AstraZeneca

Submission for

Reclassification from

Prescription Medicine

to

Pharmacist Only Medicine

Omeprazole 10 mg

AstraZeneca Limited

PO Box 1301

Auckland

July 2008

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Executive Summary

With consideration from feedback from previous submissions to the Medicines Classification Committee, this application seeks the approval to reclassify omeprazole 10 mg from a Prescription Medicine to a Pharmacist Only Medicine for the relief of reflux-like symptoms (eg heartburn) in patients aged 18 and over.

Twenty-five per cent of New Zealanders suffer from reflux symptoms including heartburn at least several times per week.

Dyspepsia / heartburn is an established self-diagnosed condition, self medicated with antacids or H2-antagonist available in either the pharmacy or supermarket.

Consumer surveys show a significant proportion of frequent heartburn sufferers are dissatisfied with the currently available OTC products.

Proton pump inhibitors are considered the gold standard of therapy in acid related diseases due to their superior acid inhibition.

Omeprazole's established efficacy, and excellent safety profile make it an appropriate Pharmacist Only Medicine.

Opening up access to PPIs such as omeprazole at a Pharmacist level provides patients with a full choice of treatment options to relieve their condition without visiting the doctor.

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PART A

1. International Non-proprietary Name of the Medicine

Omeprazole

2. Proprietary Name(s)

To be advised.

Throughout this submission the product will be referred to as ‘omeprazole OTC’.

3. Company Requesting Reclassification

AstraZeneca Limited
PO Box 1301
Auckland
NEW ZEALAND

4. Dose Form(s) and Strength(s)

Dose form: Capsule (modified release).

Strength: 10 mg.

5. Pack Size and Other Qualifications

14 capsules in bottle enclosed in carton.

6. Indications for Which Change is Sought

Relief of reflux-like symptoms (eg, heartburn) in patients aged 18 and over.

7. Present Classification of Medicine

Prescription Only Medicine

8. Classification Sought

Pharmacist Only Medicine

9. Classification Status in Other Countries

Omeprazole:

Sweden:

OTC Date of approval: April 2000

(Classification equivalent to Pharmacy Only Medicine)

The first approval for OTC sale of an omeprazole product was in 2000 when the Swedish MPA approved OTC status for Losec MUPS 10 mg and 20 mg. From 2003, a generic omeprazole was also made available OTC in Sweden.

USA:

OTC Date of approval: 20 June 2003

(Classification equivalent to Pharmacy Only Medicine)

Losec MUPS 20 mg was approved in the US with OTC status under the name 'Prilosec OTC' to treat adults with frequent heartburn (patients having heartburn two or more days a week).

Mexico:

OTC Date of approval: 25 June 2003

(Classification equivalent to Pharmacy Only Medicine)

Losec capsules 10 and 20 mg have OTC approval in Mexico for the short term treatment of symptoms related to acid peptic disorders and the prevention and relief of symptoms of heartburn, acid regurgitation and gastric pain related to flow of gastric acid contents from the stomach.

United Kingdom:

OTC Date of approval: 19 January 2004

(Classification equivalent to Pharmacy Only Medicine)

A generic omeprazole 10 mg has approval for OTC treatment of reflux-like symptoms such as heartburn for adults aged 18 years and older.

China:

Date of approval: 23 April 2004

Losec MUPS 10 mg has been approved in China for the relief of temporary symptoms of heartburn and regurgitation.

Denmark:

Date of approval: 4 December 2006

Losec MUPS 10 mg has been approved in Denmark for symptomatic gastro-esophageal reflux.

Rest of World:

Prescription Medicine.

Pantoprazole

Sweden:

OTC Date of approval: April 2000

Pantoprazole was approved concurrently with omeprazole.

Australia

Effective date: 1 May 2006.

Schedule 3 (Classification equivalent to Pharmacist Only Medicine)

Pantoprazole in oral preparations containing 20 mg or less of pantoprazole for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days of supply.

10. Extent of Usage in NZ and Elsewhere

Losec 20 mg Capsules were approved for distribution in New Zealand on 27 April 1990 and have been available to New Zealand patients since December 1990. The product line was extended in 1997 to include a 10 mg strength (approved 7 January 1997) and a 40 mg strength (21 October 1997) and again in 2001 with the approval of the Losec MUPS presentation (enteric coated tablets for all strengths) on 15 February 2001.

During 2007, 3.051 million units have been sold in the New Zealand prescription market. Each unit is a 30-day regimen of 1 capsule per day.

Prilosec (omeprazole) OTC was first approved for marketing in the US on 20 June 2003 for the treatment of frequent heartburn for patients aged 18 years and older. Since its introduction as an OTC product, around 144.7 million courses of treatment have been sold (each course of treatment is a 14-day regimen of 1 tablet per day).

Since Zanprol's (omeprazole) launch in April 2004 in the UK, 0.32 million treatment courses have been sold (each course being 14 day regimen of 1 x 10 mg tablet per day)

11. Proposed Labelling and Patient Information Leaflet

Refer Appendix 1 for draft labelling and CMI (pack insert). Please note that the actual design of the label is to be determined, the draft carton and bottle labelling is provided to indicate text.

12. Proposed Warning Statements (to be included in pack insert)

Do not use omeprazole OTC:

If you are allergic to omeprazole or any other ingredient contained in this product;
For any purpose other than that specified on the pack unless directed by your doctor.

Before you start to use omeprazole OTC:

Ask your healthcare professional for advice before taking these tablets if:

- You have any of the following symptoms:
  - trouble or pain swallowing;
  - persistent vomiting or vomiting with blood;
  - bloody or black stools;
  - unintended weight loss;
  - anaemia;
  - abdominal pain or swelling;
  - jaundice.
- You are aged 40 years or older with heartburn and/or indigestion symptoms for the first time or your symptoms have recently changed;
- You have experienced heartburn for over 3 months;
- You have experienced chest pain or shoulder pain with shortness of breath, sweating, pain spreading to arms, neck or shoulders, or light-headedness;
- You have previously had a stomach ulcer or undergone stomach surgery;
- You have a family history of gastric cancer
- You are pregnant or breast feeding.
- You are on any of the following medications:
  - warfarin (blood thinning medication);
  - phenytoin (epilepsy medication)

- prescription anti-fungal or anti-yeast medications;
- diazepam (anxiety medicine);
- digoxin (heart medicine).

Advise your healthcare professional if you are on any other medications, even those you may purchase from the supermarket or health store.

While using omeprazole OTC:

- Consult your healthcare professional if:
- Your heartburn continues or worsens;
- You have not experienced any relief from your symptoms after treatment with omeprazole OTC.
- You experience symptoms such as fever, nausea, general felling of unwellness, tiredness, blood in urine, weight loss (symptoms of interstitial nephritis).

If you are a heartburn sufferer with long-term recurrent symptoms, you should see your doctor at regular intervals.

Do not take omeprazole OTC with other “acid suppressors” such as H_2 antagonists (eg ranitidine, famotidine).

13. Other Products Containing the Same Active Ingredient(s) and which would be Affected by the Proposed Change

- Losec MUPS 10 mgEnteric Coated Tablets (AstraZeneca Ltd)
- Omeprazole Modified Release Capsules 10 mg (Affordable Healthcare Ltd)
- Omezol Modified Release capsule 10 mg (Pacific Pharmaceuticals Ltd).

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PART B

1. Introduction

At the 26th Meeting of the Medicines Classification Committee held on 11 December 2001, the Committee considered AstraZeneca's application to reclassify 10 mg omeprazole tablets from Prescription Medicine to Pharmacy-Only Medicine for the symptomatic relief and short-term prevention of the recurrence of heartburn and indigestion.

The committee's feedback was as follows[1]:

- The committee agreed that the medicine had a sufficiently favourable safety profile for it to qualify for OTC sale.
- However, the Committee raised several issues that would need to be clarified before approval could be given:
  - dose instructions;
  - suitability of short-term prevention of recurrence for self medication;
  - consent to market of short term prevention indication not obtained;
  - clinical data to support OTC indication.

The Committee agreed that they would be willing to consider a submission for reclassification to restricted medicine at a later date should the company wish to make such a submission.

As such, AstraZeneca made a subsequent submission to the 28th Meeting of the Medicines Classification Committee which was held on 19 November 2002. The revised submission proposed the reclassification of omeprazole 20 mg tablets from Prescription Medicine to Restricted / Pharmacist Only Medicine for the 24-hour prevention of the symptoms of frequent heartburn and indigestion.

The Committee stated that they had already considered the safety of the medicine and had no serious concerns about it suitability for OTC use from a safety point of view[2].
However the committee still had concerns regarding:

- The indications sought;

- The continuous use of the product over a two-week period for symptoms that were intermittent;
- The potential for a medicine with the potency of omeprazole to mask underlying pathology, particularly with repeat courses.

The Committee stated that they felt there were other medicines available that would deal with the symptoms more efficiently on an 'as required' basis and no particular benefits were apparent for consumers as they had access to better products for immediate symptom relief.

A further submission was made to the 35th meeting of the Medicines Classification Committee (held on 9 June 2006). Revised indications, dosage recommendations and pack sizes were proposed for a Pharmacy Only Medicine classification taking into consideration feedback from previous submissions.

The Committee still had concerns surrounding the indications, duration of treatment and dose, however they would be prepared to consider a submission on the basis that[3]:

- Reclassification to restricted medicine
- Pack size allowed for treatment for a maximum of 14 days
- A maximum pack size of 14 units
- The tablet size should not exceed 10 milligrams
- The indication for OTC sale in New Zealand should be the same as for OTC sale in the United Kingdom – that is, for the relief of reflux-like symptoms in sufferers aged 18 and over
- The package information should reflect safety risks, including that of interstitial nephritis.

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2. Proposed Indications and Dosage

In line with the feedback from the 35th Medicine Classification Committee meeting[4], AstraZeneca propose the following indications and dosage for a Pharmacist Only Medicine omeprazole 10 mg OTC pack containing 14 capsules in line with that approved in the UK:

Indication:

- Relief of reflux like symptoms (eg. heartburn) in adults 18 years and older.

Dose and Directions (Adults 18 years and older):

- Initially take 2 capsules once daily. If your symptoms improve, reduce the dose to 1 capsule daily. If your symptoms return, take 2 capsules once daily. The lowest dose that controls your symptoms should always be used.

  Omeprazole OTC capsules will start to suppress acid in 1-2 hours, but will not give instant relief from acid reflux and heartburn. You should take the tablets for 3-4 days to achieve maximum results.

- Swallow tablets with a glass of water. Do not crush or chew the capsules.

The following warnings will be listed on the pack insert to ensure appropriate OTC administration of the medicine and advise when to see your doctor / pharmacist if symptoms do not resolve.

- Do not give to children under 18 years of age
- Do not exceed the stated dose
- Do not use omeprazole OTC for any other purpose other than that stated on this pack unless under the direct supervision of a doctor
- Talk to your doctor or pharmacist if your symptoms get worse or are no better once you have finished your bottle of 14 capsules. If you require more capsules it is important to talk to your doctor or pharmacist as you may have another medical condition that needs different treatment.
- Do not use for more than 14 days unless directed by your doctor.

- If your symptoms reappear shortly after you stop taking omeprazole OTC capsules, talk to your doctor because your symptoms may be a sign of a more serious disease.

3. Problem Statement

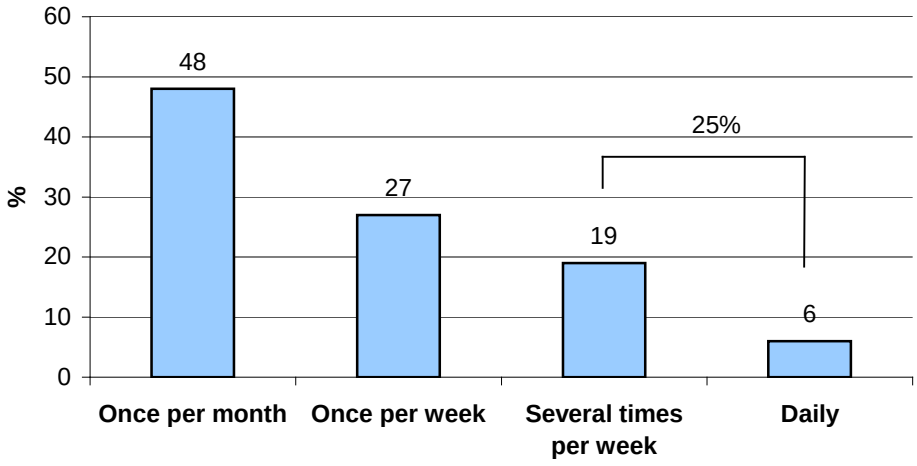
3.1 The Frequent Heartburn Population

The prevalence and severity of gastrointestinal symptoms such as dyspepsia and reflux were published in the New Zealand Medical Journal[5] in 2000. This study surveyed a sample of 1,000 adults from the Wellington region and found the overall combined prevalence of significant symptoms of dyspepsia and reflux was 45%. Significant symptoms were defined as occurring with a frequency of at least once per month. While this prevalence seems high, it is in line with other studies from Europe and North America. A survey from Great Britain found dyspepsia prevalence of 40%[6].

In the New Zealand study, heartburn was found to be the most common symptom being reported in 70% of those with reflux or dyspepsia. This is in agreement with the Genval Consensus Guidelines, which support heartburn as the most common symptom of gastrointestinal reflux in at least 75% of subjects[7].

Twenty-five per cent of the New Zealand sample reported reflux symptoms at least several times a week.

Figure 1: Frequency of reflux symptoms in New Zealand sample



Self-care featured prominently amongst the New Zealand subjects with 69% of those with reflux-like symptoms occurring with a frequency not more than weekly[5].

No formal studies on the frequency of heartburn alone have been conducted in New Zealand patients. However, US data indicates that heartburn occurs daily in approximately 7% - 10% of the adult population[8], and 2 or more days a week in up to 45% of heartburn sufferers[9]. This US data suggests that up to 78% of frequent heartburn sufferers have seen a healthcare provider and primarily turn to OTC heartburn remedies to manage their symptoms.

AstraZeneca New Zealand completed market research during 2005 on the subject of dyspepsia symptoms and treatment habits[10]. This research sampled 259 adults aged between 18 and 55+ years who suffered from heartburn at least once a week and sought treatment for it.

Table 1: Demographic data from market research.

	Percent
Gender	
Male	28
Female	72
Age (years)	
18 – 29	24
30 - 39	24
40 – 54	28
55+	24
Ethnicity	
European	87
NZ Maori/Pacific Is	5
Asian	5
Other	3

Seventy percent of those surveyed suffered from heartburn symptoms frequently (several times per week).

In terms of treatment, 50% of patients had sought their doctors advice for guidance on treatment options. In the previous 3 months, the following medications had been trialled (not exclusive):

Losec (PPI)	42%
QuickEase (Antacid)	28%
Mylanta (Antacid)	27%
Gaviscon (Antacid)	15%

Consumer surveys conducted in the US before omeprazole was available OTC, show that a significant proportion of frequent heartburn sufferers are dissatisfied with the then currently available OTC products, primarily because the medication does not last long enough[11]. Current OTC products in New Zealand are intended to treat episodic occasional heartburn and do not provide the degree of acid control needed to prevent frequent heartburn symptoms.

3.2 Current OTC Treatment Options for Heartburn

Antacids/Alginates

Antacids/alginates are the most widely used OTC products for heartburn and indigestion and act by neutralising the acid contents of the stomach or by forming a 'raft' above the contents of the stomach. The evidential base for symptomatic improvement obtained with antacids/alginates is not extensive, however the widespread use of antacids/alginates tends to suggest there is a degree of consumer satisfaction with the response achieved.

Although antacids/alginates are generally well tolerated, they do have the potential to cause side effects in susceptible patients[12]. Despite a well-documented adverse event profile, most individuals use these products in an unsupervised fashion with apparently few reported problems.

The duration of relief from antacids/alginates is short, typically requiring dosing four times daily or more. In addition, as antacids/alginates are recommended to be used 'as required', consumers need to have a pack on hand at all time, especially at meals.

Histamine H_2-receptor Antagonists

The majority of countries, New Zealand included, have approved the OTC sale of H_2-antagonists, such as Zantac Relief (ranitidine). Studies with H_2- antagonists have demonstrated a modest improvement in symptom resolution compared with antacids.

The safety profile of H_2- antagonists is similar to that of omeprazole and other Proton Pump Inhibitors. The ranitidine datasheet documents a range of adverse events comparable to those recorded for omeprazole, while IMMP reporting for cimetidine and omeprazole recorded a similar range of serious adverse reactions[13].

Clinical studies with ranitidine for the treatment of heartburn demonstrated relief of symptoms in 52-57% of all heartburn episodes in patients receiving ranitidine compared to 42% in those patients who received placebo[14]. The onset of relief with ranitidine was achieved within 30-45 minutes and lasted for up to 12 hours.

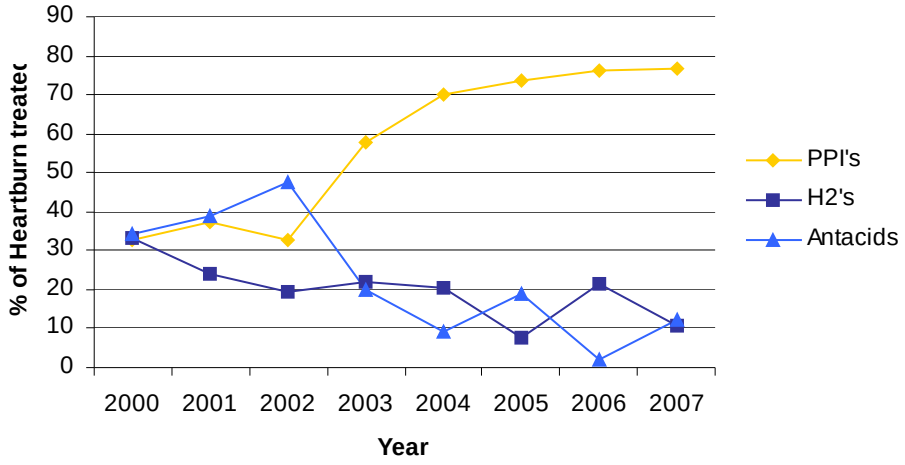
Community surveys were undertaken in the US before and after the H_2- antagonist OTC switch[15]. Around 55% of people surveyed who took OTC medication chronically used H_2-antagonists. The authors stated that expectations for the effectiveness of H_2- antagonists do not seem to have been met and as a sole treatment, complete relief was infrequently provided.

3.3 Professional Recommending Patterns

New Zealand data from the IMS Medical Index Diagnosis Section shows the changing prescribing behaviour of doctors when treating heartburn[16].

Figure 2 below shows an increase in the number of patients prescribed a Proton Pump Inhibitor in response to a diagnosis of heartburn over the last 7 years. This increase correlates to a decrease in use of H_2- antagonists and antacids.

Figure 2: Change in Treatment Choice for Heartburn over last 5 years (prescription data)



At the time of our original submission to the MCC, similar amounts of the three medicine classes were being prescribed for heartburn. However, for the year ending December 2007, almost 80% of patients with heartburn were prescribed a PPI for symptom control. Sixty-four per cent of the PPI prescriptions were for omeprazole. This increase in prescribing has not been associated with any increase in adverse events reported.

4. Benefits to Consumer and Public

Heartburn is characterised by discomfort or a burning sensation behind the sternum that arises from the epigastrium and may radiate toward the neck. Heartburn is an intermittent symptom most commonly experienced within 60 minutes of eating, during exercise or while lying recumbent. The discomfort can be relieved with water or antacids but can occur frequently and interfere with normal activities.

Patients with heartburn who self-treat with antacids and H_2-antagonists may not be aware of the possible benefits of a more effective therapy, and their satisfaction with the therapy of their choice, ie. antacids, may not be an informed judgement. Surveys have shown that even with the currently available medication, including Proton Pump Inhibitors, less than two thirds of heartburn sufferers are totally satisfied with the symptom relief they receive from medication[17].

The pharmacology of omeprazole makes it ideal for the short-term treatment of acid reflux and heartburn symptoms. Omeprazole irreversibly inhibits the H^+/K^+ ATPase on the

secretory surface 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 3-5 days. While omeprazole is effective from the first dose, the maximum inhibition of gastric acid is seen after 3 or more days of dosing, as such patients are recommended to take omeprazole-OTC for 3-4 days to achieve maximum results.

The comparison between H_2-antagonists and omeprazole has shown that omeprazole is a more effective therapy for heartburn symptoms and controls symptoms more effectively when used as short term (14-day) therapy[18,19]. In addition, the US OTC clinical trial programme for omeprazole and the study by Bardhan et al has shown that a short term courses (14-day) of omeprazole used intermittently over a 12-month period can effectively manage heartburn symptoms and may reduce the recurrence of symptoms to three episodes or less per year[19,20].

The availability of omeprazole OTC will benefit the consumer by

- improving access to a more effective therapy by removing the need to visit to their General Practitioner and in turn,
- remove the associated waiting time and costs associated with a GP visit;
- treat their heartburn more effectively and potentially inhibit the recurrence of symptoms

The availability of omeprazole OTC will benefit the public by

- removing the need to access gold standard therapy for heartburn / acid reflux, thus freeing up GPs for more serious conditions;
- allowing Pharmacists to intervene and refer a more serious condition to a GP, which may have previously continued to be treated with H_2-receptor antagonists / antacids. Earlier diagnosis of a more serious condition potentially results in reduced burden on the health system.

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5. Ease of Self-Diagnosis or Diagnosis by Pharmacist

As H_2-receptor antagonists are already available OTC, pharmacists already have experience in diagnosis and treatment of heartburn and when to refer a heartburn patient to their doctor.

AstraZeneca will, in collaboration with relevant professional bodies, produce a package of educational materials to assist pharmacist in the diagnosis and treatment of heartburn / acid reflux with omeprazole. This will include a simple algorithm to differentiate patients with more serious symptoms from those who can be treated with omeprazole OTC. The algorithm and treatment guidelines will be based on the comprehensive Practice Guidelines developed for the introduction of OTC Omeprazole in the UK[21] (copy enclosed). This will ensure that pharmacists will be sufficiently trained to restrict sales to patients who can safely benefit from omeprazole OTC.

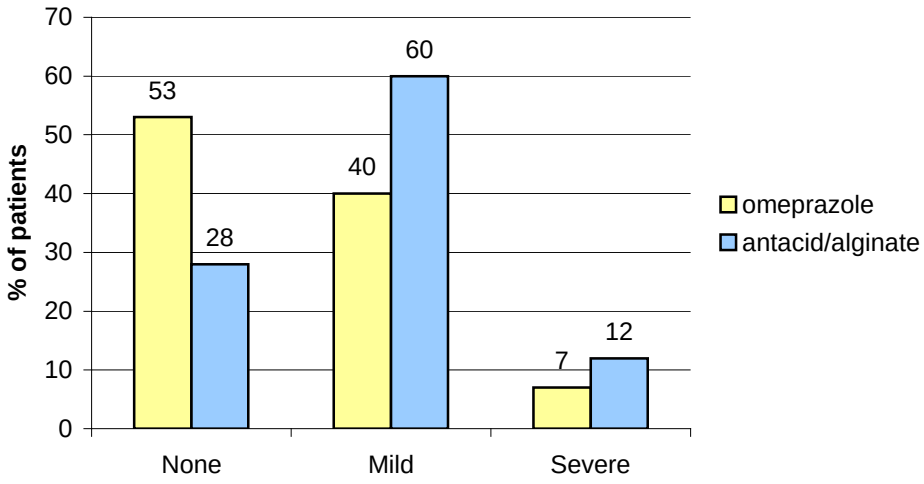
6. Comparison of Omeprazole with Current OTC Treatments

6.1 Omeprazole versus antacids/alginates

A pivotal trial of omeprazole 10 mg versus antacid/alginate liquid in dyspepsia patients with symptoms of epigastric pain and/or heartburn has demonstrated the significant superiority of omeprazole for both the symptom resolution and relief of symptoms after short term (14 days) therapy[22].

Omeprazole 10 mg provided at least twice the efficacy of Gaviscon 10 mL qid with improved patient convenience.

Figure 3: Severity of Heartburn after 2 weeks therapy



Omeprazole 10 mg provided superior symptom resolution compared with antacid/alginate therapy.

Table 2: Percentage of patients with sufficient or complete relief of symptoms after 14 days treatment

	Day 14 Complete symptom resolution	Day 14 Sufficient symptom relief
Omeprazole 10 mg	27%	39%
Gaviscon 10 mL qid	8%	17%
p value	p<0.0001	p<0.0001

In addition, Meineche-Schmidt et al[18] compared omeprazole 20 mg once daily to placebo (Arm B), however the patients were able to concomitantly used antacids during the study, hence this trial may be viewed as head-to-head comparison rather than a placebo-controlled trial.

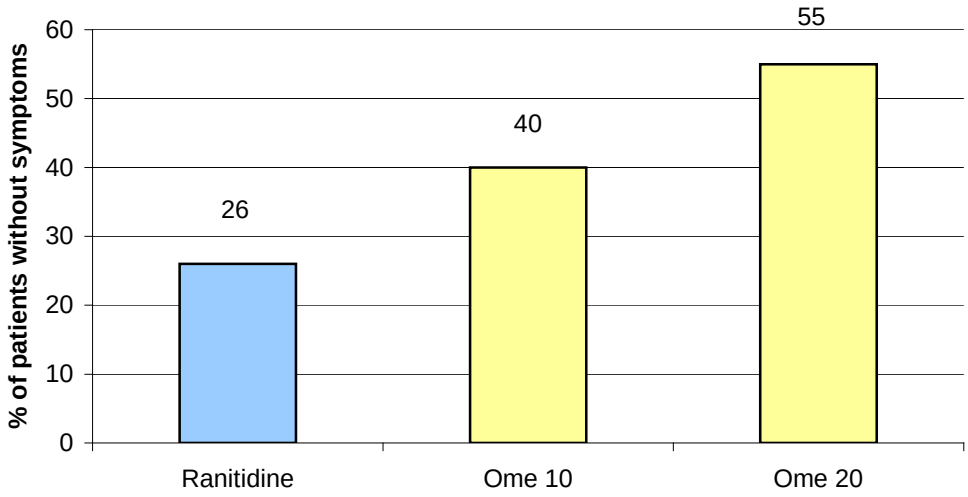
The results of this comparison show that total relief of symptoms occurred in 50% of omeprazole treated patients compared to only 36% of those patients on placebo/antacids. This result was statistically significant (p=0.009). Omeprazole was shown to be significantly more effective in the relief of those symptoms particular to heartburn (p<0.001).

Although the data above indicates that the 10 mg strength of omeprazole provides useful symptom control after 14 day therapy, the data below demonstrates superiority of omeprazole 20 mg use. The 20 mg strength provides further efficacy in the control of heartburn symptoms over and above that provided by the 10 mg strength, without significantly influencing the adverse events reported[19, 20].

6.2 Omeprazole versus H_2-antagonists

The study by Bardhan randomised 677 patients with heartburn and normal endoscopy results to either omeprazole 10 mg daily, omeprazole 20 mg daily or ranitidine 150 mg twice daily for 14 days[19]. The results at Day 14 showed the clear superiority of omeprazole over the H_2- antagonist.

Figure 4: Proportion of patients without symptoms after 14 days treatment



Significantly more subjects treated with omeprazole had symptom resolution at 14 days compared with ranitidine 150 mg bid.

Those patients who did not respond to initial therapy were readily identified due to ongoing symptoms, and were forwarded for further investigation.

A second study comparing omeprazole versus cimetidine in 427 patients with non-investigated dyspepsia showed similar results[18]. Patients in Arm A were randomised to

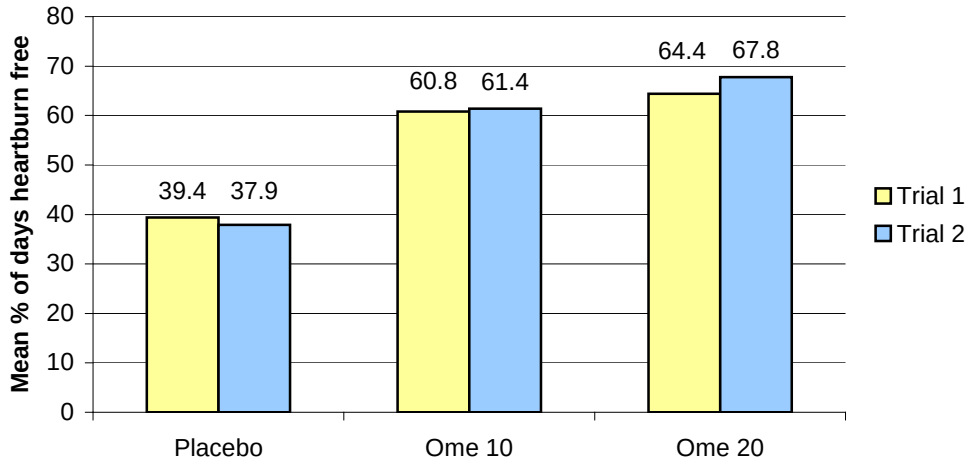
receive either omeprazole 20 mg in the morning or cimetidine 400 mg twice daily for 14 days. On day 15, 50% of omeprazole-treated patients had total relief of symptoms compared with only 35% of patients treated with cimetidine (p=0.002). Omeprazole was shown to be significantly more effective than cimetidine in reducing symptoms particular to heartburn (p<0.001). In total, out of the omeprazole treated patients, 78% had an improvement in their symptoms, 19% were unaffected and 3% had a worsening of symptoms compared to 55%, 30% and 5% respectively for the cimetidine treatment arm.

6.3 Omeprazole OTC Clinical Programme (USA)

The US OTC clinical support programme consists of two studies in prevention of frequent heartburn for 24 hours[20]. A total of 3124 subjects were included in the intention-to-treat population of these studies.

These studies evaluated both the 10 mg and 20 mg strengths of omeprazole magnesium tablets, taken for 14 consecutive days against placebo. In each study, a significantly greater percentage of subjects in the omeprazole 20 mg group were heartburn free after the first dose compared to placebo (p<0.001), after the last dose (p<0.001), and over all 14 doses (p<0.001).

Figure 5: Mean percentage of days without heartburn across 14 days of therapy



The authors concluded that omeprazole magnesium is “effective in completely preventing heartburn for one full day after the first dose”. They report that the maximum effect was seen on Day 5 and the maximum level of effect was maintained through to Day 14.

In addition to these two efficacy studies, an actual use study was conducted in the United States[23]. This observational study was conducted on 758 consumers with frequent heartburn in an OTC setting.

This study found that three months after taking <u>one</u> 14-day treatment course, 43% of subjects had no recurrence of their frequent heartburn.

This programme provides support that short term use of omeprazole relief from the symptoms of frequent heartburn and also acts to prevent the recurrence of heartburn symptoms.

The study by Bardham et al[19] shows that omeprazole used for 14-days decreases the occurrence of symptoms/relapse. Omeprazole 20 mg was used for 14 days and patients with relief from symptoms after this period of time were deemed in remission. When symptoms re-occurred, omeprazole was available as intermittent therapy as a 14-day treatment. After the initial treatment period, 33% of patients had no relapse in the entire 12-month follow-up period and needed no intermittent therapy. Of those on intermittent therapy (67%), 26.8% had no further relapses while 20.1% had only one.

80% of patients were able to effectively manage their symptoms successfully with only three short-term treatments over 12 months.

The authors concluded that after treatment with omeprazole, relapses were infrequent and control was gained rapidly with an additional short course of treatment.

7. Justification of patient population and duration of treatment

7.1 Justification of patient population

Based on the patient population recommended for OTC use in the UK[21], consumers meeting the following criteria will be recommended to be referred to their GP.

- Those with the any of the following symptoms: trouble or pain swallowing; persistent vomiting or vomiting with blood; bloody or black stools; unintended weight loss; anaemia; abdominal pain or swelling; jaundice.
- People aged 40 years or older with heartburn and/or indigestion symptoms for the first time or your symptoms have recently changed.
- Those who have experienced heartburn for over 3 months.
- Those who also experience chest pain or shoulder pain with shortness of breath, sweating, pain spreading to arms, neck or shoulders, or light-headedness.
- Those who have previously had a stomach ulcer or undergone stomach surgery
- Those who have a family history of gastric cancer.
- Those who are pregnant or breast feeding (refer to GP or LMC).

The proposed training package will include instruction for the pharmacist to gain a clinical history based on the criteria above to identify alarm symptoms which may be indicative of more serious conditions and thus recommend that the patient see their GP.

Typically in older patients symptoms of heartburn may likely be associated with organic diseases such as peptic ulcers and cancer[24], hence those aged 40 and over whom present with heartburn and acid reflux for the first time or their symptoms have changed will be referred to their GP.

The Losec datasheet[25] advises that omeprazole is safe for use during pregnancy and breastfeeding. Despite no apparent safety concerns in this population subgroup, those who are pregnant or breast feeding will be recommended to see their GP or LMC so that their condition can be monitored.

7.2 Justification of dosage and duration of treatment

The dosage of 20 mg initially (2 x 10 mg capsules) followed by one 10 mg capsule daily on improvement of symptoms is that approved for OTC use in the UK[4, 26].

An initial starting dose of 20 mg is recommended due to the superior acid suppression demonstrated for this mg dose (refer Section 4). However to ensure the lowest effective dose is used, patients are recommended to reduce the dose to 10 mg daily once on symptom improvement. If symptoms return the dose is to be increased to 20 mg daily. This is consistent with the step-down, step-up approach recommended for treating GORD in the Management of Dyspepsia and Heartburn Guidelines[24].

The pack insert and pharmacist (as instructed in the proposed practice guideline) will advise the patient that relief will not instant and patients should take the capsules for 3-4 days to achieve maximum results. This is consistent with the pharmacology of omeprazole as discussed in Section 4 and results obtained in the US OTC Clinical Programme (Section 6.3).

Therefore patients will be advised to take the medication for at least 3-4 days or until symptoms resolve. If symptoms do not resolve after taking the full course of medication the package insert advises the patient to talk to their doctor or pharmacist.

8. Interactions with Other Medicines

No interaction of omeprazole with food or concomitantly administered antacids has been found.

The absorption of ketoconazole and itraconazole has been shown to decrease during omeprazole treatment, as it does during treatment with other acid secretion inhibitors or antacids.

As omeprazole is metabolised in the liver through cytochrome P450 2C19 (CYP2C19), it can prolong the elimination of diazepam, warfarin (R-warfarin) and phenytoin, which are all in part substrates for this enzyme. Concomitant treatment with omeprazole 20 mg daily did not change the blood concentration of phenytoin in patients on continuous treatment with this medicine[25]. Similarly concomitant treatment with omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin[25].

Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration. However, clarithromycin is safely used together with omeprazole for the eradication of *Helicobacter pylori.*

Results from a range of interaction studies with omeprazole versus other medicines indicate that omeprazole 20-40 mg daily has no influence on any other relevant isoforms of CYP, as shown by the lack of metabolic interaction with substrates for CYP1A2 (caffeine, phenacetin, theophylline), CYP2C9 (S-warfarin, piroxicam, diclofenac and naproxen), CYP2D6 (metoprolol, propranolol), CYP2E1 (ethanol), and CYP3A (cyclosporin, lidocaine, quinidine, estradiol, erythromycin, budesonide)[25].

Patients will be warned on the packaging and on the patient information leaflet to consult their doctor before using omeprazole OTC if they are concomitantly taking warfarin, anti-fungal or anti-yeast medications, phenytoin, diazepam or digoxin due to the potential for interactions. The pharmacist training package will also include information on potential interactions.

9. Contraindications

Known hypersensitivity to omeprazole.

Patients will be warned on product packaging and in the patient leaflet not to use omeprazole OTC if they are allergic to omeprazole or any other ingredient in the product.

10. Possible Resistance

Some patients do not respond to omeprazole however this is due to their GI symptoms not being related to acid, as similar symptoms can be caused by reflux of strong basic bile salts.

There is no data to suggest that resistance develops after or during the use of omeprazole.

11. Adverse Events

Medicines Classification Committee has previously agreed that omeprazole had a sufficiently favourable safety profile for it to qualify for OTC sale[1, 2].

Interstitial nephritis was raised as a potential concern at the 35th MCC meeting[3]. The committee acknowledged that the risk was extremely low for short term use, however they agreed that a warning should be included in the consumer information.

The proposed pack insert (refer Appendix 1), includes the following statement.

> Contact your pharmacist or doctor immediately if you notice any for the following:
> - you experience symptoms such as fever, nausea, general feeling of un-wellness, tiredness, blood in urine, weight loss

As noted in the Medsafe Prescriber Update Article No. 20:11-13 regarding omeprazole-induced interstitial nephritis[27], the presenting features described for this disorder (fever, rash and eosinophilia) are not always seen. The article notes that analysis of published reports demonstrated that patients with interstitial nephritis involving omeprazole commonly presented with malaise, fever, nausea, lethargy and weight loss which were consistent with symptoms in the cases reported to CARM. Hence the warning included in the pack insert describes typical symptoms as well as those recorded in case reports. The proposed Pharmacist Training Pack for omeprazole OTC will include information regarding interstitial nephritis and advise that traditional symptoms for interstitial nephritis are not always seen and to and refer the patients to their GP for further investigation if any of the above symptoms appear as well as ceasing treatment with omeprazole.

12. Potential for Abuse or Misuse

Omeprazole is not a controlled-drug (psychotropic or narcotic) so no addiction or illegal use is anticipated. There is no evidence for omeprazole abuse and no evidence for omeprazole to potentiate the effects of ethanol or drugs of abuse.

Single oral doses of omeprazole up to 560 mg have not resulted in any serious symptoms. Experience with doses up to 2,400 mg shows possible symptoms of overdose to mainly be nausea, vomiting, dizziness, abdominal pain, diarrhoea and headache. The risk from overdose is negligible with the proposed omeprazole OTC pack as the total dose contained in the proposed 14-capsule bottle is restricted to 140 mg.

AstraZeneca

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2 Minutes from the 28th Meeting of the Medicines Classification Committee Meeting

3 Minutes from the 35th Meeting of the Medicines Classification Committee Meeting

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