues related to consumers' use of acute migraine OTC drug products. The TSI included performing a search of the FDA Adverse Event Reporting System (FAERS) and analyzing relevant medical literature

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U.S.C 355(j)(2)), a drug product marketed under an ANDA must bear the "same labeling" as that approved for the reference listed drug (RLD). The ANDA applicant is responsible for ensuring the labeling contained in its application is the same as currently approved labeling for the RLD. See the guidance for industry *Revising ANDA Labeling Following Revision of the RLD Labeling*, May 2000, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072891.pdf. We also update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[10] See the draft guidance for industry *Migraine: Developing Drugs for Acute Treatment* (October 2014), available at https://www.fda.gov/downloads/drugs/guidances/ucm419465.pdf. When final, this guidance will represent FDA's current thinking on this topic.

[11] The Petition references "drugs for the acute treatment of headache," "OTC combination analgesic headache medications," and "OTC pain medication" products. However, the request to revise the language in the DFL "Warning" and "Stop Use" sections is specific to information included on the DFL for OTC products indicated for migraine. Thus, FDA interprets the request as limited to OTC products indicated for migraine.

associated with MOH and the use of OTC oral analgesics.[12] As described below, available evidence suggests that overuse of acute migraine drugs, including OTC drug products indicated for migraine, may lead to MOH. Therefore, we have concluded that labeling for OTC drugs indicated for migraine headache should be updated to reflect this new information.

The prevalence of MOH is 1 to 2% in the general population and is present in up to 50% of patients seen in headache centers.[13] MOH is typically predominant in patients with a high baseline frequency of episodic migraines (more than 10 to 14 days per month).[14] One study concluded that "[in] headache centers, over 80% of patients with [MOH] use acute medications on more days than not."[15] Furthermore, MOH can occur with 10 to 15 days of nonsteroidal anti-inflammatory use per month.[16]

MOH may impact both cortical pain related areas as well as pain-related areas in the midbrain.[17] However, at least one study used functional magnetic resonance imaging to show normalization 6 months after reduced exposure to migraine medications, suggesting the potential for MOH reversal.[18] Treatment for MOH requires withdrawal from overused medications, which patients may do on their own by reviewing simple information on MOH, restricting medication intake, and seeking other treatment options for migraines.[19] Research suggests that MOH improves following discontinuation of pain medicines, although headaches initially worsen after withdrawal.[20]

The Agency's analysis of the data obtained from FAERS and the medical literature determined that there is a reasonable causal association between MOH and the use of OTC migraine headache products. The evidence discussed above suggests that overuse of acute migraine drugs may lead to MOH. Thus, FDA is requesting that sponsors of OTC migraine headache products add a warning about MOH to the DFL to educate consumers about the risk associated with overuse of OTC migraine headache products.

B. Labeling of Currently Marketed OTC Migraine Headache Products

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[12] The Agency uses the Document Archiving, Reporting, and Regulatory Tracking System to track and ensure timely evaluation and management of significant post-market safety issues.

[13] Kristoffersen ES, Lundqvist C. Medication-overuse headache: epidemiology, diagnosis and treatment. *Ther Adv Drug Saf.* 2014 Apr;5(2):87-99.

[14] Starling AJ, et al. Risk of development of medication overuse headache with nonsteroidal anti-inflammatory drug therapy for migraine: a critically appraised topic. *Neurologist.* 2011 Sept;17(5):297-299.

[15] Bigal ME, et al. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. *Headache.* 2008 Sept;48(8):1158.

[16] Tepper SJ. Medication-overuse headache. *Continuum (Minneap Minn).* 2012 Aug;18(4):807-822.

[17] Munksgaard, SB, Jensen, RH, Medication Overuse Headache. Headache. 2014 Jul/Aug 1251-1257.

[18] Id.

[19] Id.

[20] Id.

You request that FDA require the DFL for OTC migraine headache products warn patients of the potential for MOH (Petition at 1). You specifically reference the draft guidance for industry *Migraine: Developing Drugs for Acute Treatment* (Migraine Guidance) and suggest the warning language provided in the Migraine Guidance be included on the DFL for currently marketed OTC migraine headache products (Petition at 2).

The Agency agrees that a DFL change for OTC products with an approved indication for migraine is appropriate[21] and has sent a CBE Supplement Request letter to sponsors of currently marketed OTC migraine headache products advising that the class labeling for OTC drugs indicated for migraine headache should be updated to advise consumers that overuse of acute migraine drugs may lead to an exacerbation of headache.

However, the Agency does not believe that the language in the Migraine Guidance is appropriate for the OTC drug products subject to your Petition. The suggested warning language in the Migraine Guidance was intended for use in prescription labeling and is too lengthy and complex for inclusion in an OTC DFL. In addition, it references certain prescription-only drug ingredients. An OTC DFL requires concise language because of the limited size of the labeling, and must adhere to the requirements in 21 CFR 201.66. Therefore, we are not recommending that the Migraine Guidance warning language be incorporated into the DFL for OTC migraine headache products.

Instead, the Agency is requesting that sponsors clarify the risk of MOH by modifying the "Warnings" section of the DFL for OTC migraine headache products to include the following language:

> ***Medication overuse headache warning:*** *Headaches may worsen if this product is used for 10 or more days per month.*

On February 23, 2017, the Agency also added a consumer update on the Agency website informing consumers about migraines and the potential for MOH with overuse of OTC migraine headache products.[22]

We recognize the evolving science in the area of MOH and are analyzing the broader impact of other drug products on MOH. Although there are other OTC general pain indication products with the same or similar ingredients as OTC migraine headache products, the Agency has determined that consumers seeking OTC products indicated for migraine, rather than consumers seeking products with a general pain indication, are the critical population to target with the MOH warning. Accordingly, at this time, we are only requesting OTC products with a migraine indication to include the MOH warning in the DFL.

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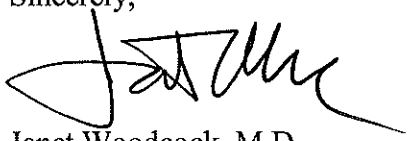
[21] Labeling for monograph products with general pain indication already includes language warning consumers not to take the product for pain for more than 10 days. "Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph," 53 FR 46204 (November 16, 1988) (IAAA TFM), available at https://cdn.loc.gov/service/ll/fedreg/fr053/fr053221/fr053221.pdf. While not specific to MOH, this language provides the same 10-day limitation as the MOH warning outlined in this Petition Response.

[22] See https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm414707.htm.

III. CONCLUSION

For the reasons set forth above, the Petition is granted in part, insofar as the Agency is requesting that the DFL for OTC migraine headache products include a specific warning informing patients about the potential for MOH.

Sincerely,



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