



Prilosec
OTCTM

P R O D U C T M O N O G R A P H

I. INTRODUCTION4
 1.1 Characterization of Frequent Heartburn
 1.2 OTC Heartburn Medications

2. DESCRIPTION5

3. COMPOSITION6
 3.1 Active Ingredient
 3.2 Inactive Ingredients

4. CLINICAL PHARMACOLOGY7
 4.1 Mechanism of Action
 4.2 Inhibition of Gastric Acid Secretion
 4.3 Pharmacokinetics

5. CLINICAL EFFICACY STUDIES10
 5.1 Primary Efficacy End Point Results (Heartburn Free for 24 Hours)
 5.2 Secondary Efficacy End Point Results (No Nocturnal Heartburn
 and No More Than Mild Heartburn)

6. OTC LABEL COMPREHENSION AND COMPLIANCE.....13
 6.1 Compliance Study Results

7. INDICATION AND USAGE14

8. SAFETY15
 8.1 Contraindications
 8.2 Drug Interactions
 8.3 Special Populations
 8.4 Adverse Events

9. AVAILABILITY AND STORAGE16
 9.1 Storage Conditions

10. REFERENCES17



I. INTRODUCTION

Prilosec OTC (omeprazole 20 mg as omeprazole magnesium 20.6 mg) has been approved by the US Food and Drug Administration as an over-the-counter (OTC) medication for the treatment of frequent heartburn, defined as heartburn occurring 2 or more days a week. With Prilosec OTC, health care professionals have an OTC therapeutic option to recommend to adult patients who have frequent heartburn symptoms.

In the past, management options for self-treating consumers have included antacids and H₂-receptor antagonists (H₂RAs). However, with Prilosec OTC, consumers have access to a proton pump inhibitor (PPI), a long-lasting treatment option for controlling frequent heartburn symptoms—one dose a day works for up to 24 hours as part of a 14-day course of therapy. This section gives an overview about frequent heartburn sufferers and their treatment habits.

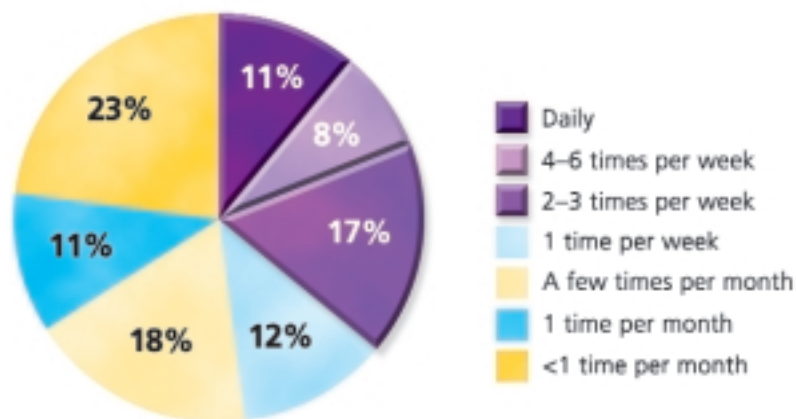
I.1 Characterization of Frequent Heartburn

Heartburn is described as a sensation of midchest discomfort moving up to the throat and neck, accompanied by a burning or painful feeling under the sternum. A 2003 survey showed that in the United States, about 65% of the total adult population experiences heartburn, with heartburn occurring daily in about 15 million adults.¹ Over 50 million people in the United States experience heartburn symptoms 2 or more days a week.^{1,2}

Slightly more women (59%) than men report frequent heartburn.^{1,3} The mean age for a consumer with frequent heartburn is 45 to 50 years,¹ and heartburn has a slight tendency to increase with age.³ Geographic location, marital status, family status (children), education level, job type and level, and socioeconomic status all play a role in the tendency to develop heartburn.⁴

Figure 1 shows the frequency of all heartburn episodes in a 2003 survey of a representative adult heartburn population.¹

Figure 1. Frequency of heartburn in the US heartburn population¹



Consumers with frequent heartburn reported having a long history of heartburn symptoms. According to a 2000 survey by the National Heartburn Alliance, 54% of consumers with frequent heartburn reported experiencing heartburn for more than 5 years, with about 40% experiencing heartburn for 1 to 5 years and approximately 5% for less than 1 year.^{1,5}

The majority of consumers with frequent heartburn have discussed their symptoms with health care professionals. Most consumers with frequent heartburn (62%) have reported their symptoms to their primary care physician; 16% and 2%, respectively, have seen gastroenterologists or cardiologists; and 30% have consulted with pharmacists.¹

1.2 OTC Heartburn Medications

Most consumers with frequent heartburn self-diagnose and self-treat using available OTC medications. In a 2001 survey, about 80% of individuals with frequent heartburn reported using OTC heartburn medications.¹

In this study, over 70% of frequent heartburn sufferers considered their symptoms moderate to severe, and most frequent heartburn sufferers reported medicating at the first sign of symptoms to prevent them from getting worse or relieve them. In general, consumers with frequent heartburn reported managing their heartburn by using antacids alone or in combination with OTC H₂RAs, or prescription PPIs.¹

2. DESCRIPTION

Prilosec OTC is supplied in 14-tablet, 28-tablet, and 42-tablet sizes. These sizes contain one, two, and three 14-day courses of treatment, respectively. Prilosec OTC is a pink-colored (salmon) tablet consisting of multiple enteric-coated pellets formulated with 20.6 mg of omeprazole magnesium, equivalent to 20 mg of omeprazole. The active ingredient is the magnesium salt of omeprazole, which allows tableting. Currently, this tablet formulation is marketed as an OTC product in Sweden and as a prescription product in over 30 other countries.¹



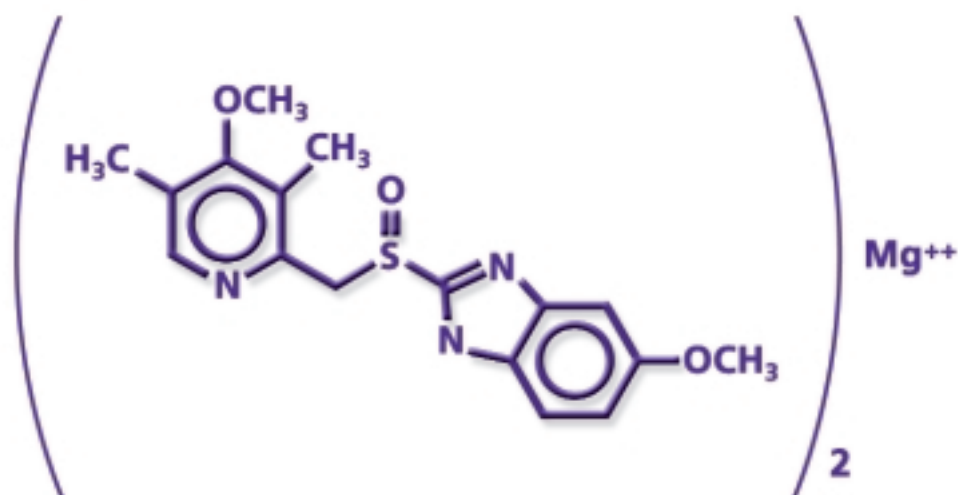
3. COMPOSITION

3.1 Active Ingredient

The active ingredient in Prilosec OTC delayed-release tablets is omeprazole magnesium; its chemical name is di-5-methoxy-2-[[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole magnesium. Omeprazole magnesium has a molecular weight of 713.1. Its structural formula is shown in Figure 2.⁶

Omeprazole magnesium is a crystalline substance that is freely soluble in methanol and slightly soluble in water. Omeprazole magnesium dissociates rapidly in water to form omeprazole and magnesium.⁶

Figure 2. Chemical structure of omeprazole magnesium⁶



3.2 Inactive Ingredients

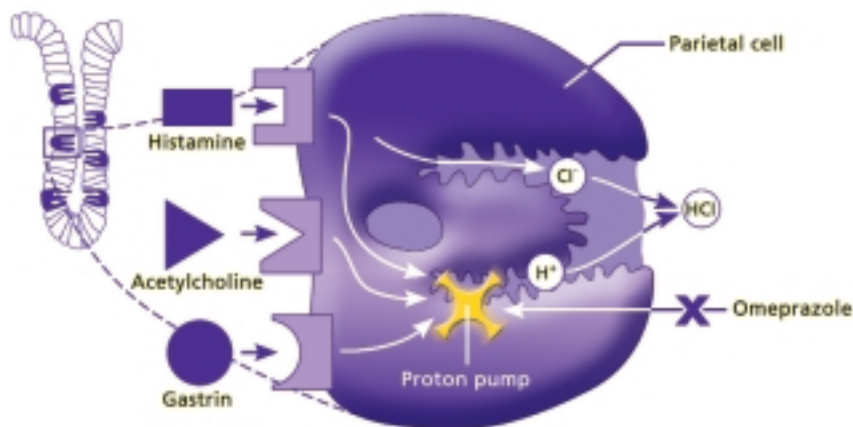
Glyceryl monostearate, hydroxypropyl cellulose, hypromellose, iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin, polyethylene glycol 6000, polysorbate 80, polyvinylpyrrolidone, sodium stearyl fumarate, starch, sucrose, talc, titanium dioxide, triethyl citrate.⁷

4. CLINICAL PHARMACOLOGY

4.1 Mechanism of Action

Omeprazole belongs to the class of drugs known as substituted benzimidazoles.⁸ Omeprazole binds irreversibly with the proton pump (H^+/K^+ -ATPase enzyme system) at the secretory surface of the gastric parietal cell.⁸⁻¹⁰ The binding inhibits or suppresses the ability of the parietal cell to secrete gastric acid (Figure 3).

Figure 3. Mechanism of action of omeprazole⁶



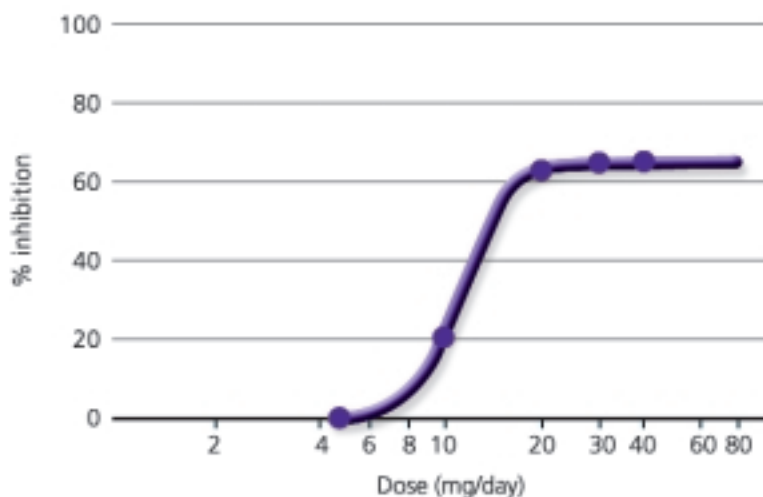
4.2 Inhibition of Gastric Acid Secretion

Reflux of gastric acid into the esophagus is the major cause of heartburn symptoms. Omeprazole inhibits both basal and stimulated acid secretion from the parietal cell, irrespective of the stimulus. At 24 hours, acid secretion by gastric parietal cells is about 50% of maximal with a single dose. When omeprazole is discontinued, the ability to secrete gastric acid returns gradually within days, as new proton pumps are generated.⁶

Pharmacodynamic data demonstrated that omeprazole 20 mg daily provides a pronounced and consistent inhibition of gastric acid secretion over 24 hours.⁶ The magnitude and consistency of this effect was significantly better for 20-mg vs 10-mg daily doses of omeprazole. Figure 4 illustrates the superior and more consistent antisecretory effects of omeprazole administered at 20-mg or higher doses.¹¹ It also shows that a daily dose of omeprazole 20 mg produces a markedly stronger and more consistent inhibition than the lower doses but not a complete blockade of gastric acid secretion over the 24-hour dosing interval.

Prilosec
OTC

Figure 4. Inhibitory effects of 1 week of treatment with daily doses of omeprazole on 24-hour intragastric acid secretion¹¹

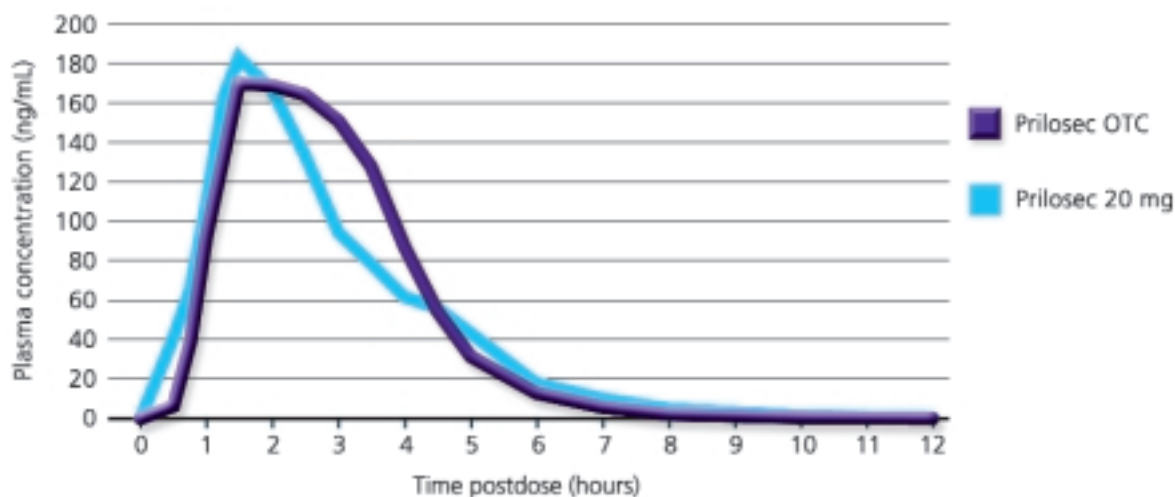


4.3 Pharmacokinetics

Bioavailability

A study involving 29 healthy US subjects demonstrated that the bioavailability of Prilosec OTC tablets is similar to that of the commercially available 20-mg prescription Prilosec® (omeprazole) capsules (see Figure 5).⁶ The subjects were administered the treatment product as a morning single dose under fasting conditions. The study was a randomized, open-label, crossover study with a 5-day washout period between treatments. The tablet formulation is marketed in Sweden as an OTC product and in over 30 other countries as a prescription product.¹

Figure 5. Mean plasma concentration of omeprazole vs time: subjects with evaluable pharmacokinetic data (n=29)⁶



Absorption, Distribution, and Metabolism

Because the pellets that contain omeprazole magnesium in Prilosec OTC tablets are enteric coated, the tablets should not be split, as this would disturb the coating. Because of the enteric coating, absorption begins only after the pellets have entered the duodenum. This is important because exposure to the acidic environment of the stomach before entering the systemic circulation would cause degradation in the omeprazole molecule that might limit its ultimate effectiveness. Once omeprazole magnesium dissolves in this near neutral environment of the duodenum, the omeprazole ion converts to its neutral form. The same form of omeprazole is available for absorption regardless of whether it is administered as the free form, omeprazole, or the salt, omeprazole magnesium.¹² Absorption is rapid, with peak plasma levels (C_{max}) of omeprazole occurring within 0.5 to 3.5 hours following oral administration.⁶ In healthy adult subjects, the plasma half-life ($t_{1/2}$) is 0.5 to 1.0 hours, and the total body clearance is 500 to 600 mL/min. The duration of action of omeprazole is more than 24 hours following a single dose, since parietal cells turn over in about 3 to 5 days. Protein binding is approximately 95%. The inhibition of acid secretion is related to the area under the plasma concentration-time curve but not to the actual plasma concentration at any given time.

Omeprazole is completely metabolized in the liver by cytochrome P450 isoenzymes. At least six metabolites are formed, which have little or no antisecretory activity. Omeprazole metabolites are removed primarily in the urine and secondarily in feces.⁶



5. CLINICAL EFFICACY STUDIES

Two well-controlled clinical studies involving 3120 subjects support the use of a consecutive 14-day therapeutic regimen of omeprazole magnesium to treat frequent heartburn. Both studies were multicenter, double blind, randomized, parallel, and placebo controlled. Each study evaluated 10-mg and 20-mg doses of omeprazole magnesium for 14 consecutive days in subjects with heartburn 2 or more days a week.¹

The studies had a 1-week placebo run-in phase to assess heartburn frequency. Eligible subjects were randomized into a 2-week double-blind treatment phase to receive a single daily dose of either omeprazole magnesium 10 mg, omeprazole magnesium 20 mg, or placebo every day. Subjects took their daily dose of study medication each morning before breakfast.¹

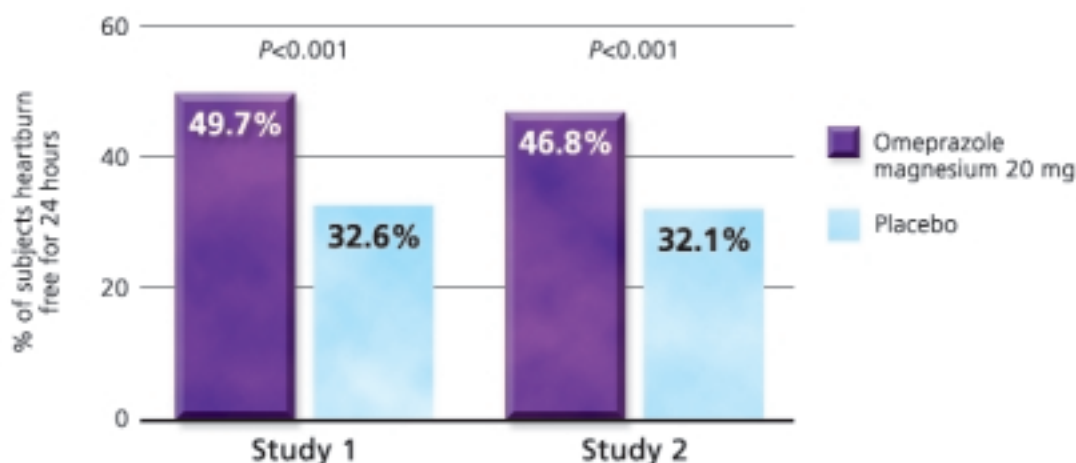
The primary efficacy end point was “no heartburn over the previous 24 hours” (ie, completely heartburn free for a full day). Efficacy was evaluated following the first dose of medication, on the last dose, and over 14 days of dosing during the double-blind phase.¹

A number of secondary efficacy end points were also studied following the first dose of medication and subsequent doses. These included “complete prevention of nocturnal heartburn” and “occurrence of no more than mild heartburn.”¹

5.1 Primary Efficacy End Point Results (Heartburn Free for 24 Hours)

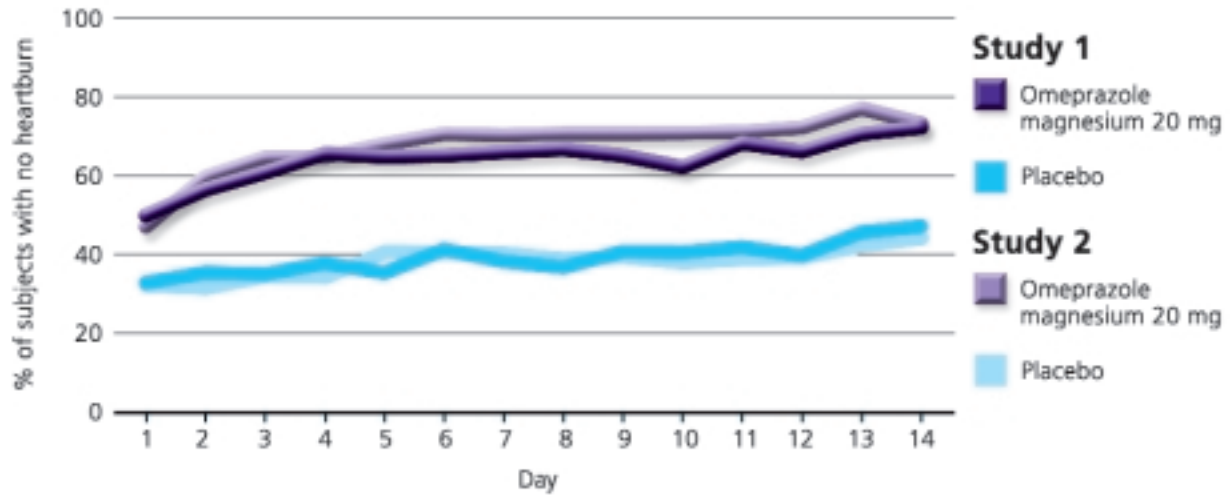
Both clinical studies showed that 20 mg of omeprazole magnesium resulted in a significant treatment effect during the first day. As shown in Figure 6, almost 50% of the subjects in the 20-mg omeprazole magnesium treatment groups were heartburn free for the full day after the first dose vs approximately 32% of subjects in the placebo group (Figure 6).¹

Figure 6. Percentage of subjects with no heartburn for 24 hours—day 1¹



On day 14, the percentage of subjects reporting complete heartburn relief was over 70% (Figure 7).¹

Figure 7. Percentage of subjects with no heartburn for 24 hours—time course over 14 days¹

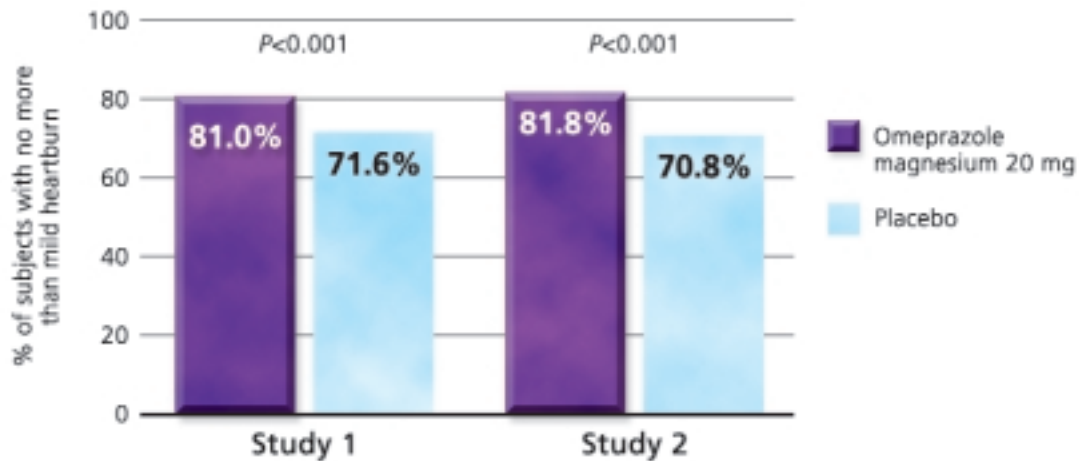


5.2 Secondary Efficacy End Point Results (No Nocturnal Heartburn and No More Than Mild Heartburn)

In general, the results for these end points corroborated the findings for the primary end points.¹

When subjects with only mild heartburn were added to the efficacy end point, more than 80% of those receiving omeprazole magnesium reported a significant therapeutic benefit on day 1 (Figure 8).¹

Figure 8. Percentage of subjects with no more than mild heartburn—day 1¹



6. OTC LABEL COMPREHENSION AND COMPLIANCE

6.1 Compliance Study Results

Consumer behavior and understanding of the use of Prilosec OTC were evaluated in label-comprehension studies and an actual-use trial. This program of studies established the compliance with label directions and use of the product in an unsupervised setting. More specifically, the program was developed to determine whether consumers understood: 1) the population for which Prilosec OTC was best suited (self-selection based on frequency of heartburn and understanding of label warning language); 2) when and how to take Prilosec OTC (one tablet per day, 14 consecutive days); and 3) when to contact a health care professional (in response to specific warning language or when frequent heartburn returns). The actual-use study determined adherence to the label directions under conditions of actual use.¹

- For each of the self-selection criteria, appropriate choice was greater than **90%** across the population¹
- Subjects who elected to use the product were highly adherent to label dosing instructions, with more than **91%** of subjects using the product as specified on the label by taking no more than 1 tablet per dose and no more than 1 tablet per day¹
- At a 3-month follow-up interview, consumers who experienced a return of heartburn symptoms continued to display behavior consistent with label-use directions¹

The results of these studies strongly support the appropriate use of Prilosec OTC by the consumer with frequent heartburn and support the ability of the consumer to correctly use the product within the proposed OTC label directions (Figure 9).¹

Figure 9. Dosing compliance¹



97%

Did not exceed
14-day course of therapy
without consulting a
health care professional
(N=758)



7. INDICATION AND USAGE

Prilosec OTC 20 mg tablets are indicated for the treatment of frequent heartburn, which is defined as heartburn occurring 2 or more days a week. The label for Prilosec OTC gives the following directions for appropriate use by consumers with frequent heartburn⁷:

LABEL EMPHASIZES SAFE AND PROPER USE

<p>Drug Facts</p> <p>Active ingredient (in each tablet) Purpose</p> <p>Omeprazole magnesium delayed-release tablet 20.6 mg (equivalent to 20 mg omeprazole).....Acid reducer</p>	<p>Drug Facts (continued)</p> <p>if pregnant or breast-feeding, ask a health professional before use. Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.</p>
<p>Use</p> <ul style="list-style-type: none"> treats frequent heartburn (occurs 2 or more days a week) not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect 	<p>Directions</p> <ul style="list-style-type: none"> adults 18 years of age and older this product is to be used once a day (every 24 hours), every day for 14 days it may take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours
<p>Warnings</p> <p>Allergy alert: Do not use if you are allergic to omeprazole</p> <p>Do not use if you have</p> <ul style="list-style-type: none"> trouble or pain swallowing food vomiting with blood bloody or black stools <p>These may be signs of a serious condition. See your doctor.</p>	<p>14-Day Course of Treatment</p> <ul style="list-style-type: none"> swallow 1 tablet with a glass of water before eating in the morning take every day for 14 days do not take more than 1 tablet a day do not chew or crush the tablets do not crush tablets in food do not use for more than 14 days unless directed by your doctor
<p>Ask a doctor before use if you have</p> <ul style="list-style-type: none"> had heartburn over 3 months. This may be a sign of a more serious condition. heartburn with lightheadedness, sweating or dizziness chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness frequent chest pain frequent wheezing, particularly with heartburn unexplained weight loss nausea or vomiting stomach pain 	<p>Repeated 14-Day Courses (if needed)</p> <ul style="list-style-type: none"> you may repeat a 14-day course every 4 months do not take for more than 14 days or more often than every 4 months unless directed by a doctor children under 18 years of age: ask a doctor
<p>Ask a doctor or pharmacist before use if you are taking</p> <ul style="list-style-type: none"> warfarin (blood-thinning medicine) prescription antifungal or anti-yeast medicines diazepam (anxiety medicine) digoxin (heart medicine) 	<p>Other information</p> <ul style="list-style-type: none"> read the directions, warnings and package insert before use keep the carton and package insert. They contain important information. store at 20-25°C (68-77°F) keep product out of high heat and humidity protect product from moisture
<p>Stop use and ask a doctor if</p> <ul style="list-style-type: none"> your heartburn continues or worsens you need to take this product for more than 14 days you need to take more than 1 course of treatment every 4 months 	<p>Inactive ingredients glyceryl monostearate, hydroxypropyl cellulose, hypromellose, iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, paraffin, polyethylene glycol 6000, polysorbate 80, polyvinylpyrrolidone, sodium stearyl fumarate, starch, sucrose, talc, titanium dioxide, triethyl citrate</p> <p>Questions? 1-800-759-4841</p>

- One pill a day treats frequent heartburn for 24 hours as part of a 14-day course of therapy
- The only OTC product specifically approved for frequent heartburn (2 or more days a week)
- QD dosing minimizes inconvenience, encourages compliance
- 14-day dosing regimen for treatment of frequent heartburn
- Label directions encourage consumers to see a physician
- Consumers advised to take no more than one 14-day course of therapy every 4 months, unless otherwise directed by a physician

8. SAFETY

8.1 Contraindications

Prilosec OTC is contraindicated for those who are hypersensitive to omeprazole. Consumers who have certain medical conditions and/or symptoms are instructed by the label to either not use the product or consult a doctor.⁷

8.2 Drug Interactions

The potential metabolic drug interactions with omeprazole (metabolized primarily by hepatic cytochrome P450 isoenzyme CYP2C19) have been systematically studied, especially with respect to warfarin, diazepam, and digoxin.⁶

While clinically significant interactions between warfarin or digoxin and omeprazole are unlikely, the narrower therapeutic window for these drugs led to the conservative precaution of listing them on the label for Prilosec OTC.⁶

Warfarin

Postmarketing reports of changes in prothrombin measures have been received among patients on concomitant warfarin and omeprazole therapy. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Diazepam

Coadministration with diazepam was also listed in the **Warnings** section because omeprazole significantly reduces diazepam clearance; although the relatively wide therapeutic window for diazepam makes it unlikely that this effect of omeprazole is clinically significant.⁶

Drugs with pH-dependent absorption

As with other PPIs and H₂RAs, omeprazole increases intragastric pH (decreases acidity), which can affect the absorption of drugs that have pH-dependent absorption, eg, ketoconazole or itraconazole. A study demonstrated that ketoconazole absorption was greatly decreased after administration of omeprazole. Similarly, another study showed that itraconazole absorption was decreased if administered after a 2-week regimen of omeprazole.⁶

Therefore, the label for Prilosec OTC lists potential drug interactions with warfarin, prescription antifungals/anti-yeast drugs, diazepam, and digoxin under the **Warnings** section.⁷



8.3 Special Populations

Use in Pregnancy and Lactation: The label for Prilosec OTC directs pregnant or lactating women to consult a physician before use.⁷

Use in Children: Prilosec OTC is indicated for the treatment of frequent heartburn for those aged 18 years or older. For children younger than 18 years with frequent heartburn, the label instructs consulting a physician before using.⁷

8.4 Adverse Events

Doctors have prescribed omeprazole to millions of patients to treat acid-related conditions safely.⁹

The safety of omeprazole was reconfirmed in 15 new OTC clinical trials with omeprazole magnesium (N>18,000). The most common adverse events were headache and diarrhea, consistent with those in clinical trials and postmarketing surveillance for prescription Prilosec. Prilosec OTC had a similar tolerability profile to placebo.¹

9. AVAILABILITY AND STORAGE

Prilosec OTC tablets in a 20-mg dose are provided in blister packs. Prilosec OTC is available OTC in three different sizes⁷:

Package of 14 tablets (one 14-day treatment course)

Package of 28 tablets (two 14-day treatment courses)

Package of 42 tablets (three 14-day treatment courses)



9.1 Storage Conditions

- Store at 20°C–25°C (68°F–77°F)⁷
- Keep out of high heat and humidity⁷
- Protect from moisture⁷

10. REFERENCES

1. Data on file. Procter & Gamble.
2. National Heartburn Alliance. *The Burn Factor: A Survey of the Effects of Frequent Heartburn on Quality of Life. A National Look*. Chicago, Ill: National Heartburn Alliance; 2003.
3. Oliveria SA, Christos PJ, Talley NJ, et al. Heartburn risk factors, knowledge, and prevention strategies: a population-based survey of individuals with heartburn. *Arch Intern Med*. 1999;159:1592-1598.
4. Profile of consumers in need. When the South rises again, it's probably just gas: a light-hearted look at heavy stomachs. *Progressive Grocer*. 1995;98-99.
5. National Heartburn Alliance. *National Heartburn Alliance Survey 2000 Results: A Community Perspective*. Chicago, Ill: National Heartburn Alliance; 2000.
6. Data on file. AstraZeneca LP.
7. Prilosec OTC [package label]. Cincinnati, Ohio: Procter & Gamble; 2003.
8. Massoomi F, Savage J, Destache CJ. Omeprazole: a comprehensive review. *Pharmacotherapy*. 1993;13:46-59.
9. Prilosec [package insert]. Wilmington, Del: AstraZeneca LP; 2002.
10. Lindberg P, Brändström A, Wallmark B, et al. Omeprazole: the first proton pump inhibitor. *Med Res Rev*. 1990;10:1-54.
11. Lind T, Cederberg C, Axelson M, et al. Long-term acid inhibitory effect of different daily doses of omeprazole 24 hours after dosing. *Scand J Gastroenterol*. 1986;21(suppl 118):137-138.
12. Losec [package insert]. Auckland, New Zealand: AstraZeneca Limited; 2002.





Prilosec is a registered trademark and Prilosec OTC is a trademark of the AstraZeneca group of companies.

