021229_Original_Approval_Package

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
21-229

Trade Name: Prilosec OTC

Generic Name: omeprazole magnesium delayed-release tablets, 20 mg

Sponsor: The Proctor and Gamble Co.

Approval Date: June 20, 2003

Indications: For the treatment of frequent heartburn

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-229

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-229

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-229

The Proctor and Gamble Co.
Attention: Linda Jones
Director, Regulatory Affairs
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

Dear Ms. Jones:

Please refer to your new drug application (NDA) dated January 27, 2000, received January 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec OTC (omeprazole magnesium delayed-release tablets, 20 mg).

We acknowledge receipt of your submissions dated December 20, 2002, February 24, March 7, and June 12 and 19, 2003. Your submission of December 20, 2002, constituted a complete response to our August 8, 2002, action letter.

This new drug application provides for over-the-counter use of omeprazole magnesium delayed-release tablets for the treatment of frequent heartburn for consumers 18 years of age and older.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (14-, 28-, and 42-count package carton labeling and consumer information leaflet submitted on June 19, 2003, and 2-count sample package labeling, plastic overlay for the 42-count package, and unit-dose blister labeling submitted on June 12, 2003), and must be in the "Drug Facts" format (21 CFR 201.66). Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-229.**" Approval of this submission by FDA is not required before the labeling is used.

In addition, we request that you submit two copies of the introductory promotional materials you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and the other copy, along with the approved labeling, to the Division of Over-the-Counter Drug Products, HFD-560.

Submit one market package of the drug product when it is available.

We remind you of the following considerations for appropriate marketing of this product.

1. [redacted]

2. We are approving 28- and 42-count package sizes for this product amid concerns that consumers follow instructions that limit duration of use to 14 consecutive days and frequency of use to not more than 3 courses in a given year. If you recall, much of the discussion of the June 2002 joint meeting of the Nonprescription and Gastrointestinal Advisory Committees focused on the issue of appropriate duration and frequency of use. The joint committees recommended a course of therapy no longer than 14 consecutive days and no more than 3 courses per year, and we have followed these recommendations. By proposing these 28- and 42-count package sizes configured as multiple 14-count units, we feel that consumers may better understand the limitations of use. However, if you should be interested in marketing other package configurations in the future (e.g., bottles containing greater than 14 capsules), we will expect submission of a prior approval supplement that includes data to adequately demonstrate appropriate consumer comprehension of the limitations of use. You are encouraged to contact the Division of Over the Counter Drug Products about the content and format of such a supplement prior to submission.

We agree with your plans to distribute the 2-count trial package only to consumers who have frequent heartburn, as defined in the approved labeling, as outlined in your December 20, 2002, submission.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Oversight of this application is being transferred to the Division of Over-the-Counter Drug Products.

If you have any questions, contact Laura Shay, Regulatory Project Manager, at 301-827-2274.

Sincerely,

{See appended electronic signature page}

Jonca Bull, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

{See appended electronic signature page}

Florence Houn, M.D., M.P.H.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures

Enclosures

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Julie Beitz
6/20/03 04:47:33 PM
Signing for Florence Houn MD, MPH

Jonca Bull
6/20/03 05:12:19 PM

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-229

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-229

AUG 8 2002

The Proctor and Gamble Co.
Attention: Douglas Ws. Bierer, Ph.D.
Director, Regulatory Affairs
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

Dear Dr. Bierer:

Please refer to your new drug application (NDA) dated January 27, 2000, received January 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for omeprazole magnesium tablets.

We acknowledge receipt of your submissions dated March 23, April 14, April 25, April 28, May 19, May 31, July 20, August 2, August 10, August 11, August 17, August 23, August 25, August 28, August 31, September 7, September 12, September 13, September 20, September 27, October 3, October 11, October 18, October 25, October 30, October 31, and November 15, 2000; February 12, April 9, April 24, May 2, and May 9, 2002. Your submission of February 12, 2002 constituted a complete response to our November 27, 2000 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Revise the labeling to include the following concepts and conduct a new label comprehension study to test these concepts. Submit the revised labeling and study protocol to IND 54,307 for our review prior to initiation of the label comprehension study.

Carton:

Uses
Consumer understanding of each of these concepts must be evaluated in a labeling comprehension study. The evolution of the label should be an iterative process whereby multiple labels are tested to determine the best one to convey the concepts.

- This section of the label must clearly differentiate the use of omeprazole magnesium tablets from the use of antacids or histamine (H_2) receptor antagonists in an over-the-counter-setting. That is, it must indicate that omeprazole magnesium tablets is intended for the 14-day treatment of frequent heartburn and is not intended for: a) the immediate treatment of heartburn; or b) the prevention of heartburn brought on by certain foods or beverages.

- This section of the label must reflect that omeprazole magnesium tablets may take 1 to 2 days of use to work. Alternatively, this concept may be placed in the *When using this product* section, but only if a labeling comprehension study shows that consumers understand it better when placed there than in the *Uses* section.

Warnings

- Delete the proposed text under [redacted] because it is confusing to consumers. The following concepts are important to convey and must be tested to ensure that they are understood by consumers:

  - Frequent heartburn caused by acid reflux may be a sign of a more serious condition.
  - Before starting treatment, see your doctor if:
    - you have had heartburn over 3 months
    - your heartburn is associated with lightheadedness, sweating, or dizziness (note: this concept needs to be emphasized)
  - After starting treatment, see your doctor if:
    - your heartburn continues with treatment
    - frequent heartburn returns soon after 14-day treatment
    - you need more than 2 to 3 courses of treatment in one year at 3 to 4 month intervals

- Move "**Allergy alert**" to the end of this section.

Do not use

- Since we agree that other heartburn medications may be used concomitantly with omeprazole magnesium tablets, delete [redacted] from this section of the label.

Ask a doctor before use if you have

- Delete the phrase [redacted] from the statement "any of the following symptoms and have not seen a doctor"
- Revise the phrase [redacted] to "chest pain or shoulder pain with"
- Revise the phrase "trouble swallowing food" to "trouble or pain swallowing food"
- Add "nausea or vomiting"
- Add "vomiting blood"
- Add "bloody or black stools"

When using this product

- Insert this section after *Ask a doctor before use if you have.* This section must test the concept that this product requires 1 to 2 days to work. (Refer to the *Use* section for additional information.)

Ask a doctor or pharmacist before use if you are taking

- Retain "warfarin (blood thinning medicine)"
- Delete [redacted]
- Consider deleting [redacted] and replacing it with "prescription anti-fungal or anti-yeast medicines"

- Add "diazepam"
- Add "digoxin" or [redacted]

Stop use and ask a doctor if

- As noted above, the information conveyed in this section should be moved to the *Warnings* section.

Directions

- Revise the direction [redacted] to delete the phrase [redacted] and to add the concept that the tablet is taken before eating.
- Revise the direction [redacted] to [redacted]
- Provide text that conveys the concept that the drug is not for use for more than 2 to 3 courses of treatment in one year at 3 to 4 month intervals. This concept should be tested to determine whether it is best understood by consumers in the *Warnings* section or the *Directions* section.

Package Insert:

- The proposed package insert is promotional in tone and contains misleading statements. The entire package insert must be revised to present factual and educational information for consumers.
- The proposed package insert must include detailed information about the critical points identified above in the carton label. It should also include information about how omeprazole magnesium tablets could be used with other heartburn medications (i.e., antacids and H_2-blockers).

Blister Card:

The established name must be relocated to appear immediately beneath the proprietary name.

Additional Comments:

A. The proposed trade name, Prilosec 1, is not acceptable. The use of a numerical suffix in conjunction with the trade name may be misinterpreted as the product strength or the number of tablets to be administered. In addition, the modifier [redacted] is promotional in tone and suggests a superiority about the drug product meaning it is "first" or "best." Submit a proposal for a different trade name.

B. The word "new" should be deleted from the labels and labeling unless you plan on submitting revised labels and labeling (without the term "new") six months post-marketing to replace the proposed labels and labeling. The term "new" may be used on labels and labeling for a period not to exceed 6 months.

C. Add the words "Delayed-Release" before "Tablets" on the carton, package insert, and blister card.

D. Add directions to the carton, package insert, and blister card to swallow the tablet whole and not to chew or crush in food. This concept must be tested in a label comprehension study.

If additional information relating to the safety or effectiveness of this drug becomes available, further revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   - Present tabulations of the new safety data combined with the original NDA data.

   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have requested deferral of the submission of your pediatric studies. We reiterate our request, dated November 27, 2000, for information regarding projected OTC usage for the treatment of frequent heartburn in the ~ 18 year old age group and information as to whether Prilosec 1 will represent a meaningful therapeutic benefit in these pediatric patients in the OTC setting.

If you believe this drug qualifies for a waiver of the pediatric study requirement for any or all age groups, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55. We will notify you whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Maria R. Walsh, M.S., Project Manager, at (301) 443-8017.

Sincerely,

{See appended electronic signature page}

Jonca Bull, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

{See appended electronic signature page}

Florence Houn, M.D., M.P.H.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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Jonca Bull
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Florence Houn
8/8/02 09:33:25 AM

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Food and Drug Administration
Rockville MD 20857

NDA 21-229

NOV 27 [illegible]

The Proctor and Gamble Company
Attention: William Kozarek, Ph.D.
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

Dear Dr. Kozarek:

Please refer to your new drug application (NDA) dated January 27, 2000, received January 27, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Prilosec 1 (omeprazole magnesium) Tablets.

We acknowledge receipt of your submissions dated March 23, April 14, April 25, April 28, May 19, May 31, July 20, August 2, August 10, August 11, August 17, August 23, August 25, August 28, August 31, September 7, September 12, September 13, September 20, September 27, October 3, October 11, October 18, October 25, October 30, October 31, and November 15, 2000.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). This application is not approvable due to the following deficiencies:

1. The present application included six clinical trials, intended to evaluate efficacy of Prilosec 1 for over-the-counter (OTC) use in three new indications:

   - relief of heartburn, acid indigestion, and sour stomach,
   - prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages, or associated with events such as stress, hectic lifestyle, lying down, or exercise, and
   - prevention of heartburn for 24 hours.

   However, the efficacy, appropriate dose and duration of therapy, and use of Prilosec 1 in the OTC setting have not been adequately established. Further, the ability of the consumer to appropriately self-select and to use Prilosec 1 safely and effectively in the OTC setting has not been demonstrated. Thus, a favorable benefit/risk profile has not been established for OTC use. A summary of the basis for these conclusions follows:

   A. You have not provided sufficient evidence to establish efficacy of single 10 mg or 20 mg doses of Prilosec 1 for relief of heartburn symptoms (studies 1997092 and 1997095) or for prevention of meal-induced heartburn (studies 1998005 and 1998006). Further, the pharmacodynamics of omeprazole appear to suggest that it is not likely to provide acute symptomatic heartburn relief.

      The data presented for prevention of heartburn for 24 hours (studies 171 and 183) do support

the efficacy of either 10 mg or 20 mg per day dosing for up to 10 days in the treatment of individuals with chronic heartburn. However, additional information is needed to establish that consumers can safely and effectively use the product for this indication, and to establish appropriate labeling. Paragraphs B through E below identify current deficiencies in the data available to support this indication.

B. The target population for a "prevention of heartburn for 24 hours" or "treatment of frequent heartburn" indication requires further clarification, with identification of the data supporting use in that population (including information on how consumers will self-select and actually use the product). Because of the inclusion/exclusion criteria used in the actual use studies performed to date, the populations enrolled in those studies may not be representative of the general OTC population that will use the drug, if it is approved for treatment of frequent heartburn. It is likely that some consumers with gastroesophageal reflux disease (GERD), including both consumers who have not seen a health care professional, and consumers who are currently being treated for GERD, would take this medication OTC. While periods of self-treatment may provide an acceptable standard of care for a subset of individuals with GERD, you need to establish that consumers understand when to contact their physicians prior to initiating therapy and also that consumers understand when to follow-up with their physicians after initiating therapy. You will also need to show that this consumer understanding generally translates into timely consumer action (i.e. timely contact of an appropriate health care provider by the consumer, when it is important for the consumer to have professional help for their condition). The label comprehension and actual use trials reviewed in this application suggested potential problems in consumer understanding and appreciation of stated warnings. Additional label comprehension studies are needed, using labeling that provides appropriate dosing, duration, self-selection, and warning information; with actual use studies to follow, when labeling has been identified that appears suitable to achieve a high level of consumer understanding of the information needed for self-care.

C. The 10-day treatment limitation for "prevention of heartburn for 24 hours" is not well supported, given the nature of the indication and the population likely to take this medication. The actual use trials presented in this application support the notion that consumers with frequent heartburn will take Prilosec 1 for longer than the 10-day restriction stated on the labeling in order to achieve benefit from the product (and this longer use may in fact be appropriate). In your initial application, data were submitted to support a 20 mg daily OTC dose for this indication. In subsequent submissions, however, a 10 mg daily dose was proposed. At this time, it is unclear which dose is most appropriate for OTC use. Thus, the appropriate dose and duration of therapy requires further consideration, and additional data are needed to support the optimal OTC dose and duration of therapy. At least some of these additional data may be available in your clinical trials database for Prilosec.

D. The implications of use of OTC omeprazole by consumers who may need long-term treatment for GERD and/or erosive esophagitis must be considered. A 10 mg daily dose may not provide adequate benefit for some of these people if they self-medicate with an OTC product. Thus, if this is the desired dose for OTC use, adequate data will be needed to support its use and to demonstrate that it will not be used by such consumers; or if used, this use will not place such consumers at increased risk for the rarer but serious consequences that might result from

incomplete healing or delayed diagnosis, such as more advanced stages of GERD or erosive gastritis, Barrett's esophagus, esophageal dysplasia, and malignancy.

Similarly, use of a 20 mg daily dose for four weeks by consumers with GERD and/or erosive esophagitis may be an adequate regimen for some but an inadequate regimen for others. Again, as specified in paragraph B above, you need to establish that consumers understand when to contact a health care professional, and that this understanding translates into appropriate and timely consumer action.

E. Both the actual use and label comprehension trials failed to demonstrate that consumers understood how and when to use Prilosec 1 in comparison to currently available OTC heartburn products that are marketed for relief and/or prevention of heartburn. In performing additional label comprehension and actual use studies, it will be important for you demonstrate that consumers understand that this product will not acutely relieve symptoms.

2. Prilosec has a number of reported drug-drug interactions. Prilosec is metabolized by the cytochrome P450 enzymes. In some individuals, there is the potential of Prilosec to reduce the clearance of drugs that are metabolized by CYP2C19, such as diazepam, phenytoin, R-warfarin, You have not adequately demonstrated the ability of consumers to comprehend the risks associated with concomitant use of Prilosec with these interacting drugs, nor have you demonstrated the ability of consumers to avoid concomitant use without the intervention of a physician. Adequately addressing this important safety issue is very important to any proposal for OTC marketing.

3. Additional safety issues not addressed in this submission are as follows:

A. You have not provided adequate safety information to support OTC omeprazole use in individuals under the age of 18 years. Labeling of an OTC omeprazole product would need to be restricted to individuals 18 years of age or older at this time.

B. Further consideration is needed regarding the risks to the fetus of potential Prilosec use in the OTC setting by women who are pregnant or of childbearing potential.

C. Because of the potential risks of long-term exposure (e.g., omeprazole-induced hypergastinemia and its genotoxic effects might increase the risk for tumorigenicity in certain susceptible individuals treated for long periods of time), further information is needed in an OTC setting to assure the safety of this product when there is no health care professional to make an appropriate benefit/risk assessment for long-term exposure. At minimum, you need to establish that consumers will not use Prilosec 1 for extended periods of time without contacting a health care provider.

D. Because exaggerated rebound of gastric acid secretion has been observed after drug discontinuation in individuals treated with omeprazole for longer than one month, you will need to submit additional information regarding the clinical import of this observation for use of Prilosec 1 in the OTC setting.

4. The proposed product name, Prilosec 1, is not acceptable. The primary concerns with this proposed name are the possibility of confusion with prescription Prilosec and the promotional and representational nature of the name. You should submit a new proposed product name, since the use of a number suffix has no obvious relevance to the product dose or use and may be misleading.

Your complete response to this letter should include a safety update as described in 21 CFR 314.50(d)(5)(vi)(*b*) and revised labeling based on data obtained from trials necessary to correct the deficiencies described above. Please provide updated information as listed below. The update should provide the data lock date and cover all studies, both U.S. and foreign, and all uses of the drug including (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will facilitate the review.

2. Retabulation of dropouts with new dropouts identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

[redacted]

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely,

/S/

Robert DeLap, M.D., Ph.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

/S/ VICTOR RACZKOWSKI, M.D. for

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert DeLap
11/27/00 05:32:58 PM

Victor Raczkowski
11/27/00 05:37:59 PM

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