Jonathan H. Smith, M.D. et. al.
Headache Specialist
(b) (6)

February 14, 2025

Re: Docket No. FDA-2022-P-0215

Dear Petitioners:

This letter responds to your citizen petition received February 24, 2022 (Petition). The Petition requests that the Food and Drug Administration (FDA, the Agency, or we) require the "manufacturers of OTC products associating the terms 'sinus' and 'headache' . . . revise product names and box labeling to remove the direct linkage of these specific terms." You state that "[r]evision of 'headache' to 'pain' or 'pressure' would be more acceptable" (Petition at 1). You also request a warning be added to these products "alerting consumers that migraine is the most common diagnoses among those with sinus pain and pressure" (Petition at 1).

We have carefully considered the Petition. For the reasons described below, your Petition is denied.

I. Background

A. Legal Framework for Nonprescription Drugs

There are two regulatory pathways to bring a nonprescription drug to market in the United States: the drug application process under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and the over-the-counter (OTC) drug monograph process under section 505G of the FD&C Act (21 U.S.C. 355h). Under the drug application process, a person who seeks to market a new drug must obtain approval of an application filed pursuant to subsection (b) or (j) of section 505 of the FD&C Act. New drug applications (NDAs) are submitted under 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 (21 U.S.C. 355(c)). Abbreviated new drug applications (ANDAs) are submitted under section 505(j) of the FD&C Act.

On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act (CARES Act; Public Law 116-136) was signed into law. The CARES Act added section 505G to the FD&C Act (21 U.S.C. 355h), which reforms and modernizes the framework for the regulation of OTC monograph drugs. An OTC monograph drug product is generally recognized as safe and effective (GRASE) and not misbranded if it meets each condition in the applicable OTC monograph and each general condition in FDA regulations at 21 CFR 330.1.

As relevant to your Petition, nonprescription drug products, including those marketed under NDA or ANDA, or according to the conditions of an OTC monograph, are required to be labeled with certain warnings.

B. "Sinus headache" and classification of headache disorders

The Petition states that "sinus headache" is an imprecise diagnosis, and "the overwhelming majority of patients presenting with physician-diagnosed or self-described 'sinus headache' have an actual diagnosis of migraine" (Petition at 1). We agree that sinus headache is an imprecise term used by laypersons to describe a symptom; and in fact, many sufferers have migraine or migrainous symptoms.[1,2] "Sinus headache" is not an indication in any OTC monograph. In addition, FDA has not approved any NDA or ANDA with an indication of "sinus headache." Professional organizations such as the International Headache Society (IHS) that set the standards for the classification of headache used for clinical trial design do not recognize the term "sinus headache."[3,4]

The IHS divides headache disorders into primary and secondary headaches. Migraine, a primary headache disorder, is defined as a recurring headache disorder with at least two of four characteristics: unilateral location, pulsating quality, moderate to severe pain intensity, and aggravated by activity. According to IHS criteria, during the headache there must be at least one of the following: nausea and/or vomiting, photophobia, and phonophobia. When headaches meet some, but not all, of these characteristics, or have atypical characteristics, they may be considered migrainous (now referred to as probable migraine).[5]

Secondary headache disorders are headaches attributed to other underlying medical conditions. One type of secondary headache described in the IHS' International Classification of Headache Disorders (ICHD-3) includes the term "headache attributed to disorders of the nose or paranasal sinuses" to include "headache attributed to acute rhinosinusitis" and "headache attributed to chronic or recurrent rhinosinusitis."[6] These terms describe a headache that is temporally related to rhinosinusitis and causes pain that can be exacerbated by applying pressure over the paranasal sinuses. Such headaches are not better accounted for by other ICHD-3 diagnoses, such as a primary headache disorder like migraine, and are hence designated as a type of secondary headache. Pathological changes on imaging that correlate with the patient's pain description alone are not enough to secure the diagnosis of headache attributed to chronic or recurring

[1] Lal D, Rounds A, Dodick DW. Comprehensive management of patients presenting to the otolaryngologist for sinus pressure, pain, or headache. Laryngoscope. 2015;125(2):303-310. doi:10.1002/lary.24926.
[2] Cady RK, Dodick DW, Levine HL, et al. Sinus headache: a neurology, otolaryngology, allergy, and primary care consensus on diagnosis and treatment. Mayo Clin Proc. 2005;80(7):908-916. doi:10.4065/80.7.908 (hereinafter, Cady et al. 2005).
[3] Robblee J, Secora KA. Debunking Myths: Sinus Headache. Curr Neurol Neurosci Rep. 2021;21(8):42. Published 2021 Jun 20. doi:10.1007/s11910-021-01127-w (hereinafter, Robblee and Secora 2021).
[4] Cady et al. 2005.
[5] https://ichd-3.org/1-migraine/1-5-probable-migraine/
[6] IHS Classification; ICHD -3. https://ichd-3.org/11-headache-or-facial-pain-attributed-to-disorder-of-the-cranium-neck-eyes-ears-nose-sinuses-teeth-mouth-or-other-facial-or-cervical-structure/11-5-headache-attributed-to-disorder-of-the-nose-or-paranasal-sinuses/11-5-1-headache-attributed-to-acute-rhinosinusitis.

rhinosinusitis as made by a healthcare provider. The patient's medical history and physical examination are important in making a diagnosis.

The American Academy of Otolaryngology-Head and Neck Surgery, another professional organization of experts, also recognizes that headache may accompany acute, subacute, and chronic rhinosinusitis, but headaches are not identified as a major symptom.[7] Major symptoms include purulence in the nasal cavity, nasal discharge, facial pain, pressure, congestion, fullness, nasal obstruction, blockage, fever, hyposmia, and anosmia. Physicians may have difficulty making a swift and accurate diagnosis even with unremarkable endoscopy or computerized tomography results.[8]

In summary, although those with rhinosinusitis may have migraine or may have nonspecific pain, the term "sinus headache" is an imprecise term that a layperson may use to describe their symptoms and a healthcare provider, often a specialist, makes the diagnosis based on the totality of presentation including history, symptoms, examination, and occasionally imaging.

We have reviewed studies provided by the Petition to support the claim that "the overwhelming majority of patients presenting with physician-diagnosed or self-described 'sinus headache' have an actual diagnosis of migraine" (Petition at 1). According to those studies provided in the Petition, individuals presenting with "sinus headache" conditions have other diagnoses as well and often require the assessment of a specialist rather than a family physician to make a diagnosis (Petition at 1 and 2). Although there are some methodological limitations to these studies, these data support the statement that patients and physicians have difficulty distinguishing migraine from sinus-related headache. However, for the reasons discussed below, this is not a basis to grant the requests in your Petition.

II. **Discussion**

A. FDA Declines Your Request to Revise Product Names and Labeling

The Petition has requested "that manufacturers of OTC products associating the terms 'sinus' and 'headache' . . . revise product names and box labeling to remove the "direct linkage" of those terms" (Petition at 1).

We decline this request because, as discussed below, the allowable labeling statements in the relevant OTC monographs do not include "sinus headache" as an allowable indication, nor do they permit what we understand you mean by "direct linkage" of the terms "sinus" and "headache." Further, there are no nonprescription drugs approved for the indication "sinus headache" under an NDA or an ANDA. However, it may be appropriate to include both the terms "sinus" and "headache" in the labeling of certain nonprescription drug products.

Final Administrative Order OTC000026, "Over-the-Counter Monograph M012: Cough, Cold, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use"

[7] Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. Otolaryngol Head Neck Surg. 2015;152(2 Suppl):S1-S39. doi:10.1177/0194599815572097.
[8] Robblee and Secora 2021.

identifies certain permitted combinations of ingredients in drug products, including combinations of certain decongestant and analgesic-antipyretic active ingredients.[9] The administrative order provides that, for OTC drug products containing certain permitted combinations, "when labeled for relief of . . . nasal congestion symptoms" (which can include temporary relief of sinus pressure), "[t]he labeling for the analgesic-antipyretic ingredients states 'temporarily relieves [bullet] minor aches and pains [bullet] headache'"[10]

It may, therefore, be appropriate to include the terms "sinus" and "headache" in the labeling of a nonprescription drug product, if consistent with the permitted ingredient combinations and indications described above. We do not understand your petition to argue that without a direct linkage, the terms "sinus" and "headache" should not both appear in the labeling of a nonprescription drug. Your petition does not request that FDA take action with respect to labeling that includes both the terms "sinus" and "headache," provided there is not a "direct linkage" between the two. The indications described above do not provide what we understand you to consider a "direct link" between the terms "sinus" and "headache."

In conclusion, it would be inconsistent with the conditions described in any OTC monograph for labeling of an OTC drug product to include claims concerning treatment of "sinus headache." Further, as noted above, there are no nonprescription drug products with treatment of "sinus headache" as an approved indication. To the extent you are requesting we take an enforcement action with respect to drug products with claims concerning treatment of "sinus headache," we note that such action would not properly be the subject of a citizen petition under FDA's regulations.[11] Therefore, we decline your request to require manufacturers to revise product labeling.

B. We Decline Your Request to Add a "Sinus Headache" Warning

The Petition requests a "sinus headache" warning be added to OTC products that associate the terms "sinus" and "headache," alerting consumers that migraine is the most common diagnosis among those with sinus pain and pressure. It is unclear what you mean by an "association" of the terms "sinus" and "headache." As discussed above, the conditions in the relevant OTC monographs, and the labeling of approved nonprescription prescription drug products, do not include a "sinus headache" indication. We respond to this request with regard to nonprescription drug products whose labeling includes both the terms "sinus" and "headache." We decline to require such a warning.

[9] *See* M012.40, "Permitted combinations of active ingredients."
[10] *See* M012.85(b)(2).
[11] Under 21 CFR 10.30, a person may petition the Agency to issue, amend, or revoke a regulation or order or to take or refrain from taking any other form of administrative action. FDA regulations in §10.30 define "administrative action" as "every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner, except that it does not include the referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or an act in preparation of a referral." Similarly, under §10.30(k), citizen petitions may not be used with respect to "referral of a matter to a United States attorney for the initiation of court enforcement action and related correspondence." Agency decisions to take, or to refrain from taking, enforcement action are decisions related to the "referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or acts in preparation of such referrals" and therefore are not properly the subject of a citizen petition. We nevertheless appreciate the information you provided. We take such information seriously, and we will evaluate the information to determine what, if any, follow-up action is appropriate.

To mitigate potential risk, combinations described in OTC Monograph M013 containing a nasal decongestant and an analgesic-antipyretic must be labeled with certain warnings. This includes, for products labeled only for adults, a warning to stop use and ask a doctor if pain or nasal congestion gets worse or lasts more than 7 days.[12] We believe the existing warnings described in the monograph are sufficient.

Further, adding the warning proposed by the Petition, "that migraine is the most common diagnosis among those with sinus pain and pressure," may imply that nonprescription drug products indicated to treat both headache and nasal congestion/sinus congestion are appropriate for use to treat migraine. However, nonprescription drug products approved for migraine include distinct warnings in the drug facts panel, including the warning to "ask a doctor before use" if, among other things, "you have never had migraines diagnosed by a health professional" or "you have a headache that is different from your usual migraines." The physician can advise the consumer about whether the nonprescription drug product is appropriate for his or her treatment. Additionally, the label for nonprescription migraine relief medications includes a medication overuse headache warning, "headaches may worsen if this product is used for 10 or more days per month." Including the proposed "sinus headache" warning on products not indicated for migraine treatment (e.g., products indicated to treat both headache and nasal congestion/sinus congestion) could misleadingly suggest that these products are appropriate for use in treating migraine, but they would lack the important warnings described above.

For these reasons, we deny your request to require your proposed warning for nonprescription drug products.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

Jacqueline A. Corrigan-curay -S

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[12] *See* M012.85(c)(3)(iii).