# Submission for Reclassification

## Omezol Relief

## (omeprazole)

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**Executive Summary**

This application seeks approval to change the current classification of Omezol 10 mg (omeprazole) from Prescription Medicine to Pharmacist-Only Medicine (OTC) for short-term symptomatic relief of reflux-like symptoms. It is also proposed that Omezol will be marketed as Omezol Relief when the proposed re-classification has been approved.

This request for reclassification of Omezol Relief 10 mg (14 pack capsules) is supported by the 1990 Commission of the European Communities, as discussed in the New Zealand Regulatory Guidelines[1], regarding the OTC sale of medicines. . Omeprazole has been available for a number of years and has a substantial safety profile for provision of symptomatic relief and prevention of heartburn and indigestion. The reclassification to Pharmacist-Only Medicine will allow patients faster access and resolve of symptoms, not justifying a medical consultation, that are easily identified by consumers.

***Consumer convenience***

Omezol Relief 10 mg (14 pack capsules) reclassification to OTC medicine for symptomatic relief and prevention of heartburn and indigestion would increase its accessibility for a commonly self-diagnosed and easily self-treated symptom. Relief and prevention of heartburn and indigestion is a suitable symptom for self-treatment as it is usually due to a minor cause (not requiring medical intervention) and is self-limiting.

There are many benefits to the consumer in reclassifying Omezol Relief 10 mg to Pharmacist-Only as people suffering from heartburn or indigestion usually prefer prompt treatment and Omezol Relief 10 mg is a proven and effective product for prompt treatment of these common symptoms[2-7]. It will be sold, as a Pharmacist-Only medicine so there would be no waiting in GP rooms or the expense of a doctor's fee. In addition, self-care for this common symptom features prominently among the New Zealand population with 69% of those with reflux-type symptoms using over-the-counter medications such as antacids[8]. Many consumers are currently unsatisfied with antacids or $H_2$ antagonists and these consumers would benefit from the availability of omeprazole as a Pharmacist-Only medicine.

***Potency***

Omeprazole has well demonstrated efficacy in the treatment of heartburn and other symptoms of indigestion which has been well documented in numerous published clinical studies[2, 4-6]. Heartburn and indigestion symptoms related to gastric hyperacidity are extremely common in the general population[9, 10]. 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[11]. 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 reflux is associated with oesophageal pH below 3. The vast majority of persons with reflux remain unseen by healthcare professionals. These persons do not seek healthcare intervention, since they can manage their symptoms through conservative measures, which require no medical intervention.

Prevalence, severity and associated features of both reflux and dyspepsia in the New Zealand general population are well known with a combined overall prevalence of 'significant' symptoms of dyspepsia and reflux being 45%[8]. While this prevalence appears high it is in agreement with other published studies. In the UK dyspepsia prevalence is reported to be 40%[12]. The most commonly reported symptom in New Zealand is heartburn being 70%[8]. This is in agreement with international sentiment (Genval Consensus), which reports heartburn as being the most common symptoms of reflux in at least 75% of persons[13, 14].

***Evidence for short-term use of omeprazole 10 mg***

Omeprazole has been studied in several clinical trials involving intermittent on-demand treatment of patients with heartburn[3, 7, 15]. A UK randomised double blind double dummy controlled trial involving 677 patients compared omeprazole 10 mg or 20 mg daily to ranitidine 150 mg twice daily for two weeks[15]. Patients receiving either omeprazole 10 mg or 20 mg or ranitidine 150 mg and who were symptomatic at the end of the initial two weeks had the dose of their medication doubled for a further two weeks of therapy. Subjects then received no further treatment until moderate or severe

symptoms recurred for at least two days or if more than three antacid tablets were needed per day to control symptoms. Upon relapse, patients received therapy to which they had initially responded with subjects being followed for 12 months. Results are summarised in Table 1 below and discussed briefly. At the end of two weeks of treatment the proportion of patients without symptoms was: 40% for omeprazole 10 mg, 55% for omeprazole 20 mg and 26% for ranitidine 150 mg twice daily ($p<0.001$). The relative risk (RR) of remaining symptomatic when omeprazole 10 mg od was compared to ranitidine 150 mg bid was 0.80 (or 0.59/0.74) with the Absolute Risk Reduction (ARR) being 0.15 (0.74–0.59) which provides a Number-Needed-To-Treat (NNT) of 7 (1/0.15). Therefore, for every seven people treated with omeprazole 10 mg od, one person would be symptom free who would not have been symptom free if they had been treated with ranitidine 150 mg bid. This trial clearly demonstrates the superior efficacy of omeprazole (compared to ranitidine) in resolving symptoms of uncomplicated gastro-oesophageal reflux disease administered over short-term.

Table 1: Two-week treatment outcome comparing omeprazole to ranitidine in the UK trial[15].

| *Two week treatment* | *Asymptomatic* | *Still symptomatic* | *Total* |
|---|---|---|---|
| Omeprazole 10 mg *od* | 91 | 136 | 227 |
| Omeprazole 20 mg *od* | 122 | 99 | 221 |
| Ranitidine 150 mg *bid* | 60 | 169 | 229 |

In addition 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 omeprazole 10 mg had symptom resolution at two weeks compared with ranitidine 150 mg twice daily. These subjects remained off therapy for a median of 281 days. Those patients not responding to initial therapy could be readily self-identified by their on-going symptoms and would be candidates for further investigation. Another study assessed the quality of life of patients with omeprazole 10 mg as being significantly better than that of patients treated with ranitidine 150 mg twice daily ($p=0.006$)[7].

An earlier extensive systematic review[16] which included 10 randomised controlled trials (1393 patients) using endoscopic healing also showed the superior efficacy of omeprazole to ranitidine. This study showed that healing occurred faster and more extensively with omeprazole than with ranitidine, and that the extent of the superiority of omeprazole was the same whether treatment was for four or eight weeks[16]. In this systematic review the overall NNT was approximately 3. Therefore, for every three patients treated with omeprazole one would be healed who would have not have been healed if they were treated with ranitidine as shown by endoscopic healing[16].

Another study randomised 424 patients with troublesome heartburn to omeprazole 10 mg, omeprazole 20 mg or placebo as on-demand therapy (PRN) and followed patients for six months[3]. In the placebo group, 50% of subjects experienced unacceptable symptoms not controlled by antacids within the first six months. Patients treated with omeprazole 10 mg showed reduced antacid use, longer periods of remission and a higher overall remission rates at six months. The six-month remission rates obtained in this study with on-demand use of omeprazole 10 mg were comparable with those obtained in similar studies using daily maintenance omeprazole 10 mg.

***Current availability***

Currently, there is no other product available as a Pharmacist-Only medication on the New Zealand market with the same active ingredient (omeprazole) or therapeutic group (proton pump inhibitor). The only other product available in New Zealand with the same active ingredient, Losec™ 10 mg, is a Prescription-Only medicine. Other products available OTC which are used to treat the symptoms of heartburn or indigestion, with varying degrees of efficacy, include low dose $H_2$ receptor antagonists, antacids and alginates.

***Therapeutic index***

Omeprazole is known to have a very wide therapeutic index and the risk of adverse events occurring is low when taken at the recommended therapeutic doses.

***Toxicity***

No concerns regarding toxicity are expected with the use of omeprazole. Many published studies have demonstrated the favourable safety profile of omeprazole and

the proton-pump inhibitors as a class[17-19]. Recent publications have shown increased reports of interstitial nephritis as 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[20,21]. However, upon withdrawal of omeprazole, symptoms resolved with no further complications. Cases of interstitial nephritis (or symptoms) occurred 2 - 26 weeks after start of treatment with omeprazole[20-22]. The current application for OTC classification is for only 2 weeks (or 14 days) treatment. Nevertheless appropriate warnings are included in the proposed labelling (please refer to Appendix 1).

***Abuse potential***

Omeprazole has a very low potential for abuse or misuse. The classification of Omezol Relief will be Pharmacist-Only and therefore any potential for abuse or misuse is not expected.

***Inappropriate use***

The classification of Omezol Relief 10 mg will be Pharmacist-Only hence requiring consumer purchase over the counter with pharmacist interaction prior to its sale. This process will ensure appropriate use and minimise the risk of misdiagnosis. Inappropriate use of omeprazole is not anticipated with its reclassification to OTC due to its very low potential for misuse or abuse.

***Precautions***

Precautions are detailed in the medicine data sheet and package; these will be revised to reflect the re-classification and to provide additional warnings as indicated in Part A (Number 12: Proposed warning).

***Communal harm***

The wider availability of this medicine is not expected to increase harm to the community due to its low potential for abuse, misuse and particularly with a Pharmacist-Only medicine classification. There is no evidence to suggest that wider availability of omeprazole would lead to increased resistance or to the development of tolerance.

**Part A**

**1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the medicine**

Omeprazole

**2. Proprietary name(s)**

Omezol Relief

**3. Name of company/organisation/individual requesting reclassification**

Pacific Pharmaceuticals Limited

**4. Dose form(s) and strength(s) for which a change is sought**

Capsule, modified release

Strength: 10 mg modified release capsules

**5. Pack size and other qualifications**

Blister packs of 14 capsules

One to two capsules to be taken once a day for no more than fourteen days. It is recommended to take Omezol Relief capsules in the morning.

**6. Indications for which change is sought**

Short-term symptomatic relief of reflux-like symptoms in sufferers aged 18 years and over.

**7. Present classification of medicine**

Prescription Only Medicine

**8. Classification sought**

Pharmacist Only Medicine

## 9. Classification status in other countries (especially Australia, UK, USA, Canada)

| *Country of Registration* | *Classification* |
|---|---|
| Sweden | OTC 10 mg (since 1999) |
| United Kingdom | OTC 10 mg (since 2004) |
| United States | OTC 20 mg (since 2003) |

## 10. Extent of usage in NZ and elsewhere (e.g. sales volumes) and dates of original consent to distribute

Omeprazole has been available as a prescription medicine in New Zealand since 1990. Medsafe consent for Pacific Pharmaceutical Ltd omeprazole was obtained on 16th August 2001.

Sales volumes for the last five years in New Zealand for the 10 mg capsules (30 pack size) have been as follows:

| Year | Sales Volume of 10 mg (30 pack size) |
|---|---|
| May 2003 | 89,645 |
| May 2004 | 2,093,098 |
| May 2005 | 2,355,312 |
| May 2006 | 2,634,627 |
| May 2007 | 2,830,459 |

## 11. Labelling or draft labelling for the proposed new presentation(s)

Draft labelling text is provided for perusal (Appendix 1). This draft labelling is intended only to show the planned packaging text for Omezol Relief. Design and styles will be applied at a later date and submitted to Medsafe for assessment prior to the marketing the product. ~~Proposed labelling is provided for perusal (Appendix 1).~~

## 12. Proposed-warning statements if applicable

*The warnings will be in accordance with previously approved medicine datasheet with additional warnings to reflect proposed classification (additional warnings underlined for ease of perusal).*

**Warnings and Precautions**

While taking Omezol Relief patients should be advised to seek advice if their symptoms get worse or are no better after taking the medicine for 14 days.

Patients should also seek medical advice if they experience any of the following symptoms while taking omeprazole: fever, nausea, lethargy, malaise or unexplained weight loss.

In the presence of any alarm symptom (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, hematemesis or melena) and when gastric ulcer is suspected or present, the possibility of malignancy should be excluded as treatment may alleviate symptoms and delay diagnosis.

*Use in Pregnancy and Lactation*

Results from numerous clinical studies indicate no adverse effects of omeprazole on pregnancy or on the health of the fetus/newborn child[23-28]. Therefore, Omezol Relief can be safely used during pregnancy. Omezol Relief is excreted in breast milk but is not likely to influence the child when therapeutic doses are used.

*Effects on ability to drive and use machines*

Omezol Relief is not likely to affect the ability to drive or use machines.

## 13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

The following prescription medicines are registered with Medsafe and contain omeprazole 10 mg.

- Losec modified release capsules 10 mg (AstraZeneca Ltd.)
- Losec MUPS enteric coated tablets 10 mg (AstraZeneca Ltd.)
- Omeprazole modified release capsules 10 mg (Affordable Healthcare Ltd.)

As this application is for an additional classification, it will not have any direct effect on the status of these products.

**Part B**

Reasons for requesting classification change.

## 1. A statement of the benefits to both the consumer and to the public expected from the proposed change

Data from the New Zealand IMS Medical Index suggests increasing use of PPIs (large majority being omeprazole) for the management of heartburn and dyspepsia. Recent data from the IMS shows that PPIs have surpassed the number of prescriptions for both $H_2$-antagonists and antacids[29].

Pharmac's latest Annual Review (2006) lists omeprazole as the third most prescribed medicine totalling 956,325 prescriptions in 2006 alone[30]. Furthermore, according to Pharmac figures the number of prescriptions for omeprazole has been steadily increasing over the years with 861,652 prescriptions in 2005[31] and 727,667 prescriptions in 2004[32]. There is little doubt that PPIs are very commonly prescribed in New Zealand for the management of symptoms of dyspepsia and heartburn.

The reclassification of Omezol Relief 10 mg as an OTC medicine will facilitate the management of the significant proportion of reflux patients who have simple, uncomplicated, mild disease. The reclassification of low dose Omezol Relief 10 mg to OTC 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. For consumers the availability of Omezol Relief 10 mg will remove the cost of GP consultations and the potential decrease in the use of therapies with sub-optimal efficacy[33,34]. Therefore, Omezol Relief 10 mg as OTC medication has potential benefits for both the consumer as well as the general public.

## 2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

It is well know that majority of reflux sufferers, and those with acid-related symptoms, self-medicate without medical advice[8]. The widespread availability of antacids for these conditions as general sale throughout the world attests to the belief that these people are able to self-diagnose such conditions and that self-

medication is appropriate. This view is further supported by the availability of $H_2$ antagonists as OTC products for the management of these conditions by the consumer. In New Zealand it is known that approximately 70% of subjects with reflux-like symptoms already self-medicate[8].

Appropriate warnings will be provided on the packet. 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 (10 mg) and short duration (14 days) of Omezol Relief therapy is unlikely to heal active peptic ulceration or severe oesophagitis. Symptoms will recur which will force the consumer to seek medical advice. It is not likely that this short-term delay in seeking medical advice would affect subsequent prognosis[35, 36]. Studies have shown that approximately 91% of patients presenting with persistent post-prandial heartburn and who underwent endoscopy[37] were free of erosions and ulcers. Therefore, the risk of masking severe disease in this self-diagnosing population is minimal.

The use of omeprazole as empirical therapy for the management of dyspepsia and heartburn is well established in New Zealand as omeprazole has been available in New Zealand since 1990 with many thousands of prescriptions being written over the years[30-32].

In addition, the British Society of Gastroenterology[10] defines dyspepsia as a group of symptoms which alerts doctors to consider disease of the upper gastrointestinal tract. It is not a diagnosis and includes symptoms of upper abdominal discomfort, retrosternal pain, anorexia, nausea, vomiting, bloating, fullness, early satiety and heartburn amongst others. Many diseases are known to cause dyspepsia and these include peptic ulcers, oesophagitis, cancer of the stomach or pancreas, and gallstones. In a large proportion of cases no clear pathological cause for a patient's symptoms can be determined. The prevalence of dyspepsia is high in Western societies (20-40%)[10 ,38] and the majority of sufferers do not consult a doctor[10]. Episodic heartburn and indigestion related to food and drink are conditions easily recognisable by the consumer and the condition is unlikely to be serious and in such cases immediate symptom relief will be sought and not a course of treatment. However, the British Society of Gastroenterology[10] advises that it is acceptable to

institute a single course of treatment with an anti-secretory agent for 2-4 weeks in such patients who have troublesome symptoms but without "alarm" symptoms. The above symptoms are easily recognised by the patient. Therefore, consumer self-diagnosis followed by a short-term treatment with low dose Omezol Relief in such patients would not only be acceptable but also recommended.

### 3. Relevant comparative data for like compounds

Some comparative data discussion has been presented under "Potency" in the previous section. Like compounds available for relief of similar symptoms include antacids that are general sale medicines. Antacids produce short-lived effect on gastric pH and they can cause diarrhoea and constipation and reduced absorption of some medicines due to change in gastric pH. Alginates seem to be more useful than antacids in controlling symptoms, but no placebo-controlled study has shown healing of oesophagitis with either of these classes[33]. Muco-protective agents such as sucralfate act locally by shielding damaged mucosa or stimulating local defence mechanisms. A problem is that swallowing induces oesophageal peristalsis so reducing mucosal protective time. There seems to be little enthusiasm for this mode of treatment[34]. Motility stimulants for example Cisapride is the one stimulant that is well studied, with a principal effect on oesophageal acid clearance. It appears to be effective in grades 1 and 2 oesophagitis but efficacy on more severe disease is not proven[34]. $H_2$ antagonists available OTC are ranitidine 75 mg and famotidine 10 mg. OTC $H_2$ antagonists are approved for short-term symptomatic relief of heartburn, dyspepsia and hyperacidity. However, omeprazole has shown significantly better rates of resolution of heartburn symptoms and relapse when compared to ranitidine in the management of acute and maintenance treatment of reflux disease[39].

### 4. Local data or special considerations relating to NZ

The proposed reclassification would allow the consumer easier access to rapid treatment for an easily self-diagnosed symptom, upon confirmation by a pharmacist. This will avoid unnecessary GP visits and provide a more timely treatment for a self-diagnosed and manageable symptom.

## 5. Interactions with other medicines

There are three known mechanisms by which omeprazole can cause drug interactions:

(a) *pH dependent drug absorption:* Affecting low gastric pH dependent medicines, for example ketoconazole, itraconazole (as the concentration in plasma is reduced[40]), digoxin (10% reduction in absorption[18]), ampicillin and iron salts. Aspirin and NSAIDs have other sites of absorption and are not considered to be affected. Absorption of nifedipine increases by 26%[18]. Co-administration with antacids does not lead to clinically significant interactions.

(b) *Inhibition of CYP450 enzyme metabolism*: Omeprazole reduces diazepam clearance by 25%, it also reduces carbamazepine clearance, increases the concentration of r-isomer warfarin (however this may not influence coagulation[41] except at high doses[18] as the r-isomer warfarin, which is more potent, is unaltered[42]). Omeprazole also reduces the absorption of vitamin B12[42] and reduces phenytoin clearance[18]. Most of these interactions via CYP2C19 inhibition are not known to be clinically significant although reductions in clearance of phenytoin, warfarin and diazepam may be important in some individuals.

(c) *Induces CYP450 system:* It is known that omeprazole exerts a concentration-dependent inhibition of CYP1A2 activity. However, even after large single oral doses of omeprazole (80 mg), this effect is weak and without clinical relevance[43]. Theophylline clearance may be affected via CYP1A/1A2 induction, although this is not well proven. Therefore, the interaction potential with phenytoin, warfarin, and diazepam seems to be the most clinically relevant[18].

Hypochlorhydria may result in malabsorption of fat, vitamin B12 and iron. In the vast majority of cases this has not been found to be of clinical relevance, however a small percentage of patients on long-term treatment have been found to have reduced serum B12 levels, and there has only been one report of overt deficiency[42]. Hypochlorhydria has also been thought to weaken the stomach's defence and cause bacterial overgrowth and enteric infection, but the significance of this has not been confirmed[42].

It is known that PPIs raise gastrin levels to at most four times baseline level[18] and that these levels are higher with PPIs than with $H_2$ antagonists. Secondary hypergastrinaemia has led to concerns about risks of gastric cancer and carcinoid tumours, as well as parietal cell hyperplasia, colonic adenomas, and adenocarcinoma. Hypergastrinaemia and cell hyperplasia leading to carcinoid has been observed in rats[42] and in humans but these changes have not led to carcinoids[44]. Studies have shown gastrin levels to return to normal within one week of stopping treatment[42].

The above-mentioned adverse effects are serious but rare and reclassification (i.e. expansion of the market) will produce an increased incidence of these adverse effects. However, most of the adverse effects reported in literature are related to longer-term treatment. Omezol Relief packaging is explicit in stating that the consumers should only use this medication for the short (14 days) duration and if symptoms persist medical advice should be sought. Interactions are already listed on the medicine data sheet ~~and will be detailed on the packet~~.

## 6. Contraindications

Contraindications are already listed on the medicine data sheet and will also be detailed on the packaging.

## 7. Possible resistance

We do not anticipate any resistance to this reclassification. In previous submissions by the innovator company (AstraZeneca™) the Medicines Classification Committee recommendation was in favour of this reclassification (MCC minutes 11 December 2001).

## 8. Adverse events - nature, frequency etc.

Omeprazole has been used extensively and has an excellent safety record. It has highly specific activity, rapid clearance and is a weak base which is converted to the active form under acidic conditions. The most common side effects in short term studies were headache, nausea, diarrhoea (overall incidence <5%), abdominal pain, constipation, and dizziness[18 ,42]. The review by Reilly[18] published in 2000 stated that "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."

Studies by Talley et al and Mason et al have also reviewed safety[4,6]. Talley et al reported that the number of adverse events was low and similar across 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 were administered omeprazole 20 mg and 15 received a 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. Although the incidence is similar for patients receiving either omeprazole or antacid/alginate/ranitidine, none of the 12 serious adverse event reported in this study were considered to be treatment related.

In addition, 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"*[21].

**9. Potential for abuse or misuse.**

Omeprazole has no known potential for abuse. The reclassification of Omezol Relief to Pharmacist-Only medicine is not expected to increase the potential for abuse or misuse. The British Society of Gastroenterologists states that a diagnostic endoscopy is appropriate when alarm symptoms or signs are present (weight loss, iron deficiency anaemia, GI bleeding, dysphagia, previous gastric surgery, persistent vomiting, vomiting, previous ulcer, severe pain). One important concern is the masking of gastric cancer with omeprazole treatment. According to the British Society of Gastroenterology Dyspepsia Management Guidelines[10] the majority of patients with gastric cancer will present with characteristic symptoms (dysphagia, weight loss) and the Guidelines quote a rate of less than 3% of gastric cancers occurring in those aged under 45. As Omezol Relief is only for 14 days, such a short delay is unlikely to affect prognosis of more serious conditions. Most of the known serious adverse effects are related to longer term use, therefore a statement that consumers should use this medicine for a maximum of 14 days is detailed on the package.

There are large numbers of people with dyspepsia and heartburn who self-medicate and do not seek medical advice. It could be perceived that there is a potentially large risk of prolonged use of omeprazole OTC. However, it could be argued that a similar risk exists with the use of OTC $H_2$ antagonists. With the packaging clearly stating that Omezol Relief be only used for short-term treatment of symptoms (and with Pharmacist assurance) this risk would be minimised and would in fact be lower than that of $H_2$ antagonists as short-term use instructions are not provided with $H_2$ antagonist packaging (although the latter are to be used on a PRN basis).

**References**


1. Medsafe. New Zealand Regulatory Guidelines for Medicines. Fifth Ed, 2001.
2. Goves J, Oldring JK, Kerr D, Dallara RG, Roffe EJ, Powell JA, 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(2):147-57.
3. Lind T, Havelund T, Lundell L, Glise H, Lauritsen K, Pedersen SA, et al. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis--a placebo-controlled randomized trial. *Aliment Pharmacol Ther* 1999;13(7):907-14.
4. Mason I, Millar LJ, Sheikh RR, Evans WM, Todd PL, Turbitt ML, et al. The management of acid-related dyspepsia in general practice: a comparison of an omeprazole versus an antacid-alginate/ranitidine management strategy. Compete Research Group [corrected]. *Aliment Pharmacol Ther* 1998;12(3):263-71.
5. Savarino V, Mela GS, Zentilin P, Cutela P, Mele MR, Vigneri S, et al. Variability in individual response to various doses of omeprazole. Implications for antiulcer therapy. *Dig Dis Sci* 1994;39(1):161-8.
6. Talley NJ, Meineche-Schmidt V, Pare P, Duckworth M, Raisanen P, Pap A, et al. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). *Aliment Pharmacol Ther* 1998;12(11):1055-65.
7. Wiklund I, Bardhan KD, Muller-Lissner S, Bigard MA, Bianchi Porro G, Ponce J, 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. The European Study Group. *Ital J Gastroenterol Hepatol* 1998;30(1):19-27.
8. Haque M, Wyeth JW, Stace NH, Talley NJ, Green R. Prevalence, severity and associated features of gastro-oesophageal reflux and dyspepsia: a population-based study. *N Z Med J* 2000;113(1110):178-81.
9. Carlsson R, Dent J, Bolling-Sternevald E, Johnsson F, Junghard O, Lauritsen K, et al. The usefulness of a structured questionnaire in the assessment of

symptomatic gastroesophageal reflux disease. *Scand J Gastroenterol* 1998;33(10):1023-9.

10. British Society of Gastroenterology. Dyspepsia management guidelines. 1996.
11. Grimley CE, Cottrell J, Mann SG, Stauffer L, Nwokolo CU. Nocturnal intragastric acidity after over-the-counter doses of famotidine, ranitidine or placebo. *Aliment Pharmacol Ther* 1997;11(5):881-5.
12. Jones RH, Lydeard SE, Hobbs FD, Kenkre JE, Williams EI, Jones SJ, et al. Dyspepsia in England and Scotland. *Gut* 1990;31(4):401-5.
13. Dent J. An evidence-based appraisal of reflux disease management - the Genval Workshop Report. *Gut* 1999;44(Suppl 2):S1-S13.
14. Dent J, Armstrong D, Delaney B, Moayyedi P, Talley NJ, Vakil N. Symptom evaluation in reflux disease: workshop background, processes, terminology, recommendations, and discussion outputs. *Gut* 2004;53 Suppl 4:iv1-24.
15. Bardhan KD, Muller-Lissner S, Bigard MA, Bianchi Porro G, Ponce J, Hosie J, et al. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. The European Study Group. *Bmj* 1999;318(7182):502-7.
16. Moore J, Phillips C. Systematic review of PPI and H2A in GORD. *Bandolier - Evidence-based health-care* 1997;4(2):294-297.
17. Arnold R. Safety of proton pump inhibitors--an overview. *Aliment Pharmacol Ther* 1994;8 Suppl 1:65-70.
18. Reilly JP. Safety profile of the proton-pump inhibitors. *Am J Health Syst Pharm* 1999;56(23 Suppl 4):S11-7.
19. Tolman KG, Chandramouli J, Fang JC. Proton pump inhibitors in the treatment of gastro-oesophageal reflux disease. *Expert Opin Pharmacother* 2000;1(6):1171-94.
20. CARM. Omeprazole-induced interstitial nephritis

*Prescriber Update* 2000;20.

21. Coulter DM. Reactions to omeprazole obscured by aging process. *NZ Family Physician* 1998;25(3):18-20.
22. Ng CS. Interstitial nephritis associated with omeprazole. *Australian Prescriber* 2005;30(3):67.
23. Diav-Citrin O, Arnon J, Shechtman S, Schaefer C, van Tonningen MR, Clementi M, et al. The safety of proton pump inhibitors in pregnancy: a

multicentre prospective controlled study. *Aliment Pharmacol Ther* 2005;21(3):269-75.

24. Kallen BA. Use of omeprazole during pregnancy--no hazard demonstrated in 955 infants exposed during pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2001;96(1):63-8.
25. Nava-Ocampo AA, Velazquez-Armenta EY, Han JY, Koren G. Use of proton pump inhibitors during pregnancy and breastfeeding. *Can Fam Physician* 2006;52:853-4.
26. Nikfar S, Abdollahi M, Moretti ME, Magee LA, Koren G. Use of proton pump inhibitors during pregnancy and rates of major malformations: a meta-analysis. *Dig Dis Sci* 2002;47(7):1526-9.
27. Richter JE. Review article: the management of heartburn in pregnancy. *Aliment Pharmacol Ther* 2005;22(9):749-57.
28. Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Wallander MA, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol* 1999;150(5):476-81.
29. IMS. Medical Index.December 2002-2003.
30. Pharmac. Pharmac Annual Review. 2006.
31. Pharmac. Pharmac Annual Review. 2005.
32. Pharmac. Pharmac Annual Review. 2004.
33. The medical management of gastro-oesophageal refulx. *Drug & Therapeutics Bulletin* 1996;34:1.1-1.3.
34. Klinkenberg-Knol EC, Festen HP, Meuwissen SG. Pharmacological management of gastro-oesophageal reflux disease. *Drugs* 1995;49(5):695-710.
35. Oster G, Huse DM, Delea TE, Colditz GA, Richter JM. The risks and benefits of an Rx-to-OTC switch. The case of over-the-counter H2-blockers. *Med Care* 1990;28(9):834-52.
36. Scotcher S, Sikora K, Freedman L. Gastric cancer and cimetidine: does delay in diagnosis matter? *Lancet* 1981;2(8247):630-1.
37. Murdock RH, Pappa KA, Geifer EE. Endoscopic findings in a target population for over-the-counter treatment of heartburn. *Gastroenterology* 1994;106(No. 4 pt 2):A146.

38. FDA. Final minutes of the Joint Meeting of the Nonprescription Drugs & Gastrointestinal Advisory Committees. Food and Drug Administration. Center for Drug Evaluation and Research, 2000.
39. Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. *Clin Ther* 2001;23(7):998-1017.
40. Jaruratanasirikul S, Sriwiriyajan S. Effect of omeprazole on the pharmacokinetics of itraconazole. *Eur J Clin Pharmacol* 1998;54(2):159-61.
41. Unge P, Svedberg LE, Nordgren A, Blom H, Andersson T, Lagerstrom PO, et al. A study of the interaction of omeprazole and warfarin in anticoagulated patients. *Br J Clin Pharmacol* 1992;34(6):509-12.
42. Bate CM, Riley SA, Chapman RW, Durnin AT, Taylor MD. Evaluation of omeprazole as a cost-effective diagnostic test for gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1999;13(1):59-66.
43. Rost KL, Fuhr U, Thomsen T, Zaigler M, Brockmoller J, Bohnemeier H, et al. Omeprazole weakly inhibits CYP1A2 activity in man. *Int J Clin Pharmacol Ther* 1999;37(11):567-74.
44. Klinkenberg-Knol EC, Nelis F, Dent J, Snel P, Mitchell B, Prichard P, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 2000;118(4):661-9.

## Appendix 1: Proposed packaging label