AstraZeneca

Submission for

Reclassification from

Prescription Medicine

to

Pharmacy Only Medicine

LOSEC (omeprazole) MUPS 20 mg

AstraZeneca Limited

PO Box 1301

Auckland

25 January 2006

AstraZeneca

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PART A

1. International Non-proprietary Name of the Medicine

Omeprazole magnesium

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
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Contact: Jennifer Gill

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

Dose form: Tablet.

The tablet form of Losec has been chosen for OTC status as a tablet is more resistant to tampering than a capsule, and therefore more suitable for OTC marketing.

Medsafe has accepted Losec MUPS tablets as being bioequivalent and therapeutically equivalent to Losec capsules[1].

Strength: 20 mg.

5. Pack Size and Other Qualifications

Pack Size: 14 or 28 tablets. The 28-tablet pack will consist of 2 x 14 day therapy packs to aid customer convenience.

Description of Pack: Two or four tamper evident blister strips of 7 tablets inside a carton fully labelled with appropriate information and warning statements. Patients will be advised not to use if blister seal is broken.

6. Indications for which Change is Sought

Proposed OTC indication: Short term treatment and prevention of symptoms of frequent acid heartburn (two or more episodes per week) in adults 18 years and older.

This is encompassed within the currently approved indication for Losec MUPS 20 mg for symptoms of acid related dyspepsia: For the 24-hour relief, and prevention of symptoms in patients with epigastric pain/discomfort with or without heartburn and indigestion[2].

7. Present Classification of Medicine

Prescription Only Medicine

8. Classification Sought

Pharmacy 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. The approved dosage in the UK uses 20 mg daily initially until relief of symptoms is achieved.

The switch to OTC status in the UK was supported by the Royal Pharmaceutical Society[3].

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.

Rest of World:

Prescription Medicine.

Pantoprazole

Australia

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.

[The pantoprazole amendment comes into effect on 1 March 2006]

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 2005, 2.643 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 136 million courses of treatment have been sold (each course of treatment is a 14-day regimen of 1 tablet per day).

11. Proposed Labelling and Patient Information Leaflet

To be provided.

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 of 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);
  - 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.

<u>While using omeprazole OTC:</u>

Consult your healthcare professional if:

- Your heartburn continues or worsens;
- You have not experienced any relief from your symptoms after 14 days of treatment;

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

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

Not applicable.

PART B

1. Executive Summary

With consideration of the feedback received from previous submissions, AstraZeneca proposes the following indications for an omeprazole 20 mg OTC pack:

- Short term treatment and prevention of symptoms of frequent acid heartburn (two or more episodes per week) in adults 18 years and older.

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

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

Results of clinical studies show:

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

- Total relief of symptoms occurred in 50% of omeprazole 20 mg-treated patients compared to only 36% of those patients on placebo/antacids.

- Significantly more subjects treated with omeprazole 20 mg had symptom resolution at 14 days compared with ranitidine 150 mg bid.

- Three months after taking one 14-day treatment course of omeprazole 20 mg, 43% of subjects had no recurrence of their frequent heartburn.

- With only three 14-day treatment periods of omeprazole 20 mg per 12 months, 80% of patients were able to effectively manage their heartburn symptoms and were treated successfully.

2. 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[4]:

- 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[5].
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.

2.1 Proposed Indications and Dosage

With consideration of the feedback from the reviews of previous submissions, AstraZeneca propose the following indications and dosage for an omeprazole 20mg OTC pack:

The revised indications, dosage recommendation and pack sizes for omeprazole OTC 20 mg as Pharmacy Only Medicine are as follows:

- Short term treatment and prevention of symptoms of frequent acid heartburn (two or more episodes per week) in adults 18 years and older.

- Not intended for immediate relief of heartburn. This medicine may take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours.

- Pack size will be limited to 14 or 28 tablets. A 28-tablet pack will be provided consisting of 2 x 14-day therapy packs for customer convenience.

- Dose Directions:
  Initial 14-day course of treatment:
  - Swallow 1 tablet with a glass of water before eating in the morning
  - Take every day for 14 consecutive days
  - Do not take more than 1 tablet per day
  - Do not crush or chew the tablets
  - Do not use for more than 14 consecutive days unless directed by your doctor.

  Repeated 14-day course:
  - Do not take for more than 14 days unless directed by your doctor.

3. Problem Statement

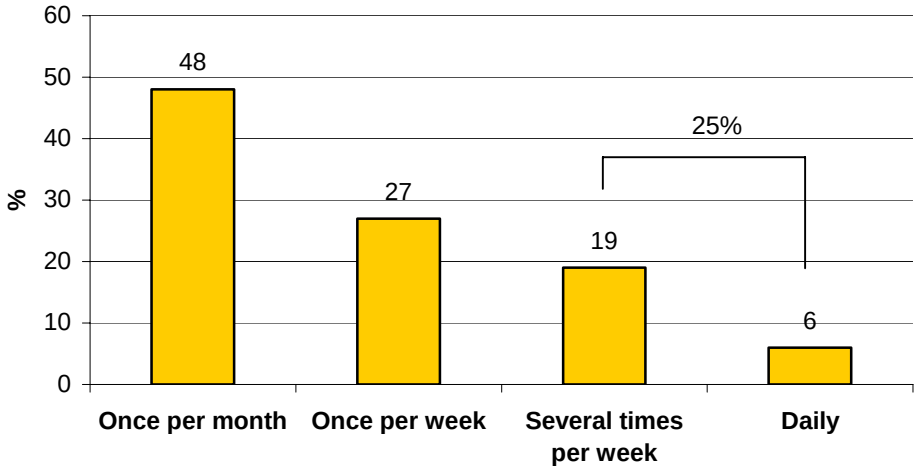
3.1 The Frequent Heartburn Population

The prevalence and severity of gastrointestinal symptoms such as dyspepsia and reflux were recently published in the New Zealand Medical Journal[6]. 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%[7].

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[8].

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



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[9], and 2 or more days a week in up to 45% of heartburn sufferers[10]. 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[11]. This research sampled 259 adults aged between 18 and 55+ years who suffered from heartburn at least once a week and seeked 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

70% 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 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[12]. 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 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[13]. 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.

Some antacids/alginates can be used during pregnancy. The 2005 Healthcare Handbook indicate that Gaviscon and Mylanta Heartburn Relief can be used during pregnancy[14].

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[15].

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[16]. The onset of relief with ranitidine was achieved within 30-45 minutes and lasted for up to 12 hours.

The use of H_2-antagonists during pregnancy is advised only when essential and only under the advice of a physician. Breast-feeding mothers should not take H_2- antagonists or should discontinue breast-feeding[17,18].

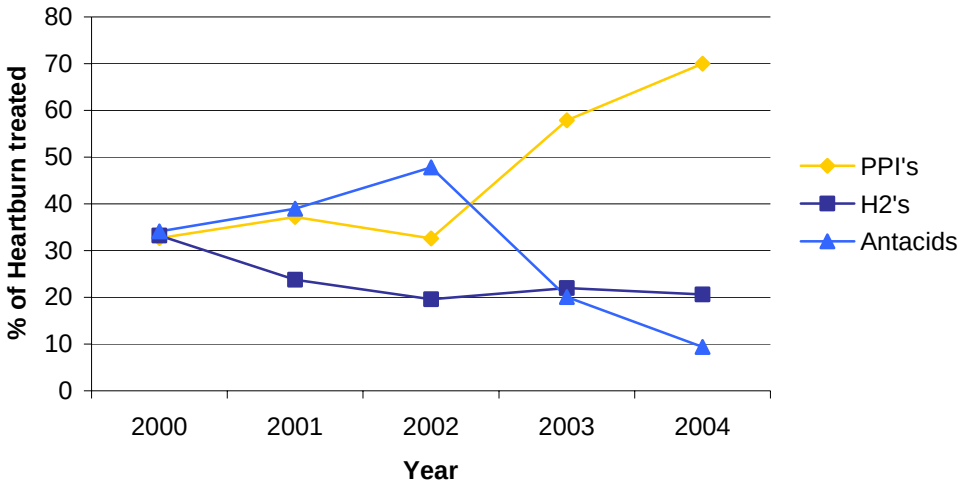
Community surveys were undertaken in the US before and after the H_2- antagonist OTC switch[19]. Around 55% of people surveyed who took OTC medication chronically used H_2-antagonists. The authors stated that expectations for the effectiveness of H_2- antagonists do not seem to have been met and as a 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[20].

Figure 2 shows an increase in the number of patients prescribed a Proton Pump Inhibitor in response to a diagnosis of heartburn over the last 5 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 2004, almost 70% of patients with heartburn were prescribed a PPI for symptom control. Eighty-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

4.1 Pharmacology of Omeprazole

The pharmacology of omeprazole makes it ideal for the short-term treatment and prevention of frequent acid 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.

4.2 Comparison of Omeprazole with Current OTC Treatments

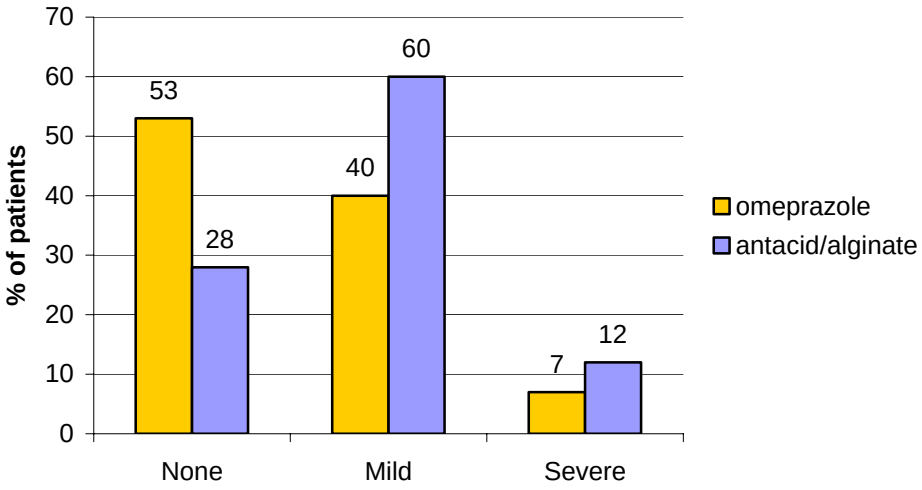
Omeprazole versus antacids/alginates

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 14 days therapy[21].

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 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[22].

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.

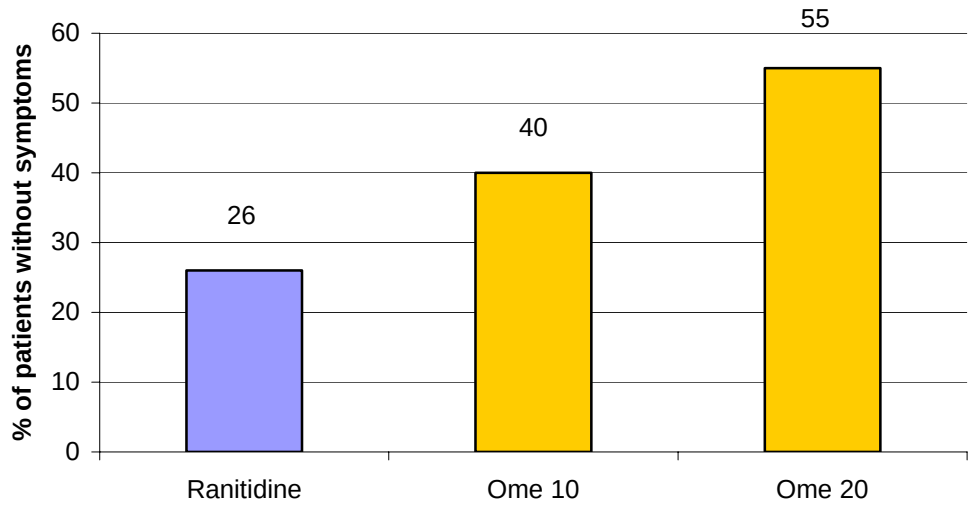
This result was statistically significant (p=0.009). Omeprazole was shown to be significantly more effective in the relief of those symptoms particular to heartburn (p<0.001).

Although the data above indicates that the 10 mg strength of omeprazole provides useful symptom control after 14 day therapy, the data below strengthens the use of omeprazole 20 mg for OTC 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 signifacntly influencing the adverse events reported [23, 24].

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[23]. 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.

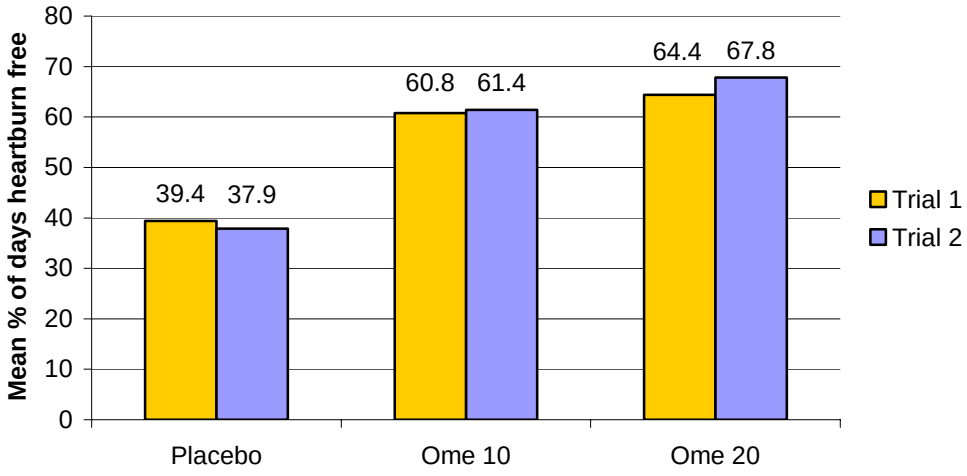
A second study comparing omeprazole versus cimetidine in 427 patients with non-investigated dyspepsia showed similar results[22]. Patients in Arm A were randomised to receive either omeprazole 20 mg in the morning or cimetidine 400 mg twice daily for 14 days. On day 15, 50% of omeprazole-treated patients 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.

4.3 Omeprazole OTC Clinical Programme

The OTC clinical support programme consists of two studies in prevention of frequent heartburn for 24 hours[24]. 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[25]. 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 omeprazole 20 mg taken once daily for 14 days provides 24-hour control from the symptoms of frequent heartburn and also acts to prevent the recurrence of heartburn symptoms.

The study by Bardham et al shows that omeprazole used for 14-days decreases the occurrence of symptoms/relapse[23]. 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.

Therefore, 80% of patients were able to effectively manage their symptoms and were treated successfully with only three 14-day treatment periods per 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.

4.4 <u>Benefits for Consumers with Omeprazole OTC</u>

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[26].

The availability of an OTC pack of omeprazole will enable heartburn sufferers to:

- access to a more effective therapy without a visit to their General Practitioner
- treat their heartburn more effectively and potentially inhibit the recurrence of symptoms

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 a 14-day therapy[22,23]. In addition, the OTC clinical trial programme for omeprazole and the study by Bardhan et al has shown that a 14-day course 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[23,24].

It is commonly recommended that dyspepsia or heartburn during pregnancy should be treated first with dietary and life-style changes, together with antacids[27]. Therapy with H2-antagonists is not recommended. A meta-analysis of available trials of Proton Pump Inhibitors used during pregnancy showed that these medications, especially omeprazole, were reasonable therapeutic options for treatment of heartburn and dyspepsia in pregnancy[27]. Not one of the five cohort studies analysed found a significant association between exposure during the first trimester and risk of major malformation. In addition, the New Zealand datasheet for Losec contains the following information[2]:

> *Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. LOSEC can be used during pregnancy.*
>
> *Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.*

Although the warning information for an omeprazole OTC product will contain the advice to seek advice from a healthcare professional before using the product if the patient is pregnant or breast feeding, patients can be satisfied that there are no apparent safety concerns if this product is used during pregnancy. In addition, if there is inadvertent use of omeprazole OTC by a pregnant or breast-feeding consumer, data indicates that omeprazole would have no adverse effects on the pregnancy or on the health of the foetus/newborn child.

5. Ease of Self-Diagnosis or Diagnosis by Pharmacist

Patients who suffer from frequent heartburn are likely to have extensive experience self-medicating with either antacids or H_2-antagonists and are likely to be cognisant of their individual signs and symptoms experienced when suffering from a episode of heartburn.

In addition, pharmacy staff are familiar with providing advice and medications for the relief heartburn.

With the introduction of OTC H_2-receptor antagonists, pharmacists were educated on when to refer a heartburn patient to their doctor. In the case of an omeprazole OTC product, the same referral criteria will apply and hence the same expertise is expected to be applied.

6. Local Data or Special Considerations for New Zealand

Not applicable.

7. 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[2]. Similarly concomitant treatment with omeprazole 20 mg daily did not change coagulation time in patients on continuous treatment with warfarin[2].

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)[2].

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, diazepam or digoxin due to the potential for interactions.

8. 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 of the product.

9. 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.

10. Adverse Events

As stated in the Introduction to Part B, the Medicines Classification Committee has previously agreed that omeprazole had a sufficiently favourable safety profile for it to qualify for OTC sale[4,5].

However, AstraZeneca would like to provide further evidence of this favourable safety profile in the form of Periodic Safety Update Reports from the OTC use of omeprazole in the United States[28-34]. The safety data submitted previously was from both prescription and OTC use of omeprazole. These PSUR's confirm the safety profile of omeprazole sold OTC as a 14-day course of treatment for frequent heartburn.

Since its introduction in June 2003 up to September 2005 (the date for the latest of the enclosed Prilosec PSURs), 137 million treatment courses of Prilosec OTC have been sold in the US. In this same time frame, approximately 4,200 case reports (including a total of 59 serious adverse event reports) met the criteria for inclusion in the safety update report. Only 0.7 % of these consumer reports were medically confirmed. (Among the Serious events 25 % were medically confirmed). Most of the reported serious and unlisted events reflect terms that could be symptoms of different types of allergic reactions, which are listed in the datasheet for omeprazole.

When reading the Prilosec OTC PSURs it should be noted that some events are included in more than one PSUR (if follow-up) and thus counted twice. It should also be noted that "medication error" and "intentional misuse" have definitions that differ from those normally used. The number of "medication errors" may seem high, but they could for example consist of "dosing taken at a time other than the morning".

The PSURs confirm the safety profile of omeprazole sold OTC as a 14-day course of treatment for frequent heartburn and AstraZeneca's conclusion is that there are no findings from the experience with OTC use of omeprazole in the United States, that alter the established favourable overall safety profile of omeprazole.

11. 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 an OTC omeprazole pack as the total dose contained in the proposed 14-day pack is restricted to 280 mg.

AstraZeneca's conclusion from the review of the US PSURs for Prilosec OTC[28-34] is that these data do not indicate any potential for drug abuse.

An Actual Use Study was completed in the US before registration of their OTC omeprazole product[25]. The study evaluated the percentages of correct self-selection and occurrences of misuse. Overall, 81% of patients correctly self-selected that the omeprazole OTC product was appropriate for their symptoms by reading the product packaging including the pack insert. Where dosage instructions were not followed, 85% of those patients contacted a healthcare professional for their symptoms before, during or soon after the trial. The authors conclude, "actual use data support that consumers accurately differentiate between frequent and occasional heartburn, appropriately self-select whether the drug is appropriate for use, comply with a 14-day dosing regimen in the OTC setting, and appropriately seek physician involvement for longer-term management of frequent heartburn".

In the minutes from the 28th Meeting of the Medicines Classification Committee, the Committee report they have concerns regarding the potential of omeprazole to mask underlying pathology, particularly with repeat courses[5]. The proposed label for an omeprazole OTC product is for a treatment duration of no more than 14 days. Those with symptoms not relieved by the 14-day treatment regimen are advised to see their doctor.

The overall risk-to-benefit to the community of OTC availability of omeprazole is regarded as favourable. The reclassification does not raise any new safety concerns and there is no need for further investigation of activity or side effects.

AstraZeneca

REFERENCES

1. Medsafe correspondence. Losec MUPS and capsules bioequivalence. 31 January 2002
2. New Zealand Approved Datasheet for Losec Capsules and Losec MUPS
3. Response to ARM7 from the Royal Pharmaceutical Society *[not available]*
4. Minutes from the 26th Meeting of the Medicines Classification Committee Meeting
5. Minutes from the 28th Meeting of the Medicine Classification Committee Meeting
6. Haque M et al. Prevalence, severity and associated features of gastro-oesophageal reflux and dyspepsia; a population based study. NZ Med J 2000; 113: 178-81 *[abstract only]*
7. Jones RH. Dyspepsia in England and Scotland. Gut 1990; 31: 401-405
8. Dent J et al. An evidence-based appraisal of reflux disease management – the Genval Workshop Report. Gut 1999; 44 (Suppl 2): S1-S13
9. Oliveria SM et al. Heartburn risk factors, knowledge, and prevention strategies: a population-based survey of individuals with heartburn. Arch Int Med 1999; 159: 1592-1598
10. Nebel OT et al. Symptomatic gastroesophageal reflux: incidence and precipitating factors. Dig Dis 1976; 21 (11): 953-956 *[abstract only]*
11. TNS Research. Point in Time Research for Losec. May 2005. *Data on file*.
12. ACNeilsen/SmithKlineBeecham Survey. Profile of consumers in need: people with sour stomachs, by demographics. Prog Groc 1995; 74 (9):98-99 *[not available]*
13. Fung MC et al. Elderly over the counter drug users at risk. Arch Fam Med 1995; 4: 718-23 *[abstract only'*
14. Pharmacy Today. 2005 Healthcare Handbook.
15. Centre for Adverse Reactions Monitoring. IMMP Summary, Cimetidine, November 1977 to August 1981. *Data on file*.
16. Application to schedule Zantac 75 mg as a Pharmacy Medicine. Released under the Official Information Act 1981. *Data on file*.

17. Zantac Datasheet. Medsafe Website

18. Pepcid AC Datasheet. Medsafe Website

19. Shaw MJ et al. Self-reported effectiveness and physician consultation rate in users of over-the-counter histamine-2 receptor antagonists. Am J Gastroenterol 2001; 96: 673-76

20. IMS Medical Index, December 2002 – December 2003

21. Goves J et al. First line treatment with omeprazole provides an effective and superior alternative strategy in the management of dyspepsia compared to antacid/alginate liquid: a multicentre study in general practice. Alimet Pharmaol Ther 1998; 12: 147-57

22. Meineche-Schmidt V et al. Antisecretory therapy in 1017 patients with ulcerlike or refluxlike dyspepsia in general practice. Euro J Gen Pract 1997; 3: 125-30 *[not available]*

23. Bardhan KD et al. Symptomatic gastro-oesophageal reflux disease: double-blind controlled study of intermittent treatment with omeprazole or ranitidine. Brit Med J 1999; 318: 502-7

24. Allgood LD et al. Comparison of Prilosec OTC (omeprazole magnesium 20.6 mg) to placebo for 14 days in the treatment of frequent heartburn. J Clin Pharm Ther 2005; 30 (2): 105-12

25. Fendrick AM et al. Self-Selection and Use Patterns of Over-the-Counter Omeprazole for Frequent Heartburn. Clin Gastroenterol Hepatol 2004; 2 (1): 17-21

26. Bytzer P. Goals of therapy and guidelines for treatment success in symptomatic gastroesophageal reflux disease patients. Am J Gastroenterol 2003; 98 Suppl: S31-S39

27. Nikfar S et al. Use of proton pump inhibitors during pregnancy and rates of major malformations – a meta-analysis. Dig Dis Sci 2002; 47 (7): 1526-29

28. Periodic Safety Update Report for Prilosec OTC (omeprazole magnesium delayed-release tablets), quarterly report. 20 June 2003 – 20 September 2003

29. Periodic Safety Update Report for Prilosec OTC (omeprazole magnesium delayed-release tablets), quarterly report. 21 September 2003 – 20 December 2003

30. Periodic Safety Update Report for Prilosec OTC (omeprazole magnesium delayed-release tablets), quarterly report. 21 December 2003 – 20 March 2004

31. Periodic Safety Update Report for Prilosec OTC (omeprazole magnesium delayed-release tablets), quarterly report. 21 March 2004 – 20 June 2004

32. Periodic Safety Update Report for Prilosec OTC (omeprazole magnesium delayed-release tablets), quarterly report. 21 June 2004 – 20 September 2004

33. Periodic Safety Update Report for Prilosec OTC (omeprazole magnesium delayed-release tablets), Semi-annual Report. 21 September 2004 – 20 March 2005

34. Periodic Safety Update Report for Prilosec OTC (omeprazole magnesium delayed-release tablets), Semi-annual Report. 21 March 2005 – 20 September 2005