1 Executive Summary

This briefing document provides a summary of information supporting the over-the-counter (OTC) use of omeprazole magnesium (Ome-Mg) tablets for heartburn. The document will summarize the efficacy and compliance results of the clinical program, safety results from the clinical program and from worldwide prescription (Rx) clinical trials, and post-marketing surveillance databases to establish efficacy in the target OTC population, safe use, and suitability for OTC status. The OTC clinical program evaluated 10 mg and 20 mg Ome-Mg doses.

1.1 Medications in the OTC Heartburn Category

Two classes of compounds, antacids and H_2RAs, are currently available OTC for the relief of episodic heartburn and H_2RAs have been approved for the prevention of heartburn associated with food and beverage.

Antacids have the longest history of use in the OTC heartburn category, are regulated for OTC status via the monograph based on *in vitro* acid neutralization, and are indicated "for the relief of heartburn, acid indigestion, and sour stomach." Antacids work by directly neutralizing existing gastric acid, and afford rapid but short-lived relief of heartburn symptoms. It is often necessary to dose several times with an antacid to adequately control heartburn symptoms.

H_2-receptor antagonists are systemically absorbed agents that work by competitively binding to histamine receptors on the surface of the gastric parietal cell, and were first approved for OTC heartburn relief and meal-induced heartburn prevention in 1995. Most of the H_2RA clinical programs utilized "Adequate" as the definition of success in achieving either prevention or relief of heartburn, although Pepcid AC® and Axid AR® did use Complete Prevention as a measure of efficacy, combined with other temporal variables. Relief was typically demonstrated by Adequate Relief over all episodes measured (Pepcid AC® and Tagamet HB®), by Overall Relief at the end of the study, or by evaluating four consecutive dosing periods (Axid AR). Each of the H_2RA programs evaluated several doses including the lowest Rx dose and half the Rx dose. In each case, the efficacy of the Rx dose was the same as half the Rx dose in the OTC clinical evaluations.

The OTC availability of H_2RAs represented an advance in the heartburn category in that they could be effectively used to prevent heartburn symptoms. This advance added a new indication to the OTC heartburn category: "prevents heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages." The duration of action for the H_2RAs is generally 8–12 hours; thus, H_2RAs can be dosed up to twice per day. Label indications for H_2RAs read as follows:

- For relief of heartburn associated with acid indigestion and sour stomach
- For prevention of heartburn associated with acid indigestion and sour stomach brought on by certain foods and beverages

1.2 Marketing History of Omeprazole

Omeprazole was the first PPI approved for Rx use. Omeprazole has been marketed worldwide under various trade names in Europe (since 1988) and was approved for marketing in the United States (in 1989). It is currently marketed under the trade name Prilosec® in the U.S. Omeprazole is one of the most frequently prescribed medications worldwide: marketed in over 100 countries, with approximately 380 million courses of patient therapy to date.

The dosage form evaluated for OTC status is a tablet consisting of multiple enteric-coated pellets (MUPS) formulated with Ome-Mg. The tablet form was chosen for OTC status because it is more resistant to tampering, and therefore more suitable for OTC marketing. The Ome-Mg tablet has a similar relative bioavailability to the oral Rx capsule forms of Ome. The tablet dosage form is approved in 29 countries worldwide including Australia, Germany, and the United Kingdom. Ome-Mg was also approved (1999) for OTC status in Sweden, for the relief of heartburn, in doses up to 20 mg.

1.3 Rationale for the Application

As discussed, the treatment and prevention of heartburn in the OTC setting is already established. This application addresses the suitability of Ome-Mg, which represents a new pharmacological class, against the criteria for OTC status. The OTC considerations addressed are presented here:

1. Can the consumer recognize and self-treat heartburn?
2. Does the drug have a predictable PK/PD profile?
3. Is the efficacy established in well-controlled clinical trials?
4. Was the drug studied in a population representative of the OTC heartburn population?
5. Is there a wide margin of safety and can it be taken safely without medical supervision?
6. Does the consumer adequately understand how to use the drug appropriately?
7. Do the benefits of making omeprazole (Ome-Mg) OTC outweigh the potential risks?

These considerations will be addressed with the supporting information contained within the Briefing Document.

1.3.1 OTC Heartburn Condition

It is widely recognized that consumers can self-diagnose heartburn. Data presented in this current application demonstrate that consumers can effectively self-diagnose, and when they predict the days in which they will experience heartburn, they can do so with a high degree of accuracy. Consumers consistently demonstrate a high level of sophistication not only in recognizing heartburn, but also in understanding how to treat the condition.

The New Drug Application (NDA) for Ome-Mg provides data showing safety and efficacy in the same indications as the H_2RAs — prevention of heartburn and relief of heartburn symptoms. The design of the clinical program and the clinical measures employed to demonstrate safety and efficacy are similar to those utilized in the H_2RA program. Ome-Mg is targeted for OTC use by the same population as has already been established with antacids and H_2RAs, that is, consumers with occasional, episodic heartburn symptoms. It is not intended to replace medical management of patients who have more serious conditions, such as gastro-esophageal reflux disease (GERD) with or without erosive esophagitis, which require medical supervision and may need more continuous use of acid-suppressing medication. The proposed label directions are similar to those for the H_2RAs, but with the convenience of a single dose due to the duration of action of Ome-Mg.

1.3.2 PK/PD

The efficacy data presented in this submission are consistent with the pharmacology of omeprazole. Omeprazole irreversibly binds to the H^+/K^+ ATPase on the secretory surface of the lumen of the gastric parietal cell, providing a long-lasting effect in reducing gastric acid secretion despite its relatively short plasma half-life of one hour. Resumption of normal gastric acid secretion involves regeneration of the proton pump, a process that occurs progressively during a period of a few days.

1.3.3 Efficacy

Omeprazole has already been approved for the treatment of heartburn associated with GERD and maintenance of healing erosive esophagitis. Data contained in this application also support the effectiveness of omeprazole for heartburn in the consumer population.

The OTC clinical program detailed in the NDA consists of six adequate and well-controlled studies (four in heartburn prevention and two in heartburn relief), one label comprehension study, and studies investigating consumer usage patterns. A total of 11,644 subjects are included in the intent-to-treat (ITT) population of this efficacy program described in Section 5 of this document. Three additional single-dose studies were completed after the NDA was filed and are described in Appendix 2.

The following conclusions are supported from the data presented from the four heartburn prevention trials in which approximately 3,700 subjects on active medication were studied. Ome-Mg was administered to prevent specific heartburn episodes:

- Ome-Mg 10 and Ome-Mg 20 are more effective than placebo in preventing heartburn for up to a full 24 hours after dosing, including a benefit for nocturnal heartburn prevention and as soon as 1 hour before a provocative meal (detailed in Section 5).

- With consecutive daily dosing, the incremental preventive benefit over placebo was greater for both Ome-Mg 10 and Ome-Mg 20 (detailed in Section 5).

- The clinical benefits were more perceivable to the study subjects who received both Ome-Mg 10 and Ome-Mg 20 than placebo based on Overall Assessment (measured in single-dose studies only; detailed in Section 5).

Five heartburn relief trials were conducted, two multi-dose trials which were included in the original NDA and are reported in the efficacy section of this document, and three single-dose trials that were completed after the NDA was filed and are included in the appendix. Ome-Mg was administered in response to heartburn symptoms. The following conclusions are supported by the data:

- A statistically significant difference was not achieved between either Ome-Mg dose and placebo for the primary analysis of the primary efficacy variable (Sustained Complete Relief in multi-dose trials and Sustained Adequate Relief in single-dose trials) after the first treated episode in any of the studies.

- Ome-Mg 10 and Ome-Mg 20 are significantly more effective than placebo in relieving heartburn symptoms across all episodes over a 2-week period in a population of people who suffer from episodic heartburn (detailed in Section 5).

- Sustained Adequate Relief of heartburn symptoms was demonstrated for both Ome-Mg 10 and Ome-Mg 20 across all treated episodes. Ome-Mg 20 provided Sustained Complete Relief across all episodes (detailed in Section 5).

- The clinical effects were more perceivable to the study subjects who received both Ome-Mg 10 and Ome-Mg 20 than placebo based on Overall Assessment after each treated episode (both studies; detailed in Section 5).

1.3.4 Comparison of Clinical and OTC Heartburn Populations

The mean age of subjects in our trials was 44 years and there were slightly more women (55%) than men (45%) enrolled into the trials. Over 90% of subjects reported they took at least one dose of an OTC medication during the 30-day period prior to study entry — 75% took an antacid product and 38% took an H_2 receptor antagonist.

In our clinical trials, subjects reported a heartburn frequency of at least two times in the 1-week lead-in period. This is comparable to the inclusion criteria utilized by the H_2 receptor antagonists in their OTC switch programs (3–5 heartburn episodes per week). While this frequency of heartburn is above the average heartburn occurrence in the OTC population (between 1.6 and 2.5 times per week), we did specify in our protocols that subjects must have a history of heartburn of at least 2 days per week in order to ensure subjects would have an adequate chance to experience heartburn during the 14-day trials. These subjects could not have had a diagnosis of GERD or erosive esophagitis, and furthermore had to have a history of effective relief from OTC heartburn medications.

1.3.5 Safety

Omeprazole has demonstrated a highly favorable safety profile over more than a decade of world-wide marketing. There is a substantial amount of experience with the compound in the treatment of many different clinical conditions.

The clinical trial safety databases include over 14,000 subjects/patients who took either Ome capsules or Ome magnesium tablets in either Rx trials or OTC clinical trials. Additional safety data are included from approximately 5,000 GERD, erosive esophagitis, and dyspepsia patients/subjects treated with placebo or an active comparator.

The summary of these safety data indicate:

- The safety profile for Ome-Mg-treated subjects was comparable to that for Rx Ome and placebo.
- There was no dose-related increase in AE reporting for treated patients during the clinical studies.
- There is no evidence that individuals “rebound” with excessive acid production after stopping treatment.
- Serious AEs are rare and do not occur at a rate greater than the background rate in the population for treated acid-related disorders.
- No dose adjustment is necessary in hepatic or renal impairment or in individuals characterized by slow metabolizers.
- Reports of overdosage are rare. Symptoms of overdose are transient, and no serious clinical consequence would be expected.
- There is no evidence to suggest that omeprazole has abuse potential nor is there evidence that it potentiates the effects of substances of abuse.
- There are no clinically significant hepatic metabolic drug-drug interactions. Drug-drug interactions involving gastric pH dependency should continue to be monitored.

- The association of esophageal or gastric cancer in individuals whose only symptom is heartburn is very low and would not be expected to be masked by OTC use of Ome.

1.3.6 Consumer Understanding

The consumer understanding of product use was evaluated in a label comprehension study and four trials to establish use and compliance of the drug product in an unsupervised setting.

The consumers demonstrated a good understanding of the label in regard to the product's intended use, when to use the product, when not to use the product, and when to seek medical attention.

Use studies determined consumer adherence with the label use directions under conditions of actual use.

Consistency of consumer's use with each of the three label use directions was examined: whether subjects took only one tablet per dose; whether they took no more than one dose per day; and whether they adhered to the direction to take no more than 10 days without seeking medical advice. Across the four consumer use studies, the results are summarized as follows:

- Among 24,802 dosing occasions, 91%–98% involved only one tablet.

- Among 24,071 dosing days, 96%–99% involved no more than one dose.

- Among 2,287 consumers, 78%–92% of subjects never exceeded 10 consecutive days of dosing. In one study, it was determined that, of the subjects that exceeded 10 days, most (73%) did in fact have the advice of a physician/health professional or were under the medical care of a physician for their heartburn.

1.3.7 Dose

Both Ome-Mg 10 and Ome-Mg 20 are more effective than placebo in preventing heartburn for up to a full 24 hours after dosing, including a benefit for nocturnal heartburn prevention and as soon as 1 hour before a provocative meal. Ome-Mg 10 and Ome-Mg 20 are significantly more effective than placebo in relieving heartburn symptoms across all episodes over a 2-week period in a population of people who suffer from episodic heartburn.

From a safety perspective, there is no difference in safety profiles between the 10 mg and 20 mg doses. Analysis of AE data demonstrates that Ome-Mg, both qualitatively and quantitatively, has a similar safety profile across doses and is similar to placebo. The wide margin of safety established through years of Rx Ome use at doses up to 80 mg daily makes Ome-Mg suitable for OTC status.

The OTC clinical trials evaluated the effectiveness and consumer use of both 10 mg and 20 mg doses of omeprazole magnesium. The 10 mg Ome-Mg is an appropriate OTC dose.