AstraZeneca

Submission for Reclassification

Losec (omeprazole)

AstraZeneca Limited
PO Box 1301
Auckland

July 25, 2001

Contents

PART A

1. International Non-proprietary Name of the Medicine

Omeprazole

2. Proprietary Name(s)

Losec

3. Company Requesting Reclassification

AstraZeneca Limited
PO Box 1301
Auckland
NEW ZEALAND

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

Dose form: solid form for oral administration

Strength: 10 mg.

5. Pack Size and Other Qualifications

Blister packs of 14, packaged into a carton with an accompanying patient information leaflet.

6. Indications for which Change is Sought

Symptomatic relief and short-term prevention of the recurrence of heartburn and indigestion.

7. Present Classification of Medicine

Prescription Only Medicine

8. Classification Sought

Pharmacy Only Medicine

9. Classification Status in Other Countries

Sweden: OTC (10 mg). 20 mg is also reclassified OTC in Sweden, but not commercially available.

Rest of the world: Prescription.

With the exception of Sweden, AstraZeneca's international business strategy does not include a switch to Losec OTC, but rather a focus on innovative prescription medicines, in particular esomeprazole.

10. Extent of Usage in NZ and Elsewhere

As of May 2001, a total of 15,456 million Losec tablets/capsules have been sold worldwide. This represents total international experience with Losec at 12, 880 treatment-days. Since its OTC launch in Sweden in April 2000, 3.6 million tablets of Losec MUPS 10mg have been sold equating to 3.0 million treatment-days (treatment-days have been calculated using an average daily dose of 1.2 as per New Zealand HBL data). Losec has been available in New Zealand as a Prescription Medicine since December 1990. Since that time sales have equated to a total of over 85 million treatment-days, with Losec 10mg use since 1998 representing 3.5 million treatment days. During this period, Losec has only been available in capsule form in New Zealand. However, the tablet formulation, known as MUPS, has been approved in New Zealand since February 2001, and is bioequivalent with Losec capsules. Losec MUPS is approved in 48 countries world-wide.

11. Proposed Labelling and CMI

See Appendix 1 (Commercially sensitive).

12. Proposed Warning Statements

Patients will be advised not to use Losec under the following circumstances:

- If you are allergic to omeprazole or any of the ingredients of Losec listed under 'product description' in this leaflet.
- Do not use Losec for any purpose other than that specified on the pack unless under the supervision of a doctor.

Patients will be advised to seek advice from their doctor or pharmacist before taking Losec if they:

- have symptoms including: unintended weight loss associated with indigestion, difficulty swallowing, recurrent vomiting, vomiting of blood or passage of stools stained with blood, persistent stomach pain, or

- have been told you have an ulcer, or
- have kidney or liver problems, or
- are over 40 years old and have indigestion symptoms for the first time or have symptoms that have recently changed, or
- are pregnant or plan to become pregnant, or
- are breast feeding, or
- have any allergies to any medicines, foods, dyes or preservatives, or
- have any other medical condition, or
- are taking any other medicine

While taking Losec patients will be advised to seek advice if

- their symptoms get worse or are no better after taking the medicine for 14 days.
- they require more tablets after finishing their pack of Losec.

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

Not applicable.

PART B

Introduction

This application seeks approval to change the current legal classification of Losec MUPS 10mg from Prescription Medicine to Pharmacy-Only Medicine for the indications of symptomatic relief and prevention of heartburn and indigestion.

The proposed indications, dosage recommendation and pack sizes for Losec 10mg as a Pharmacy-Only Medicine are as follows:

- Symptomatic relief and short-term prevention of the recurrence of heartburn and indigestion
- One to two units to be taken once a day for no more than fourteen days
- Pack size will be limited to 14 units

Losec 10mg contains the proton pump inhibitor omeprazole 10mg.

Losec 10mg was approved for non-prescription use in Sweden in December 1999 for the temporary relief of heartburn and reflux oesophagitis. The recommended dose for both indications is one to two tablets per day when needed for a maximum of 14 days [1].

Proton pump inhibitors, since their initial introduction, have been one of the most widely prescribed medicines world-wide. This widespread usage reflects the efficacy of these agents across the range of gastric acid-related diseases, as well as their excellent safety profile.

In the last few years, proton pump inhibitors have been used increasingly for the treatment of acid-related dyspepsia. Many clinical studies have now established that lower doses are effective in providing good relief from the symptoms of acid reflux and heartburn.

Losec 10mg is approved for use in acid-related dyspepsia, in a total of 22 countries world-wide (including Australia and the United Kingdom), and is approved for use in symptomatic reflux, in a total of 58 countries world-wide. The precise wording of the indications varies from country to country depending on local custom and practice. Information on the current marketing status is provided by country in Appendix 2 of this application.

As of May 2001, a total of 15,456 million Losec tablets/capsules have been sold world-wide. This represents total international experience with Losec at 12, 880 treatment-days. Since its OTC launch in Sweden in April 2000, 3.6 million tablets of Losec MUPS 10mg have been sold equating to 3.0 million treatment-days (treatment-days have been calculated using an average daily dose of 1.2 as per New Zealand HBL data). Losec has been available in New Zealand as a Prescription Medicine since December 1990. Since that time sales have equated to a total of over 85 million treatment-days, with Losec 10mg use since 1998 representing 3.5 million treatment days. During this period, Losec has only been available in capsule form in New Zealand. However, the tablet formulation, known as MUPS, has been approved in New Zealand since February 2001, and is bioequivalent with Losec capsules. Losec MUPS is approved in 48 countries world-wide.

This application evaluates the available data, which demonstrate that Losec 10mg is an appropriate product to be available as a Pharmacy-Only Medicine with the proposed indications, dosing schedule, contra-indication, warnings and precautions based on:

- very extensive experience with other products for self medication in the symptomatic relief of heartburn and related symptomatology
- safety data collected from 11 years of prescription use of Losec, including 6 years monitoring in New Zealand on the IMMP pharmaco-vigilance program

In several instances reference is made to the Genval Guidelines [2], which are evidence-based consensus guidelines for the management of reflux. These international guidelines are not only relevant in their own right, but are notable because of the co-authorship of three eminent New Zealand gastroenterologists (Dr Ian Wallace, Auckland; Dr Mark Lane, Auckland; and, Professor Gil Barbezat, Dunedin).

Trans-Tasman Harmonisation (TTH) and International Classification

The Medicines Classification Committee's minutes of May 2000 note the desire to retain harmonisation of classifications within Australian and New Zealand with respect to H2-antagonists. While the New Zealand Government is committed to achieving TTH it is not a legal requirement at this stage. In any case, the proposed form of TTH would provide for each individual authority to opt out of a recommendation adopted by the other, in other words autonomy could be retained. To the best of AstraZeneca's knowledge there are no plans for a supplier proposal for Losec 10mg to be reclassified in Australia. With the exception of Sweden, AstraZeneca's international business strategy does not include a switch to Losec OTC, but rather a focus on innovative prescription medicines, in particular esomeprazole.

Losec MUPS 10mg has been reclassified as non-prescription in Sweden since April 2000 [1].

The only other regulatory agency to which an application has been lodged is the US FDA [3]. It is important to note that in the case of the US, Procter and Gamble rather than AstraZeneca has made the application for reclassification under license from AstraZeneca, on the basis of their own limited trial data.

In a majority decision the FDA panel voted to effectively defer a decision noting both efficacy and safety questions. While the FDA panel noted that omeprazole could effectively offer 24 hour prevention of heartburn, it did not seem to relieve the symptoms of heartburn from the data submitted by Procter and Gamble. The present application to Medsafe is able to provide a wealth of additional trial data addressing Losec's efficacy in relieving heartburn.

The FDA panel noted a concern regarding the increased potential for acute liver toxicity with OTC use and a potential risk in pregnancy. This submission to Medsafe is able to address both of these potential safety concerns.

An epidemiological review of hepato-toxicity for some commonly administered agents, including omeprazole has been reported [4]. Eight retrospective cohort studies in the United Kingdom considered the incidence of drug-induced acute liver injury. Of 23,175 patients using omeprazole between the years 1990-1993, only one patient developed acute liver injury, which was diagnosed as hepatocellular disease. The patient had been receiving Losec for 359 days. This corresponds to a rate of liver injury per 100,000 patients for Losec

of 4.3. The same epidemiological study found a rate of liver injury per 100,000 patients for ranitidine and cimetidine of 8.9 and 22.7 respectively. Thus, the incidence of non-fatal acute liver injury for Losec is very low and comparable to that found with ranitidine.

Further, the Swedish expert evaluation of OTC Losec concludes, “Doses of 10-20 mg daily are safe in patients with impaired hepatic function.”

Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/new-born child [5, 6, 7]. These studies suggest that rates of malformations in those treated with omeprazole during the first trimester are similar to those untreated. In addition, these studies do not suggest higher rates of miscarriage, foetal death, or growth disturbance in those exposed to omeprazole in pregnancy. The rates of miscarriage and congenital malformation reported in these three studies are similar to the population norm.

The study by Ruigomez et al, which examined data from 2,236 pregnancies, demonstrated that the relative risk of non-genetic malformation associated with cimetidine, omeprazole and ranitidine was 1.2, 0.9 and 1.4 respectively compared to non-exposed individuals [5].

The Losec datasheet has recently been approved in New Zealand to state that Losec can be used during pregnancy. Nevertheless, the proposed labelling of the Pharmacy-Only pack will advise consumers to consult with their doctor or pharmacist if pregnant or breast-feeding, in line with labelling for the Zantac Relief 150mg pack.

Problem Statement

Heartburn and other symptoms of indigestion related to gastric hyperacidity are extremely common in the general population.

Heartburn and acid regurgitation are classic symptoms of gastro-oesophageal reflux, which is the result of one or more physiological factors affecting the competence of the gastro-oesophageal junction [8]. Reflux of the acidic gastric contents into the lower oesophagus produces the classic symptoms of heartburn and acid indigestion. Other symptoms such as epigastric pain are also common.

The occurrence of heartburn is related to the magnitude of the pH decrease and heartburn only occurs when the reflux is associated with oesophageal pH below 3.

The vast majority of the reflux population is unseen. These people are virtually invisible to the medical profession, since they manage their symptoms through conservative measures, with little or no physician intervention. Those who experience chronic stable intermittent antacid-responsive symptoms, are considered to have mildly symptomatic gastro-oesophageal reflux and are well used to managing the condition themselves.

The prevalence, severity and associated features of both reflux and dyspepsia in the general population in New Zealand have been recently published in the New Zealand Medical Journal [9]. The combined overall prevalence of 'significant' symptoms of dyspepsia and reflux was 45%. While this prevalence appears high it is in line with other studies from Europe and North America. A survey in Great Britain found dyspepsia prevalence of 40% [10]. The most commonly reported symptom in the New Zealand study was heartburn being reported in 70% of those with reflux or dyspepsia. However, there was a considerable overlap of symptoms. This is in agreement with the Genval Consensus Guidelines, which support heartburn as the most common symptom of reflux in at least 75% of subjects [2].

The frequency of 'significant' symptoms in the New Zealand survey [9] varied as follows:

- 48% once per month
- 27% once per week
- 19% several times per week
- 6% daily

The majority of subjects reported intermittent symptoms, with 75% of symptoms occurring with a frequency not more than weekly.

Self-care featured prominently amongst the New Zealand subjects with 69% of those with reflux-type symptoms using over-the-counter medications such as antacids [9].

Current Available Therapy

Currently available therapies for self medication in the majority of countries consist of antacids, alginates and low dose H2-antagonists.

Antacids-Alginates

Antacids are the most widely used products and act by neutralising the acid contents of the stomach.

The evidential base for symptomatic improvement obtained by antacids is neither impressive nor extensive. However, the widespread use of antacids attests to a degree of consumer satisfaction with the response obtained. Nevertheless, there would appear to be room for improvement.

Although antacids are generally well tolerated, they do have the potential to cause side effects in susceptible patients [11]. Antacids containing aluminium salts are constipating, whereas magnesium-containing antacids can cause diarrhoea. Many products contain a combination of the aluminium and magnesium salts to balance these two effects, but many individuals do experience some effect on gastrointestinal motility with combination antacids. Aluminium salts also bind phosphate, so chronic use can occasionally lead to hypophosphataemia [12].

Antacids containing sodium bicarbonate deliver significant amounts of sodium, which can be a problem for individuals with cardiovascular disorders who need to restrict sodium intake. Calcium-containing antacids can cause increased gastric acid secretion, and lead to acid rebound. All antacids may cause problems for individuals with severe renal impairment [13].

Another consideration with the use of antacids is their potential for interfering with, or altering the absorption of, concomitantly administered oral medications [14]. For example, tetracycline absorption is reduced by concomitant antacid administration, probably because the antacids chelate tetracycline.

Thus, antacids do have the potential for adverse effects. Despite this 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 is short, typically requiring dosing four times daily or more. In the case of rafting agents, efficacy is also compromised when the subject is not upright.

Since antacids are recommended to be used "as required" this can represent a significant inconvenience. Consumers are required to always have a pack on hand particularly at meal times. During the course of a normal day's activities, including work, there will be particular limitations regarding access and convenience with *prn* use. There is a potential benefit from a product, which provides once daily dosing with 24 hour relief, such as Losec 10mg.

The two pivotal trials [15, 16] of Losec 10mg versus antacid-alginate in dyspepsia patients with symptoms of epigastric pain and/or heartburn have demonstrated a significant superiority for both the complete resolution and relief of symptoms at 2 weeks and 4 weeks therapy. Losec 10mg at both end-points and time-points provided at least twice the efficacy of Gaviscon 10ml *qid* with improved patient convenience.

H2-Antagonists

The majority of countries, including New Zealand, have recently approved the non-prescription sale of low dose H2-antagonists, such as Zantac Relief 150mg. While studies with low dose H2-antagonists have tended to demonstrate a modest improvement in symptom resolution compared with antacids, there would still appear to be significant room for improvement.

The ranitidine datasheet documents a range of adverse events similar to that recorded for omeprazole. Transient and reversible changes in LFTs can occur and there have been occasional reports of hepatitis although these were generally reversible. Rare adverse events include:

- acute pancreatitis
- agranulocytosis

- hypersensitivity reactions (urticaria, angiodema)
- arthralgia and myalgia
- mental confusion, predominantly in the elderly

A small proportion of patients has also reported headache (sometimes severe) and sometimes dizziness.

Cimetidine was monitored on the IMMP program in 10, 526 patients from 1977-1981 in New Zealand (Appendix 3). IMMP reported a similar range of serious adverse reactions for cimetidine as those reported with Losec. Cimetidine had a reaction rate of 12.4 per 1,000. There were 3 reports of liver toxicity (0.3 per 1,000), 4 reports of amnesia/confusion (0.4 per 1,000), 1 report of myalgia (0.1 per 1,000) and 3 reports acute renal failure (0.3 per 1,000). The updated report to March 2001 included additional serious adverse events, notably, interstitial nephritis, hepatocellular damage and angiodema.

It should be remembered that today IMMP reports reaction rates from PFU regions only, where there is intensive follow-up of reporting. However, when cimetidine was monitored there were no PFU regions and reporting in general was less rigorously followed-up. Thus, the reaction rates for cimetidine are less robust than those reported for Losec and probably underestimate the true rates. However, they are indicative of the type and relative incidence of reactions. The Losec reaction rates reported from non-PFU regions in IMMP for rare serious adverse events are significantly lower than that for PFU regions. For example, reactions rates per 1,000 for PFU compared with non-PFU regions are: acute renal failure (0.6 versus 0.3), abnormal LFTs (0.6 versus 0.3), arthralgia (0.8 versus 0.1) and polymyositis (0.3 versus 0.0).

Clinical studies with ranitidine 75mg for the treatment of heartburn demonstrated a success rate of 48.5% compared with 35.8% for placebo [17]. This corresponds to a placebo-corrected success rate of 12.7%, which failed to reach statistical significance by day 4.

These results can be compared with those reported by Lind who demonstrated a 13% placebo-corrected success rate for Losec 10mg which was highly statistically significant [18]. Talley similarly reported a placebo-corrected success rate for Losec 10mg of 8% for patients with epigastric pain and 22% for those with reflux-like symptoms [19].

Furthermore, Bardhan demonstrated heartburn resolution in 40% of subjects for Losec 10mg compared with 26% for ranitidine 150mg *bid* [20]. This corresponds to an incremental benefit of 14% for Losec 10mg over and above ranitidine 150mg *bid*.

Initial success rate has been shown to highly correlate with time in remission [20]. Thus, treatment with Losec 10mg has been shown to afford around twice the time to relapse compared with ranitidine 150mg *bid*.

Losec 10mg therefore allows a greater proportion of patients to remain symptom free for longer compared with ranitidine at maximum doses.

Losec has a further important advantage of sustained 24 hour relief with the convenience of once daily dosing. This can be compared with H2-antagonists. The pivotal studies with ranitidine 75mg utilised an end-point of “adequate pain relief within 60 minutes and sustained for at least 2 hours” [17]. While ranitidine 75mg claims 12 hour relief, the extent of pain relief in these studies at 12 hours is unclear.

Contribution of Losec 10mg

Losec 10mg has been widely studied in the treatment of dyspepsia patients with symptoms of epigastric pain and /or heartburn. These studies demonstrated superior efficacy compared with both antacid-alginates as well as H2-antagonists. Studies have also been performed looking at the intermittent on-demand use of Losec 10mg in this population. Again, the results demonstrate superiority compared with antacids and H2-antagonists.

Comparative Data for Losec 10mg

Two identical Australian studies investigated the efficacy of Losec 10mg and Losec 20mg versus placebo in 1,262 patients with epigastric pain and normal endoscopy [19]. Study medication was taken daily over a 4 week period.

	Complete symptom resolution all patients	Relief of dyspepsia all patients	Complete symptom resolution in reflux-like patients	Proportion of symptom-free days
Losec 10mg	36% (p=0.02)	59%	45% (p<0.05)	50%
Losec 20mg	38% (p=0.002)	61%	54% (p<0.05)	52%
placebo	28%	51%	23%	46%

Thus, Losec 10mg provided superior symptom relief compared with placebo, the results being improved in patients with classical heartburn.

Two pivotal studies have investigated the efficacy of Losec 10mg daily versus antacid/alginate treatment in patients with dyspepsia [15, 16]. The UK study by Goves randomised 674 patients with dyspepsia symptoms of epigastric pain and/or heartburn to 2 weeks therapy with either Losec 10mg or Gaviscon 10ml *qid*. Patients who did not improve at week 2 were stepped up in their therapy [15]. The second UK study by Mason randomised 725 dyspepsia patients with epigastric pain and/or heartburn to 4 weeks therapy with either Losec 10mg or Gaviscon 10ml *qid*. Patient therapy was escalated if symptoms worsened following the initial 2 weeks therapy [16].

	Week 2 Complete symptom resolution	Week 2 Sufficient symptom relief	Week 4 Complete symptom resolution	Week 4 Sufficient symptom relief
Goves Losec 10mg	27% p<0.0001	39% p<0.0001	41% p<0.0001	49% p<0.0001
Goves Gaviscon 10ml qid	8%	17%	15%	23%
Mason Losec 10mg	NA	NA	46% p<0.0001	62% p=0.0001
Mason Gaviscon 10ml qid	NA	NA	17%	36%

In both studies, Losec 10mg provided superior symptom resolution and greater convenience to patients compared with antacid-alginate therapy.

Intermittent On-Demand Losec 10mg Data

Losec 10mg and 20mg have been studied in several pivotal trials involving the intermittent on-demand treatment of patients with heartburn and normal endoscopy results.

The UK study by Bardhan randomised 677 patients to either Losec 10mg daily, Losec 20mg daily or ranitidine 150mg twice daily for 2 weeks [20]. Patients receiving either Losec 10mg or ranitidine 150mg and who were symptomatic at the end of the initial 2 weeks had the dose of their medication doubled for a further 2 weeks of therapy. Subjects then received no further treatment until moderate or severe symptoms recurred for at least 2 days ineach of the previous 2 weeks or if more than 3 antacid tablets were needed per day to control symptoms. Upon relapse, patients received the therapy to which they had initially responded. Subjects were followed up for 12 months.

At week two, the proportion of patients without symptoms were: 40% for Losec 10mg, 55% for Losec 20mg and 26% for ranitidine 150mg *bid* ($p<0.001$). The median number of days off treatment for all patients was 142 days and 281 days for those who responded to initial therapy. The most powerful prognostic factor for patients remaining off treatment was 'symptoms controlled at 2 weeks' ($p<0.0001$).

Thus, significantly more subjects treated with Losec 10mg had symptom resolution at 2 weeks compared with ranitidine 150mg *bid*. These subjects remained off therapy for a median of 281 days. Those patients not responding to initial therapy could be readily self-identified because of on-going symptoms and would be candidates for further investigation.

A parallel study assessed quality of life for patients [21]. The total Gastrointestinal Symptom Rating Scale score improved significantly more on Losec 10mg than on ranitidine 150mg *bid* ($p=0.006$).

The Swedish study by Lind randomised 424 patients with troublesome heartburn and normal endoscopy to Losec 10mg, Losec 20mg or placebo as on-demand therapy and followed them for six months [18].

	Remission rate	Mean treatment tablets per day during therapy	Mean antacid tablets per day	Time to first consecutive 7 day treatment period
Losec 10mg	69% (p<0.01)	0.91	0.62	126 days
Losec 20mg	83% (p<0.01)	0.77	0.67	164 days
placebo	56%	1.15	0.78	61 days

In the placebo group, 50% of subjects experienced unacceptable symptoms not controlled by antacids within the first 6 months. However, the use of Losec 10mg was associated with reduced antacid use, a longer period of remission and a higher overall remission rate at six months. The 6 month remission rates obtained in this study with on-demand Losec 10mg are comparable with those obtained in similar studies using daily maintenance Losec 10mg.

Justification of Maximum Treatment Period and Dose

The Swedish heartburn study found that while 54% of subjects used on-demand therapy for at least one consecutive period of 7 days or more, 26% and 13% of subjects used on-demand therapy for 14 days and 28 days or more respectively [18]. Thus, 80% of subjects' heartburn resolved with approximately 14 days of on-demand therapy. During treatment with Losec 10mg, the median number of tablets consumed per day was 0.91.

Studies utilising Losec as a diagnostic tool have also generally employed a 2 week treatment period [22].

Superior results have been obtained with Losec 20mg compared with Losec 10mg. A commercial pack of Losec 10mg x 14 would provide for treatment at 20mg daily but for 7 days only.

Thus, a Losec 10mg x 14 pack provides the flexibility to maximise efficacy without compromising safety for the majority of patients over a range of symptom frequency and severity.

Justification for the "Short-term Prevention of the Recurrence of Heartburn" Labelling

The pivotal studies from both the UK and Sweden clearly demonstrated that intermittent on-demand Losec 10mg achieved symptom relief in a significant proportion of subjects [18, 20]. However, the studies further demonstrated that subjects who achieved symptom resolution experienced a prolongation of remission, that is, the period of symptom resolution before further anti-ulcerant therapy was required.

	Time to relapse for responders	**Time to relapse for non-responders**
Swedish Study, n= 424	126 days Losec 10mg	61 days placebo
UK Study, n= 677	281 days	142 days

Together these studies support the claim that Losec 10mg prevents the recurrence of heartburn in subjects who also achieve initial relief of their symptoms. This is in contrast to antacids where there is an absence of data to suggest prevention of symptoms. Indeed, it is noteworthy that the Swedish and UK studies cited above provided for patients in all treatment groups to continue to take *prn* antacids throughout the study. The prevention of symptoms by Losec 10mg in these studies was thus achieved over a background therapy of on-demand antacids.

Further, the Australian studies [19], although employing daily maintenance Losec therapy, also demonstrated a greater proportion of symptom-free days for Losec 10mg compared with placebo.

Hazard to Health

This section reviews omeprazole safety data. Of particular relevance are the extensive local pharmaco-vigilance data for Losec available from the IMMP monitoring programme.

The Swedish expert evaluation for OTC Losec states, "Toxicity of omeprazole is low and serious side effects are rare." Further, the report found no clinically relevant increased safety concerns from omeprazole use in special risk groups, such as slow metabolisers, the elderly, and patients with renal or hepatic insufficiency.

Safety of Losec 10mg in Clinical Trials

There are many published review articles, which demonstrate the favourable safety profile of omeprazole, and the proton-pump inhibitors as a class [23, 24, 25]. The review by Reilley [24] published in 2000 concluded, “Not only are proton-pump inhibitors well tolerated during short-term administration, but there also do not appear to be clinically important adverse sequelae associated with their long-term use.”

The studies by Talley et al and Mason et al referred to earlier in the efficacy section also reviewed safety [16, 19]. Talley et al reported that the number of adverse events was low and similar across the three treatment groups (omeprazole 10, 20 mg and placebo). A total of 34 patients discontinued due to adverse events in these studies. Of these patients, 9 were administered omeprazole 10 mg, 10 administered omeprazole 20mg and 15 administered placebo. Mason et al reported 1,345 adverse events. Of these, 662 were from 267 patients receiving omeprazole and 683 were from 259 patients receiving antacid/alginate/ranitidine. Hence the incidence is similar for patients receiving either omeprazole or antacid/alginate/ranitidine. Twelve serious adverse event reports were received in this studies, however none was considered to be treatment related.

Local Pharmacovigilance Data From IMMP

During the period 1 August 1990 to 31 December 1996, pharmaco-vigilance data from a total of 22,050 New Zealand patients were collected (Appendix 4). These patients had been prescribed either 20 or 40 mg of omeprazole as continuous therapy. Prior to 1 January 1998, Losec 10mg was not commercially available in New Zealand. However, since toxicological effects may be anticipated to be dose-dependent, the results obtained with Losec 20mg and 40mg possibly over-estimate the incidence of adverse events with Losec 10mg. Furthermore, Losec 10mg as a Pharmacy-Only Medicine would only be available for short periods of treatment.

IMMP reported that *”Omeprazole has proved to be very safe and has the lowest adverse reaction rate (2.7 per cent) of any medicine monitored recently in the IMMP.”* [26]

Reaction rates by dose are summarised in the table below:

Reaction Rates By Dose			
Omeprazole Dose (mg)	**No. of Reactions**	**No. of Patients**	**Reaction Rate per 1000 Patients**
20	279	18931	14.7
40	26	6750	11.3

The calculated rates are of comparable magnitude for both the 20 and 40 mg strengths. The reaction rate for Losec compares very favourably with that reported by IMMP for cimetidine of 15.9 per 1,000 patients (Appendix 2).

The rates of the most commonly reported reactions are presented below:

Summary: Omeprazole 10 Most Commonly Reported Reactions

Reaction	**Rate per 1000 Patients**
Nausea/Vomiting	3.3
Pruritus/Rash	2.5
Headache	2.3
Diarrhoea	2.3
Dry mouth	0.9
Falls	0.9
Arthralgia	0.8
Abdominal pain	0.6
LFTs abnormal	0.6
Renal failure	0.6

The New Zealand IMMP reaction data above are consistent with global adverse event information, summarised in the current New Zealand datasheet (19 July 2000). This document lists as **common** (frequency $\geq$ 1/100), headache, diarrhoea, nausea/vomiting, and abdominal pain; **uncommon** (frequency $\geq$ 1/1000 and < 1/100), increased liver enzymes and pruritus, and **rare** (frequency $\leq$ 1/1000), dry mouth, arthralgia and the hypersensitivity reaction, interstitial nephritis, which could cause renal failure. Apparent differences in frequency are most likely due to the fact that the datasheet summarises event data (causality

not established), whilst the IMMP summary table presents reactions (causality ”certain”, ”probable” or ”possible”).

Cimetidine was monitored on the IMMP program in 10, 526 patients from 1977-1981 in New Zealand (Appendix 3). IMMP reported a similar range of serious adverse reactions for cimetidine as those reported with Losec. Cimetidine had a reaction rate of 12.4 per 1,000. There were 3 reports of liver toxicity (0.3 per 1,000), 4 reports of amnesia/confusion (0.4 per 1,000), 1 report of myalgia (0.1 per 1,000) and 3 reports acute renal failure (0.3 per 1,000). The updated report to March 2001 included additional serious adverse events, notably, interstitial nephritis, hepatocellular damage and angiodema.

It should be remembered that today IMMP reports reaction rates from PFU regions only, where there is intensive follow-up of reporting. However, when cimetidine was monitored there were no PFU regions and reporting in general was less rigorously followed-up. Thus, the reaction rates for cimetidine are less robust than those reported for Losec and probably underestimate the true rates. However, they are indicative of the type and relative incidence of reactions. The Losec reaction rates reported from non-PFU regions in IMMP for rare serious adverse events are significantly lower than that for PFU regions. For example, reactions rates per 1,000 for PFU compared with non-PFU regions are: acute renal failure (0.6 versus 0.3), abnormal LFTs (0.6 versus 0.3), arthralgia (0.8 versus 0.1) and polymyositis (0.3 versus 0.0).

Serious Adverse Events

The following significant, but rare serious adverse events were documented through IMMP.

Interstitial Nephritis [26, 27]:

Drug induced interstitial nephritis is a hypersensitivity reaction. The incidence of omeprazole induced interstitial nephritis is rare. Only two reports were received while omeprazole was monitored on the IMMP program. On withdrawal of Losec, symptoms resolved and there are no known reports of death as a result of this adverse reaction. In published case reports of interstitial nephritis, symptoms occurred between 2-26 weeks after treatment initiation with omeprazole.

Hyponatremia [26]:

Five reports of hyponatremia were received, however 3 were attributed to causes other than omeprazole and all of the patients were over 70 years of age.

Confusion/Dementia and Amnesia [26]:

Nine and five reports respectively of confusion and dementia were received with all patients being aged 65 years or older. Only three of the 9 cases of confusion were assigned a probable relationship. The patients who suffered dementia were aged between 88-91 years, and the causal relationship of dementia with the use of Losec is considered to be coincidental.

Polymyositis [26]:

Three patients were reported with polymyositis, all of who were over 74 years. Again, it is important to note that this condition is more frequently seen in the elderly.

Gastric Polyps:

Two reports of gastric polyps were received, however causality could not clearly be established [26]. The duration of Losec treatment was 1 year and unknown respectively. Gastric polyps are considered to be a potential risk associated with continued long-term administration. The author concluded, “Since Losec was introduced, concerns have been expressed about the theoretical possibility that long term powerful acid suppression may predispose to gastric cancer. There has now been extensive use of this proton pump inhibitor and no evidence of increase in malignancy has been detected; this potential problem now seems unlikely.”

Klinkenberg-Knol has followed-up 230 refractory reflux oesophagitis patients who have been treated with maintenance Losec for a mean period of 6.5 years [38]. The authors found that, omeprazole therapy was very effective and safe in the long-term management of this difficult patient group. No dysplasia or neoplasia was observed in any of the gastric corpus biopsy specimens during treatment for up to 11 years.

Bacterial Over-Growth [26]:

The IMMP program found no evidence of bacterial over-growth due to Losec treatment.

Liver Toxicity [4]:

An epidemiological review of hepato-toxicity for some commonly administered agents, including omeprazole has been reported [4]. Eight retrospective cohort studies in the United Kingdom considered the incidence of drug-induced acute liver injury. Of 23,175 patients using omeprazole between the years 1990-1993, only one patient developed acute liver injury, which was diagnosed as hepatocellular disease. The patient had been receiving Losec for 359 days. This corresponds to a rate of liver injury per 100,000 patients for Losec of 4.3. The same epidemiological study found a rate of liver injury per 100,000 patients for ranitidine and cimetidine of 8.9 and 22.7 respectively. Thus, the incidence of non-fatal acute liver injury for Losec is very low and comparable to that found with ranitidine.

Further, the Swedish expert evaluation of OTC Losec concludes, “Doses of 10-20 mg daily are safe in patients with impaired hepatic function.”

Deaths:

IMMP reported 25.09% of all events as “Died”. While this may appear high, it must be remembered that mean age of patients in IMMP was 60 years, with 32.7% of all patients over the age of 70 years. The mean age of patients reported as “Died” was 74.6 years. Those patients who died with an event associated with Losec are listed below.

Event	Age	Association	Duration of Treatment
MI	78y	3	2y
Aplastic anaemia	86y	3	18m
Ca stomach	62y	3	16m
MI	78y	3	2y

Thus, there were few deaths in patients where there is a clear causal relationship with Losec. The overall incidence would seem reasonable in a cohort of this age.

Pregnancy

Results from three prospective epidemiological studies indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/new-born child [5, 6, 7]. These studies suggest that rates of malformations in those treated with omeprazole during the first

trimester are similar to those untreated. In addition, these studies do not suggest higher rates of miscarriage, foetal death, or growth disturbance in those exposed to omeprazole in pregnancy. The rates of miscarriage and congenital malformation reported in these three studies are similar to the population norm.

The study by Ruigomez et al, which examined data from 2,236 pregnancies, demonstrated that the relative risk of non-genetic malformation associated with cimetidine, omeprazole and ranitidine was 1.2, 0.9 and 1.4 respectively compared to non-exposed individuals [5].

The Losec datasheet has recently been approved in New Zealand to state that Losec can be used during pregnancy. However, the proposed labelling of the Pharmacy-Only pack will advise consumers to consult with their doctor or pharmacist if pregnant or breast-feeding, in line with labelling for the Zantac Relief 150mg pack.

Losec is not indicated for use in children in New Zealand. This will be reflected in the proposed labelling.

Interactions with Other Medicines

Although the Losec datasheet acknowledges possible interactions with phenytoin, warfarin and diazepam, no clinically significant interactions between Losec and these or other commonly prescribed medicines have been demonstrated [28]. In addition, no interaction has been found with alcohol [29] or concomitantly administered antacids [29].

Omeprazole does not appear to have a significant effect on the most important cytochrome for drug metabolism, CYP3A4 [28]. Results from a range of interaction studies with Losec and other medicines indicate that omeprazole 20-40 mg, given repeatedly 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) [28].

Although Losec is metabolised by CYP2C19, concomitant treatment with Losec 20 mg daily for 3 weeks did not change either the blood or urine concentration of phenytoin in epileptic patients treated with this medicine [30].

Similarly, patients who were on continuous warfarin therapy were randomised to concomitant treatment with Losec 20mg daily for 3 weeks or placebo [31]. The mean plasma concentration of R-warfarin was increased by 9.5%, while there was no change in the plasma concentration of the more active isomer S-warfarin. As a result, concomitant treatment with Losec 20mg daily did not result in a significant change to coagulation time (106s Losec versus 98s placebo), or TT-values (8.8 Losec versus 9.9 placebo). These results in patients on continuous anticoagulation therapy are similar to those found in healthy volunteers. The authors noted that "…patients on continuous warfarin therapy exhibiting an anticoagulation effect within the therapeutic range may be less prone to alteration in this effect by omeprazole treatment."

Following Losec 20mg daily, the clearance of diazepam was decreased by approximately 27%, compared with a 38% decrease observed with cimetidine 400mg *bid* [40]. There was no effect on volume of distribution. No effect was seen in slow metabolisers of omeprazole [28]. The authors commented [40], "…since diazepam has a wide therapeutic range, it is unlikely that concomitant treatment with therapeutically recommended doses of either omeprazole or cimetidine will result in a clinically significant interaction with diazepam." Further, diazepam in New Zealand is a controlled drug with a maximum 30 days supply allowed. It would therefore be reasonable to assume that patients prescribed diazepam will be under close medical supervision.

Thus, no clinically significant interactions have been reported with Losec 20mg daily and these agents. Further, it would be reasonable to assume that patients prescribed either warfarin or phenytoin (for epilepsy) would already be under close and regular medical attention. The proposed CMI for Losec 10mg OTC advises consumers to consult their doctor before initiating Losec if they were on other prescribed medicines.

As is the case with other acid secretion inhibitors, the absorption of ketoconazole and itraconazole [32] can decrease during omeprazole treatment due to decreased intragastic acidity [32]. Plasma concentrations of omeprazole and clarithromycin are increased during concomitant administration but there is no interaction with metronidazole or amoxicillin [29].

The Swedish expert evaluation of OTC Losec states, “With the recommended doses there are no risks for clinically significant interactions except with ketoconazole and possibly fluconazole.”

The IMMP report noted the following “associations”:

- no reactions reported with an association between Losec and anti-coagulation therapy.
- One reaction reported with an association between Losec and anti-epileptic therapy (sodium valproate). However, the reaction was diarrhoea and somnolence, which are known adverse events associated with Losec itself rather than any interaction with sodium valproate.
- One reaction reported with an association between Losec and fluconazole. However, again the reaction was a known adverse effect of Losec itself – vomiting.

In conclusion, Losec has no clinically significant drug interactions.

Contraindications

The only contraindication for Losec is hypersensitivity to omeprazole [29].

Risk of Misuse

In considering the risks associated with the misuse of Losec 10mg in the proposed indications, a key area to be addressed is the ability of users to self-diagnose their medical condition, which is related to the risk of masking symptoms of other underlying diseases.

The key issue in addressing the proposed reclassification of Losec 10mg to Pharmacy-Only Medicine status is whether the risks of misuse are increased if the product is sold without supervision.

Studies have shown that healing of more serious conditions, such as peptic ulcer and reflux oesophagitis, occurs over 3-4 weeks when stomach pH is reduced to >3 for a period of 18-20 hours per day [33]. Healing may still be affected, with shorter duration of effect on pH, if

therapy is continued for 6 weeks or longer. Losec 10mg has been shown to maintain intragastric pH at or below 3.0 for a mean of 13 hours [34]. It is therefore highly unlikely to heal, and therefore provide on-going symptomatic relief of, serious conditions such as peptic ulcer and reflux oesophagitis with the short course of treatment proposed for OTC use.

Median 24 hour gastric pH and the percentage of time with pH below 4 were measured for Losec 10mg *od* versus ranitidine 300mg *bid* in a cross-over design comparative trial of patients with severe oesophagitis and/or Barrett's [43]. There were no significant differences between Losec and high dose ranitidine for either end-point. The authors stated, "…it would seem that patients with moderate-severe esophagitis and Barrett's esophagus have comparable sensitivity to omperazole and high doses of ranitidine, as others have reported in healthy subjects and duodenal ulcer patients." Thus, the risk of short-term treatment with Losec 10mg masking more severe disease is no greater than with ranitidine at doses that are currently approved as Pharmacy-Only Medicine in New Zealand.

The comparable risk of masking more severe disease with Losec 10mg versus ranitidine is further supported by the meta-analysis published by Eriksson et al [44]. The healing rates at 4 weeks for Losec versus ranitidine are as follows:

	Losec 20mg	**Ranitidine 150mg bid or 300mg nocte**
Duodenal ulcer healing	62%	46%
Gastric ulcer healing	69%	59%
Oesophagitis Healing	64%	41%

The results obtained with Losec 20mg daily for 2-4 weeks are clearly superior to ranitidine 150mg bid (or 300mg nocte). However, the results obtained with Losec 10mg for 2 weeks or Losec 20mg for 7 days would be expected to be comparable to those obtained with doses of ranitidine that are currently available in New Zealand OTC.

Thus, even if a peptic ulcer or reflux oesophagitis patient should obtain sufficient relief with 7-14 days Losec 10mg their symptoms would be expected to recur following cessation of therapy, and in the meantime the patient has received the current gold standard of care for these conditions. Patient care would not have been compromised.

Self-Diagnosis

The vast majority of heartburn sufferers, and those with acid-related symptoms, self-medicate without the advice of a physician [9]. These patients, who experience chronic intermittent antacid-responsive symptoms, are considered to have mildly symptomatic gastro-oesophageal reflux and are well used to managing the conditions themselves.

The widespread availability of antacids for these conditions in general outlets throughout the world, without any supervision, attests to the belief that, in general, sufferers are able to self-diagnose these conditions and that self-medication is appropriate. This view has been endorsed in the stricter regulatory climate of the 1990's, by the approval of H_2- antagonists as non-prescription products for the treatment of these conditions.

The Losec 10mg labelling will advise the consumer not to continue treatment for more than fourteen days without the advice of a pharmacist or doctor.

There is no foolproof way for pharmacists and doctors to detect those patients with conditions for which non-prescription therapy may be inappropriate. However, a history of persistent alarm symptoms, weight loss, or difficulty swallowing, may indicate a need for further investigation. The identification of patients with so-called alarm symptoms can be achieved with appropriate wording on the CMI and pack highlighting those conditions for which self-medication is inappropriate and therefore where medical advice should be sought. This would be analogous to the situation with low dose non-prescription H2-antagonists.

The majority of consumers are likely to heed those warnings. In those who do not, it is unlikely that the level of risk will increase significantly. The low dose and short duration of Losec therapy is unlikely to heal active peptic ulceration or severe oesophagitis. Symptoms will recur which will force the user to seek further advice. The fourteen day delay in seeking advice is not therefore considered to be an issue.

In the case of an underlying malignancy, symptoms would recur and, it is unlikely that any short delay in making the diagnosis will affect the subsequent prognosis [35]. This view has been endorsed by experience with cimetidine at prescription dosage, which although

producing transient symptomatic improvement, was shown to have no adverse effect on survival [36].

The Genval Guidelines acknowledged the evidence base to support simple self-administered symptom questionnaires to substantially aid diagnosis of reflux [2]. This would not require the supervision of a pharmacist.

A description of heartburn as “a burning feeling rising from the stomach or lower chest up towards the neck” has been found to identify or recognise more reflux patients than use of the word heartburn *per se* and shows a high correlation with response to Losec therapy [37]. The use of this readily understood description as a self-administered diagnostic tool could be easily incorporated into the package insert for Losec as well as any discussion between a pharmacy salesperson and a consumer.

Unlike antacids and H2-antagonists, Losec has been successfully used as a diagnostic tool for reflux. Proton pump inhibitors as the diagnostic tool of choice were supported by the Genval Guidelines [2]. In one study, response to Losec had a positive and negative predictive value for the diagnosis of reflux amongst patients with heartburn of 68% and 67% respectively [22]. The median time to achieve a complete absence of acid-related symptoms was 3 days in this dyspeptic population. However, this study employed a higher dose of Losec, and similar results with Losec 10mg would presumably require a longer treatment period.

Thus, patients with classical heartburn can be pre-selected through an appropriate self-administered labelling. Resolution of symptoms through a short-term trial of Losec in these patients is highly predictive of reflux. Further intermittent therapy with Losec in these patients can be undertaken with a negligible risk of complications or progression of disease. Patients whose symptoms do not resolve upon the initial trial of Losec can be readily self-identified for further medical investigation.

The use of Losec to facilitate self-identification of patients requiring further investigation has been acknowledged as a very cost-effective diagnostic approach as well as one, which is non-intrusive and acceptable to patients.

In the New Zealand population we know that around 70% of subjects with reflux-like symptoms already self-medicate [9].

The use of Losec as empirical therapy in primary care for the management of dyspepsia and heartburn is already well established in New Zealand. For the year ending 31 December 2000, proton pump inhibitors represented 35.3% and 34.9% of all prescriptions written for the diagnoses of dyspepsia and heartburn respectively.

The Genval Guidelines acknowledged that for newly presenting primary care patients the evidence base supported a low prevalence (<5%) of severe oesophagitis that would be associated with any significant risk from local complications [2]. These guidelines go on to support the statement that the risk of development of oesophageal cancer is so small in unselected individuals presenting in a primary setting that this risk should not be the primary determinant for requiring an endoscopy [2].

A group of 234 patients with persistent post-prandial heartburn underwent endoscopy [39]. Around 91% of this population were free of erosions and ulcers. The risk therefore of masking more severe disease in this population is minimal.

Self-diagnosis followed by a short-term empirical trial of Losec 10mg in these patients therefore has an acceptable safety profile in-keeping with current practice as well as international guidelines.

Risk with Overdose

Rare reports of overdose with omeprazole have been received. Martindale documents 2 cases, with the major clinical symptoms being drowsiness, headache and tachycardia [41]. Both patients recovered uneventfully without specific treatment.

Gallerani et al published a case report of an overdose of 560 mg (28 x the recommended therapeutic dose) [42]. The patient completely recovered.

Omeprazole doses of up to 120 mg daily for treatment of Zollinger-Ellison syndrome have been well-tolerated [29].

In addition, acute ingestion of up to 2,400 mg has been reported without serious outcomes supporting a lack of overdose risk with omeprazole [29].

Special Precautions Related to the Indications

Due to the low risk associated with masking underlying diseases, consumers with heartburn and symptoms related to gastric hyperacidity need to be clearly told under what circumstances they should seek further advice. This advice is provided in the CMI for Losec 10mg, as is the case for H2-antagonists.

In the section entitled “Before you take your tablets” consumers are advised to get the advice of their doctor before taking the tablets if they have difficulty swallowing, persistent stomach pain or unintended weight loss associated with indigestion. The same advice will appear on the carton.

In the section entitled “After starting your tablets”, the following are the key elements of advice that are provided to the consumer:

- these small packs are for episodes of heartburn; the advice of a pharmacist should be obtained if more tablets are required
- to consult a doctor if the symptoms get worse or are no better after taking the medicine for 14 days
- in a section headed “Important Warning”, advice not to keep treating themselves without the advice of a doctor or pharmacist, as they may have another medical condition that needs different treatment.

These simple instructions should be clearly understood by the consumer. They should identify those consumers with high-risk conditions, for which alternative therapy may be appropriate and who should seek the advice of a pharmacist or physician. The risks associated with consumers ignoring this advice when the product is purchased without the supervision of a pharmacist, are considered minimal and are no greater than exist for antacids.

The pack will also contain instructions to ensure appropriate use of the product. In particular, patients will be alerted to the need for immediate medical attention if they are pregnant or breastfeeding, or have alarm symptoms:

- difficulty swallowing
- persistent stomach pain
- unintended weight loss associated with indigestion
- pregnancy
- breast feeding

All these precautions apply to the use of both antacids and H2-antagonists.

Special Precautions Related to the Product

There are no special precautions related to the product that would preclude its use as a Pharmacy-Only Medicine. Those who know that they are allergic to any of the ingredients of Losec MUPS 10mg are told not to take the product.

The following situations are identified wherein consumers should seek further advice:

- difficulty swallowing
- persistent stomach pain
- unintended weight loss associated with indigestion
- pregnancy
- breast feeding
- taking too many tablets
- needing more tablets when the pack is finished
- if the symptoms get worse or no better after taking the tablets
- if they develop symptoms of allergy
- if they feel unwell
- if they have any unusual symptoms they do not understand

The safety profile for Losec 10mg is well established and on a par with H2-antagonists.

Wider Community Benefit

New Zealand data from the IMS Medical Index Diagnosis Section reports that for the year ending 31 December 2000, diagnoses of heartburn and dyspepsia were treated with the following medicines:

	PPIs	H2-antagonists	Antacids/Alginates
Dyspepsia	35.3%	37.4%	27.3%
Heartburn	34.9%	35.4%	29.7%

Proton pump inhibitors are therefore very commonly prescribed in New Zealand to empirically treat the symptoms of dyspepsia, particularly heartburn. According to Pharmac's 2000 Annual Review, combined annual expenditure on proton pump inhibitors in 2000 amounted to over $20 million with anti-ulcerants representing the second largest therapy area expenditure.

The reclassification of Losec 10mg as a Pharmacy-Only Medicine will facilitate the management of the significant proportion of reflux patients who have simple uncomplicated mild disease with the gold standard of care according to international guidelines, that is, intermittent on-demand Losec therapy. As such, the reclassification of low dose Losec 10mg to Pharmacy-Only Medicine could have a significant impact on both primary and secondary healthcare resources. There would be an obvious potential saving in the direct cost of anti-ulcerant pharmaceuticals to the Government. In addition, there is the potential to reduce the waiting lists for secondary diagnostic procedures such as endoscopy through the diversion of appropriate patients onto empirical therapy, thereby reserving endoscopy services for the more urgent cases ie. patients with alarm symptoms or those not responding to a short course of Losec 10mg. For the consumers themselves the availability of the gold standard in empirical care, Losec 10mg, will reduce the cost of doctor consultations and the potential for multiple alternative therapies of sub-optimal efficacy. The trial results with Losec 10mg clearly demonstrate that complete symptom resolution with Losec correlates with prolonged remission for consumers and therefore a reduction in the frequency, inconvenience and expense of repeat courses of anti-ulcerant therapy.

Losec therefore has the potential for individual consumer as well as societal savings.

Conclusion

Losec 10mg tablets, for the symptomatic relief and prevention of heartburn and indigestion at a dose of one to two tablets daily fulfils the criteria for a product that can be sold as a Pharmacy-Only Medicine.

The available data have demonstrated that the hazard to health is small. Losec 10mg has been available in Sweden as an OTC medication for more than 12 months with over 3 million treatment-days sold.

Losec 10mg is approved in nearly 60 countries with over 12 billion treatment-days of prescription experience. Losec is also widely approved around the world for the indications of acid-related dyspepsia and symptomatic reflux disease.

The clinical trial data for both short-term and intermittent, on-demand therapy with Losec 10mg have demonstrated superior efficacy compared with both antacid-alginates and ranitidine. Losec provided 24 hour relief of symptoms as well as prevention of relapse in those who responded. The adverse event profile for Losec 10mg in these clinical trials has been similar to that observed with ranitidine.

Losec has been extensively studied for 6 years on the IMMP program in New Zealand. The results demonstrated that Losec was one of the safest medicines monitored by IMMP. Serious adverse events were rare, generally reversibly and non-fatal, comparable in type and incidence to those observed with cimetidine through IMMP and typically observed in an elderly population.

The risks of misuse or inappropriate usage are small. The proposed indications are appropriate for a Pharmacy-Only Medicine. Heartburn and other symptoms related to gastric hyperacidity are extremely common in the general population. Consumers are able to self-diagnose and treat their symptoms and have done so with antacids and low dose H2-antagonists for many years.

Those users, who are at increased risk of having other conditions, for whom self-medication is considered inappropriate, or who need further advice before using the product, will be alerted by the warnings in the CMI and on the pack.

Even if these warnings are not heeded, no clinically significant risks are associated with the short-term use of Losec 10mg. This situation is comparable with the use of antacids and H2-antagonists, which are freely available.

The low dose of Losec over the short period indicated will not produce healing in those with more serious underlying conditions and symptoms will continue or recur, prompting the user to seek further advice. The risk of masking more severe disease with Losec would be comparable to that anticipated with the OTC doses of ranitidine approved in New Zealand.

There are no clinically significant interactions with Losec, particularly at low dose. Losec has been safe in overdose at doses up to 2,400mg. Losec has no addictive or euphoric potential.

The wider availability of once daily Losec 10mg would be a convenience to the consumer, providing potential savings to them and the community.

The vast majority of products for heartburn are now purchased without assistance or supervision from the pharmacist.

In conclusion, Losec 10mg is an appropriate product for Pharmacy-Only Medicine and the proposed CMI ensures its safe and effective use.

References

(Note: References in italics have not been supplied)

1. Losec MUPS 10mg and 20mg OTC Assessment, Sweden.
2. Dent, J. *et al*., An evidence-based appraisal of reflux disease management – the Genval Workshop Report, Gut, 1999, 44 (Suppl. 2), S1-S13.
3. Gottlieb, S., FDA panel advises against omeprazole as over the counter drug, Brit. Med. J., 2000, 321, 1099.
4. Garcia Rodriguez, L.A. *et al*., A review of epidemiologic research on drug-induced acute liver injury using the general practice research data base in the United Kingdom, Pharmacotherapy, 1997, 17 (4), 721-8.
5. Ruigomez, A. *et al*., Use of cimetidine, omeprazole and ranitidine in pregnant women and pregnancy outcomes, Am. J. Epidemiol., 1999, 150, 476-81.
6. Kallen, B., Delivery outcome after use of acid-suppressing drugs in early pregnancy with special reference to omeprazole, Brit. J. Obstet. Gynaecol., 1998, 105, 877-881.
7. Lalkin, A. *et al*., The safety of omeprazole during pregnancy: A multicenter prospective controlled study, Am. J. Obstet. Gynecol., 1998, 179, 727-30.
8. *Grimley, C.E., Nocturnal intragastric acidity after over-the-counter doses of famotidine, ranitidine or placebo, Aliment. Pharmacol. Ther., 1997, 11, 881-885.*
9. 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.
10. *Jones, R.H., Dyspepsia in England and Scotland, Gut, 1990, 31, 401-405.*
11. *Fung, M.C. et al., Elderly over the counter drug users at risk, Arch. Fam. Med., 1995, 4, 718-723.*
12. *Shields, H.M. et al., Rapid fall of serum phosphorus secondary to antacid therapy, Am. Gastroenterol. Assoc., 1978, 75 (6), 137-*
13. *Clark, B.A., Unsuspected morbid hypermagnesemia in elderly patients, Am. J. Nephrol., 1992, 12, 336-343.*
14. *Joelsson, B. and Johnsson, F., Heartburn – the acid test, Gut, 1989, 30, 1523-1525.*
15. 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, Aliment. Pharmacol. Ther., 1998, 12, 147-157.
16. Mason, I. *et al*., The management of acid-related dyspepsia in general practice: a comparison of an omeprazole versus antacid-alginate/ranitidine management strategy, Aliment. Pharmacol. Ther., 1998, 12, 263-271.

17. Application to Schedule Zantac 75mg as a Pharmacy medicine, New Zealand.

18. Lind, T. *et al*., On demand therapy with omeprazole for long-term management of patients with heartburn without oesophagitis – a placebo-controlled randomised trial, Aliment. Pharmacol. Ther., 1999, 13, 907-914.
19. Talley, N.J. *et al*., Efficacy of omeprazole in functional dyspepsia: double-blind, randomised, placebo-controlled trials (the Bond and Opera studies), Aliment. Pharmacol. Ther., 1998, 12, 1055-1065.
20. Bardhan, K.D. *et al*., Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine, Brit. Med. J., 1999,318, 502-507.
21. Wiklund, I. *et al*., Quality of life during acute and intermittent treatment of gastro-oesophageal reflux disease with omeprazole compared with ranitidine. Results from a multicentre clinical trial, Ital. J. Gastroenterol. Hepatol., 1998, 30, 19-27.
22. Bate, C.M. *et al*., Evaluation of omeprazole as a cost-effective diagnostic test for gastro-oesophageal reflux disease, Aliment. Pharmacol. Ther., 1999, 13, 59-66.
23. Tolman, K.G. *et al*., Proton pump inhibitors in the treatment of gastro-oesophageal reflux disease, Expert Opin. Pharmacother., 2001, 1 (6), 1171-1194.
24. Reilly, J.P., Safety profile of the proton-pump inhibitors, Am. J. Health Syst. Pharm., 1999, 56 (23 Suppl. 4), S11-17.
25. Arnold, R., Safety of proton pump inhibitors – an overview, Aliment. Pharmacol. Ther., 1994, 8 (Suppl. 1), 65-70.
26. Coulter, D.M., Reactions to omeprazole obscured by aging process, NZ Family Physician, 25 (3), 18-20.
27. Omeprazole-induced interstitial nephritis, CARM, Prescriber Update, 2000, 20.
28. Andersson, T., Pharmacokinetics, metabolism and interactions of acid pump inhibitors, Clin. Pharmacol., 1996, 31 (1), 9-28.
29. Losec Datasheet.
30. Anderson, T. *et al*., A study of the interaction between omeprazole and phenytoin in epileptic patients, Ther. Drug Monit., 1990, 12, 329-333.
31. Unge, P. *et al*., A study of the interaction of omeprazole and warfarin in anticoagulated patients, Brit. J. Clin. Pharmacol., 1992, 34, 509-512.
32. Jaruratanasirikul, S. and Sriwiriyajan, S., Effect of omeprazole on the pharmacokinetics of itraconazole, Eur. J. Clin. Pharmacol., 1998, 54, 159-161.
33. Burget, D.W. *et al*., Is there an optimal degree of acid suppression for healing of duodenal ulcers? Gastroenterology, 1990, 99, 345-351.

34. Savarino, V. *et al*., Variability in individual response to various doses of omeprazole, Dig. Dis. Sci., 1994, 39 (1), 161-168.
35. *Oster, G. et al., The risks and benefits of an Rx-to-OTC switch; the case of over-the-counter H2-blockers, Med. Care,1990, 28, 834-842.*
36. *Scotcher, S. et al., Gastric cancer and cimtidine: does delay in early diagnosis matter? Lancet, 1981, ii, 630-631.*
37. Carlsson, R. *et al*., The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease, Scand. J. Gastroenterol., 1998, 33, 1023-1029.
38. Klinkenberg-Knol, E.C. *et al*., Long-term omeprazole treatment of resistant gastroesophageal reflux disease: Efficacy, safety and influence on gastric mucosa, Gastroenterology, 2000, 118, 661-669.
39. Murdock, R.H. *et al*., Endoscopic findings in a target population for over-the-counter treatment of heartburn, Gastroenterology, 106 (No.4, pt. 2) A146.
40. Andersson, T. *et al*., Effect of omeprazole and cimetidine on plasma diazepam levels, Eur. J. Clin. Pharmacol., 1990, 39, 51-54.
41. Martindale, 32nd Edition, 1204-6.
42. Gallerani, M. *et al*., Omeprazole overdose: A case report, Clin. Drug Invest., 1996, 11 (2), 117-9.
43. Fiorucci, S. *et al*., Effect of omeprazole and high doses of ranitidine on gastric acidity and gastroesophageal reflux in patients with moderate-severe esophagitis, Am. J. Gastroenterol., 1990, 85 (No.11), 1458-1462.
44. Eriksson, S. *et al*., Omeprazole and H2-receptor antagonist in the acute treatment of duodenal ulcer, gastric ulcer and reflux oesophagitis: a meta-analysis, Eur. J. Gastroenterol. Hepatol., 1995, 7, 467-475.