

IN THE FOOD AND DRUG ADMINISTRATION

Citizen Petition for Denial of
Over-the-Counter Status
to Omeprazole Magnesium
(Brand-Name Prilosec)

Docket No. _____

Submitted on Behalf of Andrx Pharmaceutical Corp.

November 20, 2002

02P-0493

CP1

Citizen Petition

Pursuant to 21 C.F.R. § 10.30, Andrx Pharmaceutical Corp. hereby submits this Citizen Petition to the Food and Drug Administration (“FDA”) concerning the Agency’s review of an over-the-counter (“OTC”) version of the anti-heartburn drug omeprazole magnesium (brand name Prilosec1), manufactured by Procter & Gamble (“P&G”) and AstraZeneca. The OTC version of omeprazole magnesium is hereafter referred to in this Petition as “OTC Prilosec” or “Prilosec1.”

A. Action Requested

P&G/AstraZeneca seek to have OTC Prilosec approved for the general, 24-hour prevention of heartburn in individuals who suffer from “frequent” heartburn – a different use from prescription Prilosec, which is indicated for the treatment of heartburn and other symptoms associated with gastroesophageal reflux disease (“GERD”). Petitioner requests that, pursuant to 21 U.S.C. § 355(d), FDA deny P&G/AstraZeneca’s New Drug Application (“NDA”) seeking Agency approval of this new OTC use.

In this petition, we make three basic points. First, the NDA for Prilosec1 should be denied outright because the sponsors have not met their burden of showing that consumers can use Prilosec1 safely and effectively in an OTC setting. Second, even if OTC Prilosec *could conceivably* be used safely and effectively by consumers, P&G/Astra-Zeneca have not conducted sufficient clinical studies to assess the risks associated with OTC use of the product or to establish how best to ensure its safe and effective use by consumers. Third, even if no additional clinical studies are necessary, Prilosec1 should not be approved until the sponsors make significant modifications to the product label, including but not limited to those changes recommended by the FDA Advisory Committee that has studied this issue.

B. Statement of Grounds

While Prilosec has been shown to be safe and effective when prescribed by and used under the care of a physician to address symptomatic heartburn associated with GERD, P&G/AstraZeneca have not demonstrated that Prilosec1 can be used safely and effectively by consumers who purchase the drug OTC for the different purpose of frequent heartburn prevention and who must therefore rely on their own, largely inexperienced, judgment in deciding whether, when, and how to use the drug. Indeed, much of the evidence gathered by FDA, as well as by the Agency's Gastrointestinal and Nonprescription Drug Advisory Committees ("Advisory Committee")¹, reveals that consumers will *not* use OTC Prilosec properly in the absence of guidance from a physician – *i.e.*, that some consumers will purchase and use the drug even though they are not in need of frequent heartburn prevention medication, and that other consumers, for whom the drug may be appropriate, will not use it in a safe or effective manner. This evidence therefore suggests that Prilosec1 should not be approved for the new OTC use for which it has been proposed.

Even if Prilosec1 could be used safely and effectively by consumers in an OTC context for the prevention of heartburn, P&G/AstraZeneca have not sustained their burden of showing that conditions for safe and effective use are present now. To meet this burden, the manufacturer must demonstrate that it has (1) studied the unsupervised use of the drug and identified the risks that are likely to result from such use and (2) developed adequate labeling that will apprise consumers of, and help protect them from, these risks. P&G and AstraZeneca have done neither,

¹ The Gastrointestinal and Nonprescription Drug Advisory Committees acted jointly in considering whether to approve Prilosec1 for OTC use and are therefore referred to in the singular in this Petition.

despite the abundant evidence that consumers will not use OTC Prilosec in the manner directed by the manufacturer and that such misuse can cause Prilosec1 to be used in an unsafe and ineffective manner. Until P&G/AstraZeneca (1) conduct additional clinical studies to determine the risks associated with OTC use of Prilosec1 *and* (2) make all necessary labeling changes to address and notify consumers of those risks, the risks of using Prilosec1 in an OTC setting outweigh the benefits and FDA should deny the sponsors' amended NDA.

FDA has already notified P&G/AstraZeneca that they must develop and test new labeling for OTC Prilosec before approval can be granted. While these labeling changes are certainly necessary, they are insufficient to make Prilosec1 appropriate for OTC use. As discussed below, there are many issues regarding the use of OTC Prilosec that P&G/Astra-Zeneca have not studied *at all*, that are nowhere addressed in the product label, and that require full clinical review before OTC approval can be granted. One point bears repeating – the use for which Prilosec1 is proposed in the OTC context differs from the uses for which *prescription* Prilosec has been approved. Thus, there remains a great deal of uncertainty as to whether consumers can use Prilosec1 safely and effectively (1) for this new indication and (2) in the absence of physician supervision. P&G/AstraZeneca must establish, through additional clinical studies and by making appropriate labeling changes, that such safe and effective use is possible. It is insufficient for the sponsors to simply revise the product label based on the currently existing data for OTC Prilosec – data which fails to address many aspects of the sponsors' newly proposed use.

In Section 1, below, we discuss the review of OTC Prilosec that has taken place to date, focusing on the key findings by FDA and the Advisory Committee regarding consumer selection,

use and understanding of the OTC product. In Section 2, we discuss in greater detail the specific issues that make OTC approval inappropriate for Prilosec1 at this time.

1. Background

Prilosec is a “proton pump inhibitor” (“PPI”) and was approved for prescription use in 1989. P&G/AstraZeneca first submitted an original NDA seeking an “Rx-to-OTC” switch in January 2000. OTC approval for Prilosec1 would make that drug the first PPI to be available without a prescription.

There are currently two other types of anti-heartburn medication available over the counter – antacids (*e.g.*, Tums, Roloids) and “H2-Antagonists” (*e.g.*, Zantac 75 and Pepcid AC). These medications are all indicated for the *treatment* of heartburn symptoms – *i.e.*, to respond to episodic attacks of heartburn. H2-Antagonists are also indicated for the *prevention* of episodic, meal-induced heartburn, but general 24-hour prevention is not currently available OTC.² The original NDA for OTC Prilosec sought to market that drug as a means of addressing episodic heartburn *and* for the 24-hour prevention of heartburn.³ On October 20, 2000, the Advisory Committee considered this application and declined to recommend the approval of OTC Prilosec on the grounds that, *inter alia*:

- The efficacy, appropriate dose and duration of therapy, and use of Prilosec1 in the OTC setting had not been adequately established;
- consumers would be unable to appropriately self-select and to use Prilosec1 safely and effectively in an OTC setting;

² May 23, 2002 Memorandum from FDA’s OTC Omeprazole Magnesium (Prilosec1) Review Team to Gastrointestinal and Nonprescription Drug Advisory Committee Members, Consultants, and Guests (hereafter “*FDA Review Memorandum*”), available at http://www.fda.gov/ohrms/dockets/ac/02/briefing/3861B1_02_A-summary%20memo.pdf, at p.1.

³ As mentioned above, *prescription* Prilosec is not indicated for 24-hour prevention, but rather to treat symptomatic heartburn associated with GERD.

- the data had not adequately demonstrated the ability of consumers to comprehend the risks associated with specific drug interactions, nor the ability of consumers to avoid concomitant use of specific interacting drugs without the intervention of a physician; and
- the manufacturer had not established that consumers would not use OTC Prilosec for extended periods of time without contacting a health care provider.

FDA Center for Drug Evaluation and Research, *OTC Medical Officer's Review for Prilosec1*, April 16, 2002 (hereafter "*FDA Medical Officer's Review*"), available at http://www.fda.gov/ohrms/dockets/ac/02/briefing/3861B1_03_A-Actual%20use.pdf, at pp. 6-7 (recounting October 2000 Advisory Committee findings). In short, the Advisory Committee's original conclusions were that Prilosec1 was not effective in preventing heartburn in an OTC setting; that consumers did not have a sufficient understanding of how to use Prilosec1 safely and effectively in that setting; and that, notably, consumers could not independently evaluate and avoid the risks posed by the interactions of Prilosec1 with certain other drugs.

In response to the Advisory Committee's October 2000 decision not to recommend approval of OTC Prilosec, P&G/AstraZeneca modified its NDA to identify a new target population -- those suffering from "frequent heartburn," with "frequent" defined as two or more days a week. This modification contemplated that OTC Prilosec, unlike prescription Prilosec, would not be indicated to address symptomatic heartburn associated with GERD, but only for the *24-hour prevention* of heartburn suffered by the subpopulation of *frequent* heartburn sufferers. In conjunction with this new use, the sponsor recommended that Prilosec1 be used according to a 14-day dosage regime (one 20 mg tablet per day for 14 days), a different regime from that recommended for prescription Prilosec.

In submitting this amended NDA, P&G/AstraZeneca did not provide FDA with any additional clinical evidence to demonstrate the safety and effectiveness of OTC Prilosec for this

new use, relying instead on the studies it had submitted in support of its original NDA for Prilosec¹. P&G/AstraZeneca did, however, submit additional actual use and label comprehension studies to support its contention that consumers would properly select OTC Prilosec for the treatment of frequent heartburn and would use the drug in the manner directed on the OTC label.

In the Spring of 2002, in anticipation of a second Advisory Committee hearing on the proposed Rx-to-OTC switch for Prilosec, FDA reviewed the amended NDA, including the safety and efficacy studies conducted as part of the original NDA for OTC Prilosec and the supplemental actual use and label comprehension studies submitted by P&G/AstraZeneca. In the course of this review, FDA found that:

- OTC Prilosec did not provide immediate relief from heartburn on Day 1 of use, although it grew in effectiveness over the course of the 14-day dosing regime.⁴
- Even at the end of the 14-day dosing regime, approximately 30 percent of the participants in the actual use study experienced an episode of heartburn despite using the OTC medication according to directions, and approximately 40 percent of subjects with high frequency heartburn experienced such episodes.⁵

⁴ *FDA Review Memorandum* at 2 (noting that Prilosec¹ offered only modest therapeutic gain on Day 1 relative to placebo); *FDA Transcript of Joint Public Meeting between Nonprescription Drugs Advisory Committee and Gastrointestinal Drugs Advisory Committee*, June 21, 2002 (hereafter “*Advisory Committee Transcript*”), available at <http://www.fda.gov/ohrms/dockets/ec/cder02.htm#gastrointestinal%20drugs> at 139 (FDA Testimony noting modest therapeutic gain from Prilosec¹ on Day One relative to placebo); *FDA Medical Officer’s Review* at 31 (determining that OTC product label should not state that Prilosec¹ prevents heartburn for 24 hours). See also *Advisory Committee Transcript* at 103 (comments of Advisory Committee Member Dr. Michael Camilleri noting sponsor data showing that Prilosec¹ provided relief from heartburn in less than 50 percent of tested subjects on Day One).

⁵ *FDA Review Memorandum* at 2; *Advisory Committee Transcript* at 139, 141 (FDA Testimony).

- Of those individuals who suffered a recurrence of heartburn after completing the 14-day treatment regimen, only 20 percent consulted their physicians, despite instructions on the proposed OTC label to do so.⁶
- Despite warnings on the proposed OTC product label that a consumer should consult a physician if he/she suffered from heartburn for three months or more before using Prilosec1, over half of those individuals who self-selected OTC Prilosec as part of the actual use study had not done so in the past year and over one third had not done so at all.⁷ Further, only 20 percent of those individuals who had not done so at all consulted a physician during the actual use study.⁸ These results, FDA concluded, “suggest that most people who should consult a physician before using the [OTC] product may not understand that they should do so.”⁹
- Many consumers who suffered from infrequent heartburn inappropriately self-selected OTC Prilosec.¹⁰
- Consumers were likely to select OTC Prilosec for episodic relief, not just for prevention of heartburn, and therefore would use the drug in an ineffective and improper manner.¹¹ FDA further concluded that the proposed OTC label “d[id] not adequately convey to consumers that the product is not for episodic use and that it is only for prevention,”¹² finding that only half of those consumers tested in label comprehension studies correctly identified episodic use of Prilosec1 as inappropriate.¹³

⁶ *FDA Medical Officer’s Review* at 33.

⁷ *FDA Review Memorandum* at 3; *FDA Medical Officer’s Review* at 4, 25.

⁸ *FDA Medical Officer’s Review* at 32.

⁹ *FDA Review Memorandum* at 3.

¹⁰ *Id.*; *FDA Medical Officer’s Review* at 25. *See also Advisory Committee Transcript* at 236 (comments of Advisory Committee Member Dr. Sonia Patten noting that rate of improper self-selection was “unacceptably high”); *id.* at 165 (FDA Testimony noting that actual use study “showed that Prilosec[1] is likely to be used . . . by consumers with infrequent heartburn.”).

¹¹ *FDA Review Memorandum* at 3 (discussing label comprehension study); *FDA Medical Officer’s Review* at 25 (“the data of the [actual use] study show that Prilosec1 is likely to be used for episodic heartburn”), 33; *Advisory Committee Transcript* at 146-47, 153 (FDA Testimony discussing label comprehension studies).

¹² *FDA Review Memo* at 3.

¹³ *Advisory Committee Transcript* at 146 (FDA Testimony).

- Many consumers (37 percent of actual use participants) failed to follow the dosing directions set forth on the proposed OTC label (1 tablet per day for 14 days).¹⁴ FDA concluded that the sponsors' actual use study did not allow the Agency to determine whether individuals who exceeded the 14-dose regimen set forth on the product label consulted with a physician, as directed by the label, and that the study therefore did not address one of the principal concerns raised by the Agency when it rejected OTC Prilosec in October 2000.¹⁵
- Consumers were likely to take OTC Prilosec in conjunction with other anti-heartburn medication and other contraindicated medications, despite warnings on the proposed OTC label not to do so or to consult a physician before doing so.¹⁶ FDA also concluded that the proposed label warnings were not useful in preventing this.¹⁷
- Consumers with contraindicated symptoms took OTC Prilosec, despite label warnings cautioning against such use.¹⁸
- Consumers who were unlikely to follow up with a physician if their heartburn symptoms returned after the conclusion of a 14-day dosing regime might instead "simply choose to continue treatment chronically if symptomatic relief is afforded."¹⁹ FDA determined that this course of conduct raised significant safety concerns, in light of the possibility that long-term usage would "'mas[k]' symptoms associated with

¹⁴ *FDA Medical Officer's Review* at 34; *FDA Review Memorandum* at 3; *Advisory Committee Transcript* at 162 (FDA Testimony). This finding matched the results of a national usage study presented at the October 2000 Advisory Committee on OTC Prilosec, which study revealed that more than 60 percent of individuals using Prilosec for the prevention of heartburn exceeded 10 consecutive days of treatment despite a labeled instruction not to treat beyond that point. See *Advisory Committee Transcript* at 137 (summarizing study).

¹⁵ *FDA Medical Officer's Review* at 30.

¹⁶ *FDA Medical Officers Review* at 26; *FDA Review Memorandum* at 3; *Advisory Committee Transcript* at 153.

¹⁷ *Advisory Committee Transcript* at 148, 149 (FDA testimony) ("[W]e are concerned that the self-select responses suggest there is a problem in applying the label to oneself where one . . . is taking medications listed on the label.") ("[I]t is not clear that people can apply the label well to their own situation if they take any of the medicines listed on the label")

¹⁸ *FDA Medical Officer's Review* at 33; *FDA Review Memo* at 3.

¹⁹ *FDA Review Memorandum* at 4. See also n.14, above.

underlying medical conditions that warrant early diagnosis and adequate treatment,” including cancer of the esophagus or stomach.²⁰

- Some consumers purchased more than one carton of OTC Prilosec, thereby further suggesting use of the drug that did not comply with product labeling directions. FDA noted that in an OTC context, “there is no safeguard to prevent [consumers] from repurchasing the drug.”²¹
- As a general matter, rates of proper self-selection were lower for low-literacy and non-Caucasian consumers.²² In fact, label comprehension among some low-literacy groups ranged around only 50%.²³

Notwithstanding these findings, which raised serious questions about the ability of consumers to use Prilosec safely and effectively in an OTC context, the Advisory Committee on June 21, 2002, determined that P&G/AstraZeneca had provided “enough information to support the approval of [OTC Prilosec] for the prevention of frequent heartburn.”²⁴ The Advisory Committee, however, did not reach this decision unconditionally. Rather, the Committee also found, by an overwhelming vote of 15-3, that P&G/AstraZeneca had failed to demonstrate that consumers with heartburn could adequately self-select use of OTC Prilosec,²⁵ and determined that significant changes to the OTC Prilosec label needed to be made and subjected to testing before the product could be marketed.²⁶ The Committee was further divided

²⁰ *Advisory Committee Transcript* at 135.

²¹ *FDA Medical Officer’s Review* at 31.

²² *Id.*

²³ *Advisory Committee Transcript* at 107, 129 (FDA Testimony).

²⁴ *See Advisory Committee Transcript* at 279-282 (vote), 282-317 (discussion of vote).

²⁵ *Id.* at 234-235 (vote); 235-246 (discussion of vote).

²⁶ *Id.* at 282-317.

as to whether consumers who had a recurrence of heartburn after completing the 14-day course of therapy responded appropriately, with 5 of the 18 members of the Committee concluding that consumers did not respond appropriately under those circumstances because the overwhelming majority (80%) did not consult a physician.²⁷

The Advisory Committee's views were confirmed by FDA in an August 8, 2002, approvable letter from the Agency to P&G/AstraZeneca, in which the FDA mandated changes to the OTC product label, and the subsequent testing of the modified label through comprehension studies, prior to final Agency approval of OTC Prilosec. See "'The Pink Sheet': Prescription Pharmaceuticals and Biotechnology," August 26, 2002, p.11 (Attachment A hereto).

2. Discussion

The evidence before FDA and the Advisory Committee reveals that consumers are unlikely to use Prilosec1 in a safe and effective manner in the absence of guidance from a physician. The risks associated with unsupervised use of Prilosec1 make the drug inappropriate for OTC approval. At a minimum, it is incumbent on P&G/AstraZeneca to study more thoroughly the risks and consequences of unsupervised uses of Prilosec1²⁸ and to develop labeling for the product that informs consumers of, and protects them against, these risks.

Therefore, while Petitioner agrees with the Advisory Committee and FDA that the labeling for OTC Prilosec is seriously deficient and that new labeling should be developed and tested before OTC approval is granted, Petitioner also believes that more than mere product

²⁷ *Id.* at 250-251 (vote), 251-264 (discussion of vote).

²⁸ As discussed below in detail, these risks include, among other things, the potential masking of serious diseases – including cancer – as a result of long-term, unsupervised use of Prilosec1 and adverse drug-drug and food-drug interactions.

labeling changes are necessary to make PrilosecI suitable for OTC approval. Before OTC approval is granted, P&G/AstraZeneca must conduct additional *clinical studies* to determine the risks associated with OTC use of PrilosecI *and* must then make all necessary labeling changes to address those risks. Indeed, there is a significant question as to whether, given the effectiveness of OTC Prilosec and the risks associated with its unsupervised use, OTC approval should be granted *at all*.

- a. P&G/AstraZeneca have not carried their burden of demonstrating that consumers will appropriately self-select OTC Prilosec and that those who do appropriately self-select OTC Prilosec will use the drug in a safe and effective manner.

In its presentation before the Advisory Committee, FDA identified several critical issues regarding actual use of OTC Prilosec by consumers: “First of all, are consumers able to self-select and deselect appropriately? Do they understand what precludes them from the use of Prilosec[1]? Are consumers able to treat themselves to follow product label use directions for duration of use and do they follow directions when to seek advice from a healthcare provider?” *Advisory Committee Transcript at 156.*

The evidence culled from P&G/AstraZeneca’s actual use and label comprehension studies for OTC Prilosec suggests that the answer to each of these questions is “no.” As discussed above, this evidence demonstrates that a significant number of consumers are:

- (1) likely to use OTC Prilosec even though they do not suffer from “frequent” heartburn;
- (2) likely to use OTC Prilosec for episodic heartburn, instead of for heartburn prevention;
- (3) likely to use OTC Prilosec concomitantly with other acid reducers (defined as antacids, H2-Antagonists and other PPIs), in spite of product label warnings not to do so;
- (4) likely to use OTC Prilosec despite the presence of contraindicated symptoms, in spite of label warnings not to do so;

- (5) unlikely to follow the label's directions to see a physician before using OTC Prilosec if the consumer had previously suffered from heartburn for three months;
- (6) unlikely to see a physician if they suffer a recurrence of heartburn after the completion of treatment, despite product label warnings that a recurrence of heartburn could signal the presence of a serious condition; and
- (7) unlikely to administer the drug according to the labeling directions (*i.e.*, one 20 mg tablet per day for 14 days).

As FDA itself has recognized, this consumer behavior raises serious questions as to whether Prilosec1 can be used safely and effectively in an OTC context. In the prescription context, a physician can provide his or her patient with guidance on (1) whether the consumer is in fact suffering from the kind of frequent heartburn which Prilosec1 is supposed to treat; (2) whether use of Prilosec1 might be problematic given other medications that the patient might be taking, or given the other symptoms from which the patient is suffering; (3) the importance of following the directed course of treatment; and (4) the importance of seeking additional medical care if heartburn is not quelled in the first instance or returns after the 14-day course of treatment is completed. In the OTC context, consumers are left entirely on their own to evaluate these issues, and the evidence clearly shows that many of them are unsuccessful at doing so. This problem is particularly acute for low-literacy populations; the evidence presented by P&G/AstraZeneca suggested that *nearly half* of the individuals in some such populations were unable to understand the proposed labeling for OTC Prilosec. This statistic demonstrates that the benefit to be gained by certain segments of the population from increased access to Prilosec1 would largely be negated by lack of product label comprehension. *Advisory Committee Transcript* at 232 (comments of Advisory Committee Member Dr. Byron Cryer) (noting public health implications of poor label comprehension among low-literacy populations); *see also id.* at 107, 129 (FDA Testimony). In short, if Prilosec1 were approved for OTC use, many consumers

who are *not* likely to benefit from the drug would be purchasing and using it, and many other consumers who *might* conceivably benefit from proper use of the drug would in fact be taking it in an unsafe and ineffective manner. These facts alone preclude approval of OTC Prilosec.

There are several specific health and efficacy problems associated with the potential misuse of Prilosec1 in the OTC context. These are discussed below.

- b. The use of Prilosec1 in an OTC context creates the potential for masking of serious diseases and for delays in the treatment of these diseases.

Throughout its review of OTC Prilosec, FDA has identified as its principal concern the possibility that if “[Prilosec1 were] available OTC, consumers might not appropriately follow-up with a health care practitioner to identify and treat their underlying condition and may, simply choose to continue treatment chronically if symptomatic relief is afforded.” *FDA Review Memorandum* at 4. This possibility, FDA found, would in turn lead to the “potential of the drug to [mask] symptoms associated with underlying medical conditions that warrant early diagnosis and adequate treatment”, including “severe forms of erosive esophagitis, Barrett’s metaplasia and dysplasia, or cancer of the esophagus or stomach.” *Advisory Committee Transcript* at 135-136 (FDA Testimony).

The evidence before the Advisory Committee strongly suggested that the unsupervised use of Prilosec1 that occurs in an OTC setting will lead to the masking of serious diseases. First, that evidence indicated that the effectiveness of Prilosec1 for heartburn prevention increased over time, thereby making it likely that consumers would continue to take the drug after the end of the 14-day course of treatment in order to prevent heartburn. *See Advisory Committee Transcript* at 133 (“It is FDA’s concern that omeprazole’s buildup effect of acid suppression over consecutive daily doses may reinforce continuous unsupervised usage by consumers seeking optimal relief of chronic heartburn.”) Second, the evidence also showed that consumers

did not follow labeling instructions on how to take the drug and when to consult a physician. Third, the evidence demonstrated that consumers in fact did not see a physician if their heartburn returned after 14 days – despite product label warnings that recurring symptoms could be the sign of a serious condition -- and would therefore certainly be unlikely to do so if the continued use of Prilosec1 *worked* to prevent heartburn. Finally, FDA recognized that there was nothing to prevent consumers in an OTC context from repurchasing Prilosec1 and therefore from engaging in repeated self-medication beyond 14 days.

In the prescription context, the duration of treatment, compliance with label directions, and degree of physician consultation can all be monitored by a physician. In the OTC context, they cannot. And the above data clearly suggests that consumers, without the guidance of a physician, will seek to self-treat their heartburn symptoms in a way that might prevent diagnosis of potentially fatal diseases. As noted in the June 21, 2002 Advisory Committee public meeting, the data presented as part of the 2000 NDA for OTC Prilosec showed evidence of 49 cases of stomach cancer in patients taking Prilosec1 and “[i]n at least four of these cases, [Prilosec1] therapy caused masking of symptoms and/or temporary healing of gastric mucosal with a one to 12 month delay in diagnosis of malignancy.” *Advisory Committee Transcript* at 99 (comments of Advisory Committee Member Dr. Frank F. Davidoff) (quoting FDA findings from Agency’s 2000 review of OTC Prilosec). *See also id.* at 218-219 (comments of Advisory Committee Member Dr. Ronald Fogel) (“The concern I have is that the use of this drug may remove the physicians from the care of patients with esophageal reflux. If you have a treatment that is available over the counter that removes your symptoms, there is no need to see a doctor We won’t be able to identify and treat [patients] appropriately because of the fact that their symptoms will be controlled with this over-the-counter medication. The greater concern to me is

. . . what happens to the people who take the medication more than twice. From the use data and the comprehension data, it appears that is a significant risk.”).

The potential for the masking of serious diseases precludes the approval of OTC Prilosec. At a minimum, the sponsors of Prilosec1 bear the burden of conducting studies to assess the extent of the masking problem with respect to Prilosec1 and of developing OTC labeling that will minimize the risk of masking. P&G/AstraZeneca have thus far completely failed to confront the masking problem in the context of OTC Prilosec, despite admitting at the June 21, 2002 public hearing that the masking issue is “ripe for review.” *Advisory Committee Transcript* at 100 (comments of Dr. Keith Triebwasser, Senior Director, Regulatory Affairs, Procter & Gamble). The sponsors’ actual use study for Prilosec1, FDA found, “was of a short duration and did not address the issues of repeat courses of self-medication” *FDA Medical Officer’s Review* at 34; *Advisory Committee Transcript* at 164 (FDA Testimony) (actual use study did not address how Prilosec1 would be used and “what the consequences of such use would be.”) *See also FDA Medical Officer’s Review* at 30 (methodology of actual use study “does not allow [FDA] to address concern [about repeated uses]”), 32 (noting that methodology for study of repeat dosing was “deficient”); *Advisory Committee Transcript* at 227 (comments of Advisory Committee Member Dr. Louis Cantilena) (noting the fact that “[consumers of OTC Prilosec] will probably recurrently treat themselves inadequately possibly” and that “the consequences of that *hasn’t [sic] been studied obviously*”) (emphasis added); *id.* at 239 (Comments of Advisory Committee Member Dr. Nancy Geller) (noting that sponsors didn’t address issue of “repeat use”). Thus, there is no data tracing whether consumers of OTC Prilosec will simply continue to self-medicate beyond the 14-day course of therapy (although, as suggested above, the data suggests that they might well do so), or identifying the risks of such repeated use.

Before Prilosec1 can be approved for OTC use, P&G/AstraZeneca must, at a minimum conduct actual use studies of appropriate duration to assess (1) whether consumers of OTC Prilosec continue to use the product beyond the directed 14-day duration of treatment; (2) the extent of such extended self-medication; (3) the reasons for such extended self-medication; and (4) the effects of such extended self-medication – *i.e.*, whether, and to what extent, masking occurs. If masking is linked to the use of OTC Prilosec, the sponsors must also develop product labeling that will highlight this problem and that will help consumers avoid it. As the Advisory Committee found, the labeling proposed thus far for OTC Prilosec is ineffective in ensuring either consumer compliance with the directed course of treatment or appropriate consultations with healthcare providers, and is therefore ineffective in preventing masking. If after additional clinical studies improved product labeling cannot be developed, OTC Prilosec cannot be approved.

- c. The fact that Prilosec1 is ineffective in preventing heartburn on Day One of treatment creates the potential for unsafe and ineffective uses of the drug in an OTC context.

The data on Prilosec1 clearly indicates that the drug is not effective in preventing heartburn during the first 24 hours of treatment and that only after several days does the drug achieve its maximum effect. And indeed, as discussed above, the data also suggests that even after the 14-day course of treatment is complete, Prilosec1 is sometimes ineffective in preventing heartburn. Even putting aside the general issue of efficacy, the data regarding Prilosec1's initial (and in a significant number of cases, eventual) lack of effect in preventing heartburn raises difficult questions relating to the propriety of approving the drug for OTC use.

For example, does Prilosec1's lack of initial (and eventual) effectiveness in preventing heartburn cause consumers to take other anti-heartburn medication at the same time they take

Prilosec1? As discussed above, the evidence suggests that some consumers in fact did use other anti-heartburn medications at the same time as Prilosec1 during actual use trials, despite product label warnings not to do so. Further, does Prilosec1's lack of initial (and eventual) effectiveness cause consumers to ignore label directions and take excessive doses of Prilosec1 (e.g., more than one tablet per day) in an effort to alleviate their symptoms? As also discussed above, there is evidence to suggest that such misuse did in fact occur during the actual use trials.

Both the overuse of Prilosec1 and the concomitant use of other anti-heartburn medication with Prilosec1 may well be tied to the desire for acute symptomatic relief that is unavailable from Prilosec1 at the initial stages of treatment (and in other cases, after treatment is complete). In other words, if a consumer does not receive the desired relief from Prilosec1 on Day One (or after Day 14) of treatment, he or she might be tempted either (1) to take other anti-heartburn medication with Prilosec1 or (2) to take additional doses of Prilosec1 in an effort to achieve the desired relief. In the prescription context, these misuses of Prilosec are far less likely to occur – a physician can inform his or her patient not to expect immediate relief from heartburn and to comply with the product label directions for use, including the direction to see a physician if heartburn recurs after 14 days. In the OTC context, a consumer receives no such guidance and may well ignore label directions at the first sign that his or her heartburn is not subsiding, especially given that *nothing* in the product labeling proposed for OTC Prilosec informs consumers of the drug's initial ineffectiveness. *Advisory Committee Transcript* at 180-181 (comments of Advisory Committee Member Dr. Donald Uden) (“Nowhere do I see in the label any statement that you will not see this medication work for one to two days. There is nothing in there to tell people that if you take this for a day and you are expecting a response in six hours or 12 hours you're not going to see a response.”)

The misuses of Prilosec1 that potentially will result from the drug's initial (and often eventual) ineffectiveness may have important health and safety implications.

i. Concomitant use of other anti-heartburn medication: As discussed by Dr. Michael Wolfe in his testimony at the June 21, 2002 public meeting, animal studies indicate that use of H2-Antagonists in conjunction with the use of PPIs renders the PPI completely ineffective. *Advisory Committee Transcript* at 33-34 (Testimony of Dr. Michael Wolfe). There is also some question as to the effect of antacids on the effectiveness of Prilosec. One P&G/AstraZeneca study has found that coadministration of antacids with Prilosec *increased* bioavailability; another P&G/AstraZeneca study has found that such coadministration *decreased* bioavailability. See July 26, 1989 Memorandum from C.T. Viswanathan, Acting Director of Biopharmaceutics, CDER, Office of Drug Standards to Stephen B. Fredd, M.D., Director, Division of Gastrointestinal and Coagulation Drug Products (Attachment B) at 91 (commenting on discrepancy in studies in conjunction with original NDA for Prilosec).²⁹

Given the evidence that Prilosec1 does not work on Day 1 of treatment and the fact that consumers are likely, despite label warnings, to take OTC Prilosec with other acid reducers (including H2-Antagonists), approval of Prilosec1 in the OTC context is inappropriate. At a minimum, P&G/AstraZeneca must undertake substantial additional studies to examine the issue

²⁹ It is this discrepancy in sponsor data that distinguishes the NDA for Prilosec1 from other NDAs for OTC heartburn medications in the area of drug-drug interactions. To our knowledge, these other NDAs were not based on data that left uncertain the nature and extent of the drugs' interactions with other antacids. The data presented by P&G/Astra-Zeneca, conversely, has left the issue of antacid interactions unresolved with respect to Prilosec1, to the detriment of consumers who have been left without guidance on whether Prilosec1 may be coadministered with antacids. The burden therefore lies on the sponsors to undertake studies to resolve the confusion and to provide consumers with the guidance they need to take Prilosec1 safely and effectively.

of Prilosec1's interaction with other acid reducers. FDA, during its review of OTC Prilosec, expressly found that the studies relied on by P&G/AstraZeneca "did not address the concomitant use of other heartburn medications" (*Advisory Committee Transcript* at 164) and that label warnings ("do not take with other acid reducers") were not useful in preventing the concomitant use of Prilosec1 and H2-Antagonists, antacids, or other PPIs. In light of these findings, Prilosec1 should not be approved at least until the sponsors (1) *do* study whether, and to what extent, consumers will respond to the initial ineffectiveness of Prilosec1 by taking other acid reducers in conjunction with Prilosec1 and the safety and efficacy effects of any such interactions, and (2) proceed to develop product labeling that, unlike the current label for OTC Prilosec, effectively communicates the risks of these drug/drug interactions to consumers and adequately warns consumers not to respond to Prilosec1's initial ineffectiveness by taking other anti-heartburn medication at or about the same time as that drug.

The likelihood that consumers will use other acid reducers in response to the initial (or eventual) ineffectiveness of Prilosec1 in preventing heartburn raises an additional question: why is there *any* need to approve OTC Prilosec, in light of the relative effectiveness of these other products? H2-Antagonists are currently approved for the relief and the prevention of heartburn, and these products may, unlike Prilosec1, be used for an unlimited number of days (notably, P&G/AstraZeneca did not test Prilosec1 against other anti-heartburn medications, only against a placebo, and even in that test, Prilosec1 was only marginally more effective than placebo in preventing heartburn on Day 1). The fact that consumers resort to H2-Antagonists and other heartburn medications when Prilosec1 fails to prevent heartburn suggests that the availability of OTC Prilosec does not add anything to a consumer's arsenal of anti-heartburn remedies. Given the product's lack of efficacy in preventing heartburn and the availability OTC of other,

efficacious heartburn prevention medications, it cannot be argued that the acknowledged risks associated with the use of OTC Prilosec are outweighed by the fact that consumers now have available OTC a product that is different from, or better than, what is already available to them. In fact, the lack of efficacy of Prilosec1 suggests that any significant risks associated with the use of Prilosec1 should be sufficient to block FDA approval of P&G/AstraZeneca's NDA.

ii. Overdoses of Prilosec1: While the evidence suggests that consumers might take excessive dosages of Prilosec1 in response to the perceived initial ineffectiveness of the directed dosages, P&G/AstraZeneca have done nothing to study the reasons for overdosing, the extent of any such overdosing, or the risks associated with it. The answers to these questions could have profound safety implications for consumers. For example, the package insert for *prescription* Prilosec proposes a maximum daily dosage of 40 mg/day for gastric ulcers and 20 mg/day for GERD, GERD maintenance and duodenal ulcers. If studies show that, in response to the initial ineffectiveness of 20 mg doses of OTC Prilosec, consumers are taking dosages that are even greater than the recommended dosage for prescription Prilosec (except for hyper-secretory conditions), then OTC approval might carry with it serious health risks for consumers (*e.g.*, enhanced adverse drug-drug interactions). Under these circumstances, at a minimum, labeling would be needed to adequately warn consumers not to engage in such overdosing in response to Prilosec1's initial ineffectiveness in preventing heartburn. It is incumbent on P&G/AstraZeneca to study the overdosing issue, like the issue of concomitant uses of other heartburn medications, before Prilosec1 is approved for OTC use.

- d. Drug/food interactions, which have generally been found to hinder the effectiveness of Prilosec, have not been sufficiently studied to permit use of the drug in an OTC context.

At the June 21, 2002, public meeting, FDA noted for the Advisory Committee that “there is significant food effect” on Prilosec and other PPIs (*Advisory Committee Transcript* at 25) – that is, these drugs will work differently depending on when they have been administered in relation to eating. More specifically, the evidence suggests that Prilosec1 will *not* work effectively if it is taken after meals. P&G/AstraZeneca’s own presentations at the public meeting confirmed FDA’s conclusion that food significantly affects the pharmacokinetics of Prilosec. *See Advisory Committee Transcript* at 195-196 (Procter & Gamble testimony noting different Cmax and Tmax under fasted versus fed conditions).

Despite the fact that there is an acknowledged food effect with Prilosec and other PPIs, the evidence also suggests that there is insufficient data on food/drug interactions, and that even in the prescription setting, patients are often instructed improperly on how to take Prilosec1 in conjunction with food. *Advisory Committee Transcript* at 21-22 (Testimony of Robert Niecestro, Andrx Pharmaceutical Co.) If these kinds of problems exist in the prescription setting, they will increase significantly in the OTC setting, where consumers will not be able to rely on a physician’s expertise in deciding how to use Prilosec1 in conjunction with food. The proposed labeling for OTC Prilosec illustrates the confusion surrounding omeprazole/food interactions. The label instructs consumers to take Prilosec1 “with a glass of water *in the morning.*” *FDA Medical Officer’s Review* at 44 (emphasis added). This instruction fails completely to explain to consumers how to take Prilosec1 in conjunction with food – *e.g.*, whether the drug should be taken before or after a meal. The reason for this lack of clarity is that the necessary food/drug interaction studies simply have not been done.

In short, the confusion surrounding the food effect on Prilosec1, and the potential for ineffective use of Prilosec1 arising out of that confusion, will be particularly great in the OTC context. Thus, before Prilosec1 can be approved OTC, it is incumbent on the sponsors to conduct definitive clinical studies on the food/drug interaction issue and to craft OTC labeling that will clearly spell out the proper way to take Prilosec1 in conjunction with food.

- e. P&G/AstraZeneca have not adequately explained the risks associated with the use of contraindicated medications other than anti-heartburn medications in conjunction with OTC Prilosec, nor have they adequately justified their decision as to which drug/drug interactions to note on the OTC Prilosec label.

FDA has found that:

there is the potential of Prilosec to reduce the clearance of drugs that are metabolized by CYP2C19, such as diazepam [brand-name Valium], phenytoin [brand-name Dilantin], R-warfarin [brand-name Coumadin], and tolbutamide [brand-name Orinase]. These effects may be clinically significant in susceptible individuals, such as those having liver disease. Thus, caution, in general, needs to be exercised when co-administering the above drugs [with Prilosec].

FDA Review Memorandum at 2. The Agency has also noted clinically significant interactions between Prilosec and anti-fungal agents like ketoconazole (brand-name Nizoral). *Advisory Committee Transcript* at 134-35 (FDA Testimony).

In a prescription setting, a physician can ask his or her patient what medications they are using and can steer the patient away from Prilosec if there are significant drug-drug interactions between Prilosec and any such drugs. In the OTC context, consumers do not have the benefit of a physician's guidance; thus, the product labeling regarding contraindicated medications must be *complete and effective* if consumers are to be able to avoid any adverse safety or health effects associated with drug/drug interactions. The OTC Prilosec labeling regarding contraindicated medications is neither – another reason why OTC approval for Prilosec1 is inappropriate at this time.

P&G/AstraZeneca's handling of the issue of contraindicated medications is flawed in two principal respects. First, while the proposed label for OTC Prilosec does in fact alert consumers that they should see a physician before using Prilosec1 if they are taking warfarin, phenytoin, or ketoconazole, FDA has found that the product label is likely to be ineffective in steering people away from use of Prilosec1 when they are taking these medications. *See Advisory Committee Transcript* at 147 (FDA testimony noting that only 50 percent of frequent heartburn sufferers who were taking contraindicated medications responded correctly during label comprehension studies), 149 (FDA testimony noting that "it is not clear that people can apply the label well to their own situation if they take any of the medicines listed on the label as requiring physician consultation before using the product.")³⁰ At the June 21, 2002, public meeting, it was explained that the existence of contraindicated medications can be cause for concern even though the interactions may not be clinically significant for large percentages of the population. As explained, where an OTC product is marketed directly to large numbers of consumers, and where, as here, there might be significant interactions in small percentages of the population, the overall numbers of significant interactions may be sizeable and could pose a serious public health problem. *See, e.g., Advisory Committee Transcript* at 167-168 (comments of Dr. Michael Alfano noting the potential for significant public health problems arising out of drug interactions with OTC products and noting existence of postmarketing reports showing that interactions

³⁰ At least one contributing factor to this lack of consumer comprehension is that fact that the OTC Prilosec label refers to the drug product name, not the brand name – *e.g.*, warfarin instead of Coumadin, or phenytoin instead of Dilantin. The label comprehension study for Prilosec1 demonstrated that consumers' recognition of the brand name drugs contraindicated with Prilosec was 82 percent, whereas their recognition of the drug product name was only 50 percent. *Advisory Committee Transcript* at 147 (comments of FDA's Dr. Karen Lechter). Yet the proposed OTC label for Prilosec1 lists the brand names, not the drug product names. *Medical Officer's Review* at 44.

between warfarin and Prilosec caused “clinically significant bleeding.”). In such cases, label comprehensibility and consumer compliance with instructions regarding contraindicated medications is a critical requirement for OTC approval, and these preconditions are not present here. PrilosecI should not be approved for OTC use until the sponsors develop product labeling that will better protect against misuse of PrilosecI with the contraindicated medications listed on the proposed OTC label.

But even assuming the labeling on contraindicated medications were adequate with respect to the three medications listed on the product label, P&G/AstraZeneca has also failed to list in the OTC label *other* drugs that have been suggested, per the *prescription* Prilosec label, to interact in a clinically significant manner with omeprazole. These include drugs needed for the proper absorption of gastric acid – for example, ampicillin esthers, iron salts, and itraconazole (brand-name Sporanox) --, as well as drugs such as the immunosuppressant cyclosporine (Sandimmune) and the alcohol suppressant disulfiram (Antabuse). P&G/AstraZeneca offer little explanation for this discrepancy other than to suggest that space on the product label could only accommodate three contraindicated medications. This response bears little weight both because (1) clinically significant interactions should not be ignored due to mere space constraints and (2) even if such limitations are acceptable, P&G/AstraZeneca has offered no evidence showing that its decision on which contraindicated medications to include on the label was actually based on an empirical comparison of the relative risks associated with taking PrilosecI with each of these medications. As suggested by Advisory Committee Member Dr. Julie Johnson, if P&G/AstraZeneca chose to include only three contraindicated drugs on the label, “there has to be a really critical assessment of what are the three most clinically significant drug interactions

because I'm not sure those three are the three that are on the list." *Advisory Committee Transcript*. at 173-174.

No such assessment appears to have occurred here. If Prilosec1 is to be marketed for OTC use, P&G/AstraZeneca must (1) conduct thorough studies evaluating the drug-drug interactions associated with Prilosec1 and comparing the relative severity of these interactions with one another, and (2) provide FDA with a clear and compelling reason for the inclusion or exclusion of any particular contraindicated medicine on the product label. Only by taking such action can P&G/AstraZeneca adequately determine for, and communicate to, consumers the risks associated with taking OTC Prilosec for the new use the sponsors have proposed.

- f. P&G/AstraZeneca have not adequately evaluated the risks associated with the use of OTC Prilosec by certain subpopulations, and have not developed product labeling to warn these subpopulations of these risks.

In his testimony at the June 21, 2002 Public Meeting, Dr. Michael Wolfe noted that problems associated with the long-term, unsupervised use of Prilosec1 might particularly affect people of Asian origin. *Advisory Committee Transcript* at 35. A single dose of a PPI, studies have shown, can inhibit acid secretion in Asians longer than in non-Asians. See Medical Officer's Review for OTC Prilosec (January 27, 2000), at 3, available at http://www.fda.gov/ohrms/dockets/ac/02/briefing/3861B1_09_safety.pdf. And as suggested by Dr. Wolfe, inhibited acid secretion for extended periods – which, as FDA noted, could well be the outcome of the unsupervised use of Prilosec1 in the OTC setting – leads in turn to elevated gastrin levels and potentially to more serious diseases long-term. *Id.* It is also unclear whether certain subpopulations experience different *drug-drug* interactions from the rest of the population.

As Dr. Wolfe further noted, a review of the Summary Basis of Approval for Omeprazole and the available public information reveals no drug demographic studies regarding the effect of long-term, unsupervised use of Prilosec1 on Asians or related subpopulations (e.g., Native Americans). *Id.* at 4 (noting “negligible” representation of Asians in 2000 safety studies for OTC Prilosec); *Advisory Committee Transcript* at 34-35 (Wolfe testimony). Nor are there any studies on drug-drug interactions relating to these subpopulations’ use of omeprazole. P&G/Astra-Zeneca must conduct such studies and develop labeling that alerts members of these subpopulations to any risks that they in particular are likely to encounter from long-term, unsupervised use of Prilosec1, before this product can be approved for use in an OTC setting.

- g. Even if Prilosec1 were approved by FDA for OTC use, it should be renamed to avoid consumer confusion.

As is clear from the foregoing discussion, it is critical that consumers be able to use a drug safely and effectively without a physician’s direction if that drug is to be approved for OTC use. We have discussed throughout this Petition the reasons why Prilosec1 cannot be safely and effectively used OTC. There is one additional reason, which requires a change to the OTC product *even if* the product is otherwise deemed appropriate by the Agency for OTC use. That is, Prilosec1 must be renamed.

As we have emphasized in this Petition, Prilosec1 is for a different use than prescription Prilosec. The latter is to be used to treat symptomatic heartburn associated with GERD; the former is to be used by any *frequent heartburn sufferers* for the general prevention of 24-hour, non-GERD-related heartburn. Further, as FDA and the Advisory Committee have noted, one of the principal problems with OTC use of Prilosec1 is that consumers do not distinguish between these two uses – *i.e.*, individuals who suffer from GERD and who require long-term treatment of their heartburn symptoms will nonetheless use Prilosec1, although it provides for a different

treatment regime than its prescription counterpart. Clearly, one of the reasons for this confusion is the *name* of the proposed OTC product, which virtually mirrors the name of the prescription product. Given this similarity, it is completely foreseeable that consumers who are familiar with, or have used, prescription Prilosec will think that the OTC product can be used in the same manner and for the same purposes. In the OTC context, there is no physician to tell consumers that the products are in fact for different purposes and are to be used differently, and consumers acting on their own are likely to be confused or misled by the similar names of the prescription and OTC product.³¹

Thus, even if FDA determines that, after implementation of the labeling changes the Agency has ordered, Prilosec1 is fit for OTC marketing over-the-counter, the Agency should require that Prilosec1 be renamed to avoid a misleading association between the prescription and OTC products. This change, while perhaps not enough by itself to ensure the safe and effective use of the OTC product by consumers, would nevertheless assist in clarifying the different uses of the two products and would reduce, if not eliminate, the concerns expressed by FDA, the Advisory Committee and Petitioner.

* * *

In the end, the decision whether to approve a drug for use OTC depends on an assessment of the risks versus the benefits of such approval. In this case, the risks of OTC approval, at least at this time, clearly outweigh the benefits. On one hand, there are clear risks associated with the

³¹ It is also true that the use of "1" after Prilosec in the OTC product name may lead consumers to believe that the OTC product is *superior to*, rather than *different from*, the prescription product, a misunderstanding that would further contribute to the unsafe and ineffective use of Prilosec1 by consumers.

use of Prilosec1 in an OTC setting. The evidence unequivocally shows that consumers will not use OTC Prilosec safely or effectively, and that the risks of ineffective or unsafe use that are greatly reduced in the prescription setting (*i.e.*, risks of delayed diagnosis of cancer and other diseases, risks of improper drug/drug and food/drug interactions) exist to a far greater degree when consumers are left to judge for themselves when and how to use the drug. The evidence further shows that P&G/AstraZeneca have done little to respond to these risks, either by conducting appropriate studies to assess the reasons for, extent of, and consequences of consumer misuses of Prilosec1 in the OTC setting, or by designing product labeling that improves on the many deficiencies of the current proposed labeling.

On the other hand, OTC Prilosec has been shown to have limited effect on the prevention of heartburn on Day 1 of treatment, and, in many cases to have limited efficacy in preventing heartburn even after the 14-day course of treatment is complete. Given the availability of other OTC medications that may actually do a better job of preventing heartburn, the benefits to consumers of having OTC Prilosec available are limited. Given these circumstances, OTC approval for Prilosec1 is inappropriate unless and until the sponsors can, by conducting appropriate studies and designing effective labeling, effectively evaluate and communicate to consumers the risks associated with the use of Prilosec1 in an OTC setting.

C. Conclusion

For the foregoing reasons, FDA should deny the amended NDA for OTC Prilosec.

D. Environmental Impact

This petition qualifies for categorical exclusion under 21 C.F.R. §§ 25.15, 25.30-25.32, and therefore does not require the preparation of an environmental assessment or an

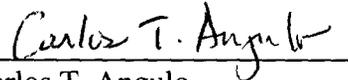
environmental impact statement. In any event, the action requested in this petition will not have any significant effect on the quality of the human environment.

In accordance with the requirements of 21 C.F.R. § 25.15, we assert we are not aware of any extraordinary circumstances.

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.

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