DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 28 2014

Matthew M. Malloy
Associate General Counsel
The Procter & Gamble Company
299 East 6th St.
Cincinnati, OH 45202

Re: Docket No. FDA-2013-P-1286

Dear Mr. Malloy:

This responds to the citizen petition (Petition) you submitted on behalf of The Procter & Gamble Company (P&G) dated October 11, 2013. In the Petition, you request that the Food and Drug Administration (FDA) take the following actions:

1. Continue to require similar labeling applicable to all over-the-counter (OTC) proton pump inhibitors (PPIs), substantially equivalent to that approved for Prilosec OTC [(omeprazole, 20 milligrams (mg), as omeprazole magnesium, 20.6 mg) (Prilosec OTC)] for subsequent OTC PPIs approved for marketing; this includes:
   (a) Appropriate statements conveying that the product is not intended for immediate treatment of heartburn and instead may take one or more days for full effect, in both the "Use" and "Directions" sections of the Drug Facts Box, such as: "Use . . . not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect" and "Directions . . . It may take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours";
   (b) "Directions" that the patient must use the product once a day (every 24 hours), every day for 14 days;
   (c) Statements detailing the appropriate 14-day course of treatment, such as: swallow 1 tablet (capsule) with a glass of water before eating in the morning; take every day for 14 days; do not take more than one tablet (capsule) a day; and do not use for more than 14 days unless directed by your doctor; and
   (d) Appropriate statements conveying that the 14-day course of treatment may be repeated every 4 months, but do not take more than 14 days or more often than every 4 months, unless directed by a doctor.
2. Impose the same rigorous standards upon any pending or future application seeking approval to market a PPI over the counter for treatment of frequent heartburn as were imposed during the review of [new drug application] (NDA) 21-229 for OTC use of Prilosec OTC.

3. If data submitted in support of any pending or future application seeking approval to market an OTC PPI for treatment of frequent heartburn suggests that the label statements referenced in 1.(a)-(d) above could differ from the currently approved statements in the "Use" and "Directions" sections of the Prilosec OTC Drug Facts Box, assure that:

   (a) the differences are clinically significant; and

   (b) the label statements do not explicitly or implicitly convey an impression as to relative safety or efficacy of one OTC PPI over another that lacks adequate substantiation in the form of well-designed comparative studies or that are false or misleading.

(Petition at 1-2)

Additionally, you argue that FDA should develop appropriate class labeling applicable to all OTC PPIs (Petition at 5).

We begin by noting that when appropriate, based on the data presented to us in individual applications submitted for approval, FDA does, to the extent possible, attempt to approve consistent labeling across products in a given product class. We seek to avoid artificial labeling distinctions that have the potential to lead to misleading advertising claims or consumer misunderstanding. The application you mention in the Petition, an OTC PPI with esomeprazole magnesium as the active ingredient, 20 mg (with the trade name Nexium 24HR), was approved today, and the labeling for that product is similar, in all relevant respects addressed in the Petition, to the approved labeling for Prilosec OTC. The approval of this product and the similarities in the two labels makes some aspects of the requests in your Petition moot. With regards to your request that FDA establish class-wide labeling for OTC PPIs and to the extent that you are asking FDA to make predeterminations about labeling for future OTC PPIs, your Petition is denied.[1]

I. BACKGROUND

A. Proton Pump Inhibitors

PPIs are inhibitors of the gastric H+,K+-ATPase (proton pump) and can diminish the daily production of acid (basal and stimulated) by 80 percent to 95 percent. Six active ingredients are approved as PPIs for clinical use: omeprazole and its S-isomer esomeprazole, lansoprazole and its R-isomer dexlansoprazole, rabeprazole, and pantoprazole. All of these PPIs have different substitutions on their pyridine and/or benzimidazole groups. Maximal suppression of acid secretion requires several doses of the PPIs because a PPI can only inactivate an activated proton pump and not all pumps are active simultaneously.

[1] We note that your requests echo the requests in your April 9, 2009, citizen petition (FDA-2009-P-0183) to which we responded on October 2, 2009.

B. Prilosec OTC

On June 20, 2003, FDA approved NDA 21-229 for Prilosec OTC with the indication "treats frequent heartburn (occurs 2 or more days a week)" (emphasis in original).[2] The "Use" section of Prilosec OTC's current label states: "not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect." The current "Directions" section of the Prilosec OTC label reads: "it may take 1 to 4 days for full effect; some people get complete relief of symptoms within 24 hours." This label was developed and implemented in conjunction with the approval of NDA 21-229 for Prilosec OTC.

C. Nexium 24HR

In the Petition you state that you believe there is an application pending before FDA seeking approval to market an OTC PPI with esomeprazole magnesium as the active ingredient, 20 mg. An application with the trade name Nexium 24HR was approved today (NDA 204655). Like Prilosec OTC, Nexium 24HR was approved with the indication "treats frequent heartburn (occurs 2 or more days a week)." In addition, the Nexium 24HR label contains statements in the "Use" and "Directions" sections that are similar to those quoted above with respect to the Prilosec OTC label.

D. Labeling for OTC Drugs

Labeling for OTC products approved under an NDA is generally governed by 21 CFR 201.60, et seq. The specific format and content requirements for OTC drug product labeling, including the "Drug Facts" labeling, are set forth in 21 CFR 201.66. Additional labeling requirements can be found in 21 CFR Part 201.

II. DISCUSSION

You request that FDA develop appropriate class labeling applicable to all OTC PPIs or conform future approved labeling to that approved for Prilosec OTC (Petition at 5). You also request that FDA impose the same approval standards upon any pending or future application seeking approval to market a PPI over the counter for treatment of frequent heartburn as were imposed during the review of Prilosec OTC (Petition at 1). Lastly, you request that if data submitted in support of any pending or future application seeking approval to market an OTC PPI for treatment of frequent heartburn suggests that label statements referenced in the Petition could differ from the currently approved statements in the "Use" and "Directions" sections of the Prilosec OTC Drug Facts Box, FDA assure the differences are clinically significant and do not convey an impression as to relative safety or efficacy of one OTC PPI over another that lacks adequate substantiation or that is false or misleading (Petition at 2).

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[2] Omeprazole capsules (10 mg, 20 mg, and 40 mg) are approved as a prescription product (under the trade name "Prilosec") for the treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (GERD), treatment of duodenal and gastric ulcer, pathological hypersecretory conditions, and eradication of H. Pylori as part of triple therapy.

We appreciate your request for consistency across labeling of similar products. However, we note that FDA does not intend to (1) require all OTC PPIs to carry similar labeling in the "Use" and "Directions" sections of the label without regard to the data submitted in the NDAs for individual products or (2) prospectively develop class labeling for all OTC PPIs. In accordance with our regular practice, FDA will continue to review and approve the final product labeling for proposed products based upon data submitted in connection with each product and may approve labeling that differs from a similar product if warranted. Accordingly, as elaborated upon below, we deny your requests.

A. Your Request Requiring Class Labeling for All OTC PPIs and Labeling Language Similar to Prilosec OTC

In addition to requesting that FDA develop class labeling for all OTC PPIs (Petition at 5), you request that FDA continue to require similar labeling applicable to all OTC PPIs, "substantially equivalent" to that approved for Prilosec OTC, for subsequent OTC PPIs approved for marketing (Petition at 1).

FDA attempts to keep labeling consistent across individual products within a given product class when appropriate. PPIs as a class have a similar mechanism of action. Symptom data from clinical trials for available OTC PPIs demonstrate 2 to 5 days of therapy are required to reach a plateau effect in the relief of frequent heartburn. In light of these similarities, at present the labeling for OTC PPIs, including that for Nexium 24HR, is consistent across this product class and, in this case, is substantially similar to Prilosec OTC. However, we cannot preclude the possibility that different labeling might be appropriate for an OTC PPI drug if warranted based on the specific data submitted for that product.

Next, you argue that differences in "Use" and "Directions" are likely to be misunderstood by consumers to mean that there are clinically significant differences between products (Petition at 6). With regards to Nexium 24HR, this point is moot since the Nexium 24HR labeling is similar to the approved labeling for Prilosec OTC. Should a sponsor seek non-similar labeling for an OTC PPI, FDA would consider the issue of consumer confusion as appropriate.

Accordingly, we deny your request that FDA develop class labeling for all OTC PPIs and your request for similar labeling for all OTC PPIs "substantially equivalent" to that approved for Prilosec OTC.[3]

B. OTC PPI Drug Application Standards

You request that FDA impose the "same rigorous standards" that were imposed during the review of Prilosec OTC upon any pending or future application seeking to market an OTC PPI for treatment of frequent heartburn (Petition at 1).

[3] Our denial of your request that we develop class labeling for all OTC PPIs, however, does not preclude the possibility that specific class labeling may be appropriate in the future based on an identified risk, for example.

Every NDA must demonstrate that the drug product at issue is safe and effective under Section 505 of the FD&C Act to be approved by FDA. Prilosec OTC, Nexium 24HR, and all other NDA prescription to nonprescription "switch" applications are subject to the same statutory and regulatory requirements for approval to market a new drug outlined in section 505(d) of the FD&C Act and 21 CFR Part 314. In general, when a drug product changes from prescription to nonprescription status FDA requires consumer studies such as labeling comprehension and actual use studies to help establish safety and efficacy in the OTC setting. However, consumer studies may not need to be conducted if the proposed labeling is highly similar to previously approved OTC products.

The applicant for Nexium 24HR was required to perform two phase 3 clinical studies to demonstrate safety and efficacy for the frequent heartburn indication. This was the same requirement imposed on P&G for its Prilosec OTC NDA. However, the Nexium 24HR applicant was not required to perform consumer studies because the proposed labeling was almost identical to the labeling for other OTC PPIs.

In sum, FDA already imposes and will continue to impose the same statutory and regulatory requirements for approval for all drug products, including OTC PPIs. To the extent you may be asking FDA to impose some other approval standard on any pending or future application seeking to market an OTC PPI for the treatment of frequent heartburn, your request is denied.

C. OTC PPI Labeling Different From Current OTC PPIs

You also request that:

> [i]f data submitted in support of any pending or future application seeking approval to market an OTC PPI for treatment of frequent heartburn suggests that the label statements . . . could differ from the currently approved statements in the "Use" and "Directions" sections of the Prilosec OTC Drug Facts Box, assure that:
>
> (a) the differences are clinically significant; and
>
> (b) the label statements do not explicitly or implicitly convey an impression as to relative safety or efficacy of one OTC PPI over another that lacks adequate substantiation in the form of well-designed comparative studies or that are false or misleading.

(Petition at 2)

As stated above, you are asking in part that FDA not approve labeling for an OTC PPI that is false or misleading. Under the FD&C Act and FDA's implementing regulations, FDA cannot approve labeling that is false or misleading. The labeling that is approved for any particular drug product is dependent on the data submitted in the NDA for that drug product. FDA approves the final product labeling for any given product based upon the clinical data submitted to support the approval of the NDA for that product. Any claim in the final product labeling, including any suggestions of relative safety or efficacy of one OTC PPI compared to another, must be supported by appropriate data substantiating the claim. If a sponsor provides supporting data based on adequate and well-controlled trials through the NDA process that would support

alternate labeling, we will consider whether that labeling is appropriate for the particular product. Please note that we decline to impose a "clinically significant differences" standard on any alternate labeling that may be proposed in the future in connection with an OTC PPI drug. However, as mentioned above, any such labeling has to be supported by adequate data.

Therefore, these requests are denied.

III. CONCLUSION

Based on the reasons described in this response, your Petition is denied.

Sincerely,

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