Bayer HealthCare
Consumer Care

Proposal for Reclassification

of

Losec®
Tablets

Omeprazole 10 mg

to

Pharmacy Medicine

July 2010

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PART A

The current classification of the medicine omeprazole in New Zealand is:-

Restricted
In tablets or capsules containing 20 milligrams or less when sold in a pack approved by the Minister or the Director-General for distribution as a restricted medicine.

Prescription
Except when specified elsewhere in this schedule.

This submission to the Medicines Classification Committee proposes changing this current classification to:-

Pharmacy Only
In tablets or capsules containing 10 milligrams or less when sold in a pack approved by the Minister or the Director-General for distribution as a pharmacy only medicine.

Restricted
In tablets or capsules containing 20 milligrams or less when sold in a pack approved by the Minister or the Director-General for distribution as a restricted medicine, ***except in tablets or capsules containing 10 mg or less which have received consent of the Minister or Director-General of Health to their distribution as pharmacy only medicines.***

Prescription
Except when specified elsewhere in this schedule.

Reclassification of Losec 10 mg tablets to Pharmacy Medicine is considered safe and appropriate in New Zealand for the following reasons:-

Improved consumer choice of effective treatments - the availability of omeprazole 10 mg as a Pharmacy Medicine will improve the choice of effective treatments available to consumers for self-selection.

Safety Profile/Toxicity – omeprazole has an excellent safety record, with few serious or frequent side-effects or medicinal interactions.

New Zealand Precedent – treatment of reflux/heartburn is already well established in New Zealand as being suitable for consumer self-selection of treatment options.

International Precedents – in the last decade omeprazole has been reclassified to an over-the-counter medicine (effectively at Pharmacy Medicine level) in many countries, without subsequent adverse events of any consequence.

Encourage Selfcare – reclassification of omeprazole 10 mg to Pharmacy Medicine would empower patients to further address their health care needs for reflux/heartburn treatments.

Consumer Convenience/Accessability – omeprazole at the lowest strength is suitable to be added to range of products that can be self-selected in pharmacy, offering consumers the opportunity to consider and compare at the point of purchase.

A1. Name of the Medicine

The International Non-Proprietary Name of the medicine is omeprazole.

The proprietary or brand name of the product is Losec®.

This application is specifically related to the tablets dosage form, containing omeprazole magnesium.

A2. Name of the Company

This submission is made by:-

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Brand Manager – Losec

Bayer Consumer Care currently markets Losec tablets 10 mg as a Pharmacist Only Medicine in New Zealand.

A3. Dose Forms, Strengths and Pack Sizes

As stated above, the current classification of omeprazole is:-

> Restricted
> In tablets or capsules containing 20 milligrams or less when sold in a pack approved by the Minister or the Director-General for distribution as a restricted medicine.
>
> Prescription
> Except when specified elsewhere in this schedule.

In order to gain approval from the Minister or Director-General for distribution as a restricted medicine, Medsafe have provided the following guidelines:-

"Omeprazole may be sold as a **Restricted Medicine** when the following conditions apply:

Strength: Not more than 20 mg in each dose unit.

Pack size:	Not more than 14 dose units.
Indications:	Short-term, symptomatic relief of gastric reflux-like symptoms in sufferers aged 18 years and over.
Dosage:	Maximum daily dose of not more than 20 mg and should be reduced to 10 mg once symptomatic relief has been attained.
Warning statements:	For short-term use only, except on medical advice. Do not use the medicine for any purpose other than that specified on the pack, except on medical advice. Do not use if you are experiencing weight loss, persistent regurgitation of food or vomiting, difficulty swallowing or symptoms of gastro-intestinal bleeding, except on medical advice. Consult a doctor if symptoms persist, recur or worsen or if new symptoms occur. Consult a doctor or pharmacist before use if you are pregnant or are taking any other medicines. Do not take for more than 14 days; consult a doctor if symptoms persist.
Note:	The package insert should include all interactions specified on the data sheet.

Bayer considers these requirements reasonable and appropriate for omeprazole, and that they apply equally well to omeprazole 10 mg tablets as a Pharmacy Only Medicine.

Therefore, in terms of dose form, strength and pack size, it is proposed that tablets or capsules of omeprazole 10 mg be reclassified from Restricted Medicine to Pharmacy Medicine with pack size limited to 14 tablets for this category.

A4. Indications

Medsafe have stipulated, in accordance with previous recommendations from the Medicines Classification Committee, that the appropriate indication for omeprazole as a Restricted Medicine, is:-

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

This indication is considered reasonable and appropriate for omeprazole as an over-the-counter medicine, and the same indication is proposed for omeprazole 10 mg tablets as a Pharmacy Medicine.

A4.1 Dosage Recommendation

The current dosage instructions on the carton label for Losec 10 mg tablets approved by Medsafe (see Appendix One) are:-

> Take 2 tablets once daily until symptoms improve, then reduce the dose to 1 tablet once daily. If symptoms return, the dose may be increased to 2 tablets once daily.
>
> Use the lowest dose that controls your symptoms.

This same dosage recommendation is proposed for Losec 10 mg tablets as a Pharmacy Medicine.

A5. Classification

The current classification of omeprazole, taken from the Medsafe Web site on 12 July 2010, is:-

Omeprazole, except when specified elsewhere in this Schedule	Prescription
Omeprazole; in tablets or capsules containing 20 mg or less and when sold in packs approved by the Minister or the Director-General for distribution as Restricted Medicines	Restricted

The classification sought for omeprazole is:-

Omeprazole, except when specified elsewhere in this Schedule	***Prescription***
Omeprazole; in tablets or capsules containing 20 mg or less and when sold in packs approved by the Minister or the Director-General for distribution as Restricted Medicines, except in tablets or capsules containing 10 mg or less which have received consent of the Minister or Director-General of Health to their distribution as pharmacy only medicines.	***Restricted***
Omeprazole; in tablets or capsules containing 10 mg or less and when sold in packs approved by the Minister or the Director-General for distribution as Pharmacy Only Medicines	***Pharmacy Only***

Essentially, this submission supports and embraces all of the current restrictions for the non-prescription sale of omeprazole, the only change being that the 10 mg strength of the medicine be reclassified to Pharmacy Medicine.

A5.1 Classification Status in Other Countries

Over the last decade there has been a world-wide trend towards removing restrictions on the sale of proton pump inhibitor medicines, in recognition of their favourable efficacy and safety profiles. The table below lists the movement of omeprazole from prescription medicine to OTC medicine in various countries, and provides information on the nature of the OTC status in countries of interest i.e. those with regulatory agencies that Medsafe considers recognisable.

Switch Status of Omeprazole Oral Presentations

Country	Current Classification	Year of Switch from Prescription
Sweden	Omeprazole 10 mg, 20 mg – classification equivalent to Pharmacy Only Medicine	April 2000
United States of America	Omeprazole 20 mg – classification equivalent to General Sales Medicine (available in all stores, with or without pharmacist presence)	June 2003
Mexico	Omeprazole 10 mg, 20 mg – classification equivalent to General Sales Medicine	June 2003
United Kingdom	Omeprazole 10 mg – classification equivalent to Pharmacy Only Medicine Medicine i.e the medicine is available in pharmacies, and the customer can purchase from any employee. A pharmacist must be present/available, but pharmacist involvement in the sale process is not required.	January 2004
China	Omeprazole 10 mg	December 2004
Argentina		2005
Croatia	Omeprazole 10 mg	March 2005
Norway	Omeprazole 10 mg	May 2006
Denmark	Omeprazole 10 mg	December 2006
Estonia, Latvia, Lithuania, Czech republic	Omeprazole 10 mg	2007
Portugal	Omeprazole 10 mg	2008

Netherlands	Omeprazole 10 mg – classification equivalent to Pharmacy Only Medicine Medicine i.e the medicine is available in drug stores and pharmacies, and the customer can purchase from any employee of these businesses. A pharmacist must be present/available, but pharmacist involvement in the sale process is not required.	2008
Germany	Omeprazole 20 mg - classification equivalent to Pharmacy Only Medicine i.e the medicine is available in drug stores and pharmacies, and the customer can purchase from any employee of these businesses. A pharmacist must be present/available, but pharmacist involvement in the sale process is not required.	August 2009
Poland	Omeprazole 10 mg	2009
France	Omeprazole 20 mg - classification equivalent to Pharmacy Only Medicine i.e the medicine is available in drug stores and pharmacies, and the customer can purchase from any employee of these businesses. A pharmacist must be present/available, but pharmacist involvement in the sale process is not required.	May 2010
Australia	Omeprazole 20 mg – S3 (equivalent to Pharmacist Only or Restricted Medicine)	Recommended by NDPSC Feb 2010 meeting. To be effected 1 September 2010.

Table adapted from AESGP/WSMI publications http://www.aesgp.be status 19 December 2008 and data on file.

Cleary, since 1990, there has been a world-wide trend towards reducing restriction on the availability of omeprazole. Apart from Australia and New Zealand, this trend has embraced an OTC classification that does not require the direct involvement of a pharmacist in each and every sale i.e. in most countries omeprazole has an OTC status equivalent to Pharmacy Medicine or less.

Furthermore, many markets have several years of experience with omeprazole as an OTC medicine. Of particular note are the United States with 7 years experience and the United Kingdom with 6 years. Neither of these two populous countries have reported concerns with the OTC availability of omeprazole, effectively as a Pharmacy Medicine, demonstrating that consumers can safely and effectively self-select omeprazole for the treatment of reflux-like symptoms without the direct intervention of a pharmacist at every purchase occasion. The presence/availability of a pharmacist is sufficient to ensure appropriate consumer use and safety for this medicine.

A6. Extent of Usage

Due to the entry of generic omeprazole presentations into the New Zealand market in recent years, the extent of usage (particularly of different omeprazole products) is difficult to assess. As such, figures quoted below are from 2007 but are considered to be a fair reflection of the current situation.

Losec 20 mg capsules were approved for distribution in New Zealand on 27 April 1990 and have been available to New Zealand patients since December 1990. The product line was extended in 1997 to include a 10 mg strength and a 40 mg strength, and again in 2001 with the approval of the Losec MUPS tablets.

During 2007, 3.051 million units of omeprazole were sold in the New Zealand prescription market. Each unit is a 30 day regimen of 1 capsule per day. To date (2010) more than 970 million oral treatment courses have been provided worldwide by AstraZeneca. Patient exposure is therefore significant and the safety and efficacy profile is well understood.

Prilosec (omeprazole) OTC was first approved for marketing in the United States on 20 June 2003 for the treatment of frequent heartburn in patients aged 18 years and older. From its introduction as an OTC product until 2007, around 144.7 million courses of treatment have been sold, each course being a 14 day regimen of 1 tablet per day. As with the prescription market, patient exposure to omeprazole as an OTC medicine is significant.

In New Zealand, Losec 10 mg tablets have been marketed as a Pharmacist Only Medicine since August 2009, and in that time 46,000 packs have been sold. Since launch, Bayer New Zealand Limited has been notified of only one adverse event (constipation) associated with Losec purchased over-the-counter. This reporting reinforces the very good safety profile of omeprazole, already known for the product as a prescription medicine in New Zealand and as an OTC product in other countries. It strongly suggests that availability of the product over-the-counter in New Zealand has not led to an increased incidence of adverse events associated with the product.

A7. Labelling

See Appendix One for the currently approved labelling (14 tablet pack) for Losec 10 mg tablets. These labels meet all of the requirements of the Medicines Classification Committee for omeprazole 10 mg as a Pharmacist Only Medicine, and were approved by Medsafe on 3 April 2009.

Virtually identical packs are envisaged for Losec 10 mg packs as a Pharmacy Medicine, apart from the necessary classification statement and one additional warning discussed below.

The pack insert would be a copy of the proposed Consumer Medicine Information, very similar to the current CMI as provided in Appendix Two.

A8. Proposed Warnings

In order to gain approval from the Minister or Director-General for distribution as a restricted medicine, Medsafe have provided the following guidelines:-

"Omeprazole may be sold as a **Restricted Medicine** when the following conditions apply:

Strength:	Not more than 20 mg in each dose unit.
Pack size:	Not more than 14 dose units.
Indications:	Short-term, symptomatic relief of gastric reflux-like symptoms in sufferers aged 18 years and over.
Dosage:	Maximum daily dose of not more than 20 mg and

	should be reduced to 10 mg once symptomatic relief has been attained.
Warning statements:	For short-term use only, except on medical advice. Do not use the medicine for any purpose other than that specified on the pack, except on medical advice. Do not use if you are experiencing weight loss, persistent regurgitation of food or vomiting, difficulty swallowing or symptoms of gastro-intestinal bleeding, except on medical advice. Consult a doctor if symptoms persist, recur or worsen or if new symptoms occur. Consult a doctor or pharmacist before use if you are pregnant or are taking any other medicines. Do not take for more than 14 days; consult a doctor if symptoms persist.
Note:	The package insert should include all interactions specified on the data sheet.

Bayer considers these requirements reasonable and appropriate for omeprazole, and that they apply would equally appropriately to omeprazole 10 mg tablets as a Pharmacy Only Medicine.

One additional warning for the outer carton is proposed:-

"Consult your doctor or a pharmacist before use if you are taking any other medication."

See Part B, Section 2 for the reasoning behind adding this warning to the outer carton. The warning is already present in the pack leaflet.

A9. Other Products

In addition to the Losec 10 mg tablets that are the subject of this submission, there are a number of other omeprazole products registered to be sold in the New Zealand market as restricted medicines at the time of this submission. These are:-

Brand Name	**Strength and Pack Size**	**Sponsor Company**
Losec	Tablets 20mg	Bayer New Zealand Limited
Dr. Reddy's Omeprazole Modified Release Capsule	Capsule 10 mg	Dr Reddy's New Zealand Limited
Dr. Reddy's Omeprazole Modified Release Capsule	Capsule 20 mg	Dr Reddy's New Zealand Limited
Omeflux Modified Release Capsule	Capsule 10 mg	Dr Reddy's New Zealand Limited

The two 10 mg capsule presentations above would be affected by the proposed reclassification of omeprazole 10 mg to Pharmacy Medicine.

PART B

This proposal to reclassify omeprazole 10 mg capsules or tablets to Pharmacy Medicine, including the restrictions as outlined in Part A, is based on and essentially similar to the current conditions for omeprazole 10 mg and 20 mg as Restricted Medicines. Reclassification of Losec 10 mg tablets Pharmacy Medicine offers:-

Improved Consumer Choice of Effective Treatments - some consumers have troublesome heartburn that is not adequately relieved by antacids, antacid / alginate mixtures or H_2-receptor antagonists. Omeprazole 10 mg as a Pharmacy Medicine will improve access to effective treatment, and will make available the recommended treatment for reflux and heartburn for self-selection.

Suitable Safety Profile – omeprazole has an excellent safety record, with few serious or frequent side-effects. Omeprazole's safety record is comparable to that of ranitidine, which is already available as a Pharmacy Medicine for similar indications.

Parity with Similar Treatments (New Zealand Precedent) – treatment of reflux/heartburn is already well established in New Zealand as being suitable for consumer self-selection of treatment options, with both ranitidine and a full range of antacids being available as pharmacy only or general sale medicines.

Parity with International Precedents – in the last decade omeprazole has been reclassified to an over-the-counter medicine in many countries, effectively sold as a Pharmacy Medicine. International experience to date has endorsed such classification, as the availability of omeprazole to consumers has been relatively incident-free. No regulators have reviewed the availability of omeprazole as an OTC medicine due to increased adverse events.

Encouragement for Selfcare – reclassification of omeprazole 10 mg to Pharmacy Medicine would empower patients to further address their health care needs for reflux/heartburn treatments.

Consumer Convenience – generally, consumers seeking a reflux/heartburn treatment can self-select a product from the shelf in a pharmacy or supermarket. Bayer wishes to add omeprazole to the range of products

that can be self-selected in pharmacy, offering consumer's the ability to consider and compare all options available at the point of purchase, and potentially reducing cost and the influence of irrelevant factors such a pharmacy personnel dynamics. Increased consumer involvement in product choice is like to encourage compliance.

Many of the usual considerations taken into account for reclassification of a medicine, such as the suitability of the indication, ease of self-diagnosis, possibility of resistance, etc. have already been resolved for omeprazole and so are not discussed further in this submission.

Reclassification of Losec 10 mg tablets to Pharmacy Medicine has the potential to offer consumers improved choice and convenience with little increase in the risk of unwanted side effects, medicinal interactions or masking of serious disease. It would offer consumers the opportunity to directly access best practice medication for the treatment of reflux and heartburn.

Risk to benefit analysis favours the proposed reclassification.

1. Efficacy of Losec 10 mg Tablets

The efficacy of omeprazole has been studied extensively, and reported to the Medicines Classification Committee in previous submissions. The efficacy of the compound is without question. As such, a summary is considered sufficient for the purposes of this submission.

A recent (2006) meta-analysis conducted by the Cochrane Collaboration[1] summarised the results of 31 randomised controlled trials focussing on the symptomatic outcome after short-term treatment for Gastro-Oesophageal Reflux Disease (GORD) using proton pump inhibitors, H_2-receptor antagonists or prokinetic agents. The studies in the meta-analysis were those where the participants could be classed in the empirical treatment group (no endoscopy

used in treatment allocation) or in the endoscopy negative reflux disease group (ENRD, no endoscopic signs of erosive oesophagitis). Thirty-one trials (9457 participants) were included: fifteen in the empirical treatment group, twelve in the ENRD group and four in both. In empirical treatment of GORD, the relative risk (RR) for heartburn remission (the primary efficacy variable) in placebo-controlled trials for proton pump inhibitors was 0.37 (two trials, 95% confidence interval (CI) 0.32 to 0.44), for H_2-antagonists 0.77 (two trials, 95% CI 0.60 to 0.99) and for prokinetics 0.86 (one trial, 95% CI 0.73 to 1.01).

In a direct comparison proton pump inhibitors were more effective than H_2-antagonists (seven trials, RR 0.66, 95% CI 0.60 to 0.73) and prokinetics (two trials, RR 0.53, 95% CI 0.32 to 0.87). According to this data, proton pump inhibitors are more effective than H_2-antagonists in relieving heartburn in patients with GORD who are treated empirically. Analysis confirmed that this was also true for those with ENRD, although the magnitude of benefit is greater for those treated empirically.

The current United Kingdom NHS Clinical Knowledge Summary (CKS, formerly Prodigy guideline)[2] and NICE guidelines[3] for dyspepsia now recommend that empirical treatment with a proton pump inhibitor should be the first line treatment in patients with typical dyspepsia without alarm symptoms. When symptoms resolve, the lowest dose should be used to maintain patients symptom free. The New Zealand Guidelines Group Best Practice Guidelines default to those of the British Medical Journal as recommended in the United Kingdom. This recommendation is also reflected in the New Zealand Guidelines Group – Management of Dyspepsia and Heartburn[4]. Thus, the recommendation above applies equally in New Zealand. The availability of omeprazole 10 mg as a Pharmacy Medicine will allow consumers convenient direct access to the recognized best, recommended first-line treatment for heartburn and reflux.

2. Safety Profile

Omeprazole has a broad therapeutic window and the safety profile for the approved over-the-counter indications is both well established and satisfactory. The safety and tolerability of omeprazole when self-administered is demonstrated by its record of safe use in the pharmacy environment, both in New Zealand and in many other countries since 2003[5].

2.1 Ability to Mask Serious Disease

In the event that there is incorrect self-diagnosis, the patient would not unduly aggravate the condition as the label instructs the patient to seek medical advice if symptoms persist for more than 14 days. This reflects a balance between dosing for long enough to achieve an effect and avoiding the risk of masking or delaying diagnosis and treatment of a more serious condition. This balance has already been accepted by MCC for omeprazole 10 mg and 20 mg as a Pharmacist Only Medicine, and is considered to apply equally well to the proposed Pharmacy Medicine classification.

2.2 Potential for Misuse or Abuse

Misuse has not been observed with omeprazole during more than 20 years of sale and supply[6]. Furthermore, omeprazole has no psychotropic or narcotic characteristics. There are no reports of abusive use of omeprazole as an addictive substance or intoxicant. This very low potential for misuse or abuse has already been recognized for omeprazole in New Zealand, and applies equally well to the proposed Pharmacy Medicine classification.

2.3 Adverse Effects

According to several comparative studies, the profile of adverse effects during short-term omeprazole therapy (for between 2 and 12 weeks) does not differ significantly from H_2-antagonists or from placebo regarding either severity or frequency[6,7].

Adverse events (AEs) that may occur with use of 10 mg or 20 mg omeprazole as a single daily dose are mainly mild and reversible. More serious reactions occur rarely or very rarely. The most common adverse events involve the gastrointestinal tract (such as abdominal pain, diarrhoea, constipation, flatulence, nausea and vomiting) or appear as non-specific symptoms such as headache. The occurrence of adverse reactions does not show any dose-dependent increase. Dose adaptation is not required with daily doses of up to 20 mg in patients with diminished liver function.

Interstitial nephritis is a very rare, but serious, side effect of omeprazole. The current pack insert for Losec has the following warning statement:-

See your doctor if:

- **you experience fever, nausea, a generally unwell feeling, tiredness, blood in the urine or weight loss. These are symptoms of interstitial nephritis, a rare side effect of omeprazole.**

With several years of international OTC experience with omeprazole, interstitial nephritis has not emerged as a cause for concern, sufficient to consider up-scheduling, in any market. Nonetheless, this warning would be retained in the pack insert for Losec 10 mg as a Pharmacy Medicine.

2.4 Medicinal Interactions

Although the absorption of some medicines might be altered due to decreased intragastric acidity caused by omeprazole, clinically relevant adverse drug reactions (ADRs) based on interactions have seldom been observed with omeprazole. Of especial importance, there are no reports of interactions between omeprazole and other substances used for self-medication, such as antacids or analgesics.

Dose adjustment may be required for some prescription medicines, when combined with omeprazole, in some circumstances. In such cases, however, the patient and the drug therapy is already being monitored by a physician. All relevant interactions are listed in the patient information leaflet, and patients who are taking these medications will be advised they should first consult with either their pharmacist or doctor before taking omeprazole.

The potential for drug/drug interactions with omeprazole may be grouped as follows:

1. *Based on gastric pH effects:* The higher stomach pH with omeprazole treatment may interfere with the absorption of some drugs (nelfinavir, atazanavir, ketoconazole, itraconazole) while potentially increasing the bioavailability of others (e.g. digoxin).

2. *Based on metabolic effects:* Omeprazole is, to a major extent, metabolised in the liver via the cytochrome P450 isoenzyme CYP2C19. It is also, in therapeutic doses, an inhibitor of CYP2C19 and therefore has the potential to interact with drugs handled by the same enzyme systems:
    - Omeprazole may delay the elimination of certain drugs and increase their plasma levels (e.g. digoxin, R-warfarin, other Vitamin K antagonists, diazepam, phenytoin)

- Omeprazole may decrease the efficacy of some drugs that serve as prodrugs and are activated by the CYP 2C19 system (e.g. clopidogrel).
- Some drugs may increase levels of omeprazole through inhibition of CYP2C19 or CYP 3A4 (clarithomycin, voriconazole)
- Drugs that induce liver enzymes may decrease levels of omeprazole (rifampicin)

3. Unknown mechanisms (tacrolimus, saquinavir plasma levels may be increased when co-administered with omeprazole).

Empirically, interactions that increase or decrease plasma levels of omeprazole are unlikely to produce adverse events due to direct toxicity. Omeprazole may compromise the efficacy of some co-administered drugs by interference with absorption or through effects on metabolism. Interactions that raise the levels of co-administered drugs have been the focus of particular attention in surveys of prescription use, and data presented to the FDA confirms that such interactions are reassuringly rare.

A summary of adverse events and drug interactions occurring during therapy with proton pump inhibitors – which were reported to the Food and Drug Administration – was published by Labenz and co-workers[8] in 2003. The study involved a search of the Food and Drug Administration's database for adverse events and drug interactions with omeprazole, lansoprazole or pantoprazole as the primary or secondary suspect drug. An estimate of the amount of drug dispensed during the adverse event collection period (from US drug launch) was obtained from the International Medical Statistics health database. Of the suspected drug interactions recorded, vitamin K antagonist interactions, although rare, were the most common. The frequency of vitamin K antagonist interactions was 0.09 per million packages for omeprazole and 0.11 per million packages for lansoprazole and pantoprazole respectively. Interactions with benzodiazepines or phenytoin were even rarer, being reported in less than 10 patients treated with each proton pump inhibitor.

Clearly, the incidence of drug interactions over all dosage regimes (including prescription) is exceptionally low, and is likely to be lower for the low-dose short-term therapy associated with over-the-counter use of omeprazole. Nonetheless, the following statement is suggested as an additional warning statement on the outer packaging (carton) principally to ensure appropriate safeguards are in place for supply as a Pharmacy Medicine:

"Consult your doctor or a pharmacist before use if you are taking any other medication."

3. New Zealand Precedent

Treatment of reflux and heartburn is well-established in New Zealand as being suitable for consumer self-care. A large range of antacids and antacid/alginate mixtures have been available as general sales medicines for many years. Over the last decade more effective medicines such as H_2 antagonists and proton pump inhibitors have become available over the counter as pharmacist only or pharmacy medicines.

When considering reclassification of omeprazole 10 mg to Pharmacy Medicine, the most appropriate compound for comparison is ranitidine, which is indicated for the same symptoms and has been the subject of progressive down-scheduling in New Zealand.

The current classification of ranitidine in New Zealand is:-

Ranitidine, except when specified elsewhere in this schedule; except in medicines containing 150 milligrams or less per dose unit which have received the consent of the Minister or the Director-General to their distribution as general sale medicines and which are sold in the manufacturer's original pack containing not more than 7 days' supply	***Prescription***
Ranitidine; in medicines which have received the consent of the Minister or the Director-General to their distribution as pharmacy-only medicines and which are sold in the manufacturer's original pack containing not more than 14 days' supply; except in medicines containing 150 milligrams or less per dose unit which have received the consent of the Minister or the Director-General to their distribution as general sale medicines and which are sold in the manufacturer's original pack containing not more than 7 days' supply	***Pharmacy Only***
Ranitidine; in medicines containing 150 mg or less per dose unit which have received the consent of the Minister or the Director-General to their distribution as general sale medicines and which are sold in the manufacturer's original pack containing not more than 7 days' supply	***General Sales***

The Medicines Classification Committee recommended that ranitidine be reclassified from restricted medicine to pharmacy-only medicine when it fulfilled the requirements for sale as an OTC medicine as specified in Volume 1 of the New Zealand Regulatory Guidelines for Medicines at its 23rd meeting on 25 May 2000. Ranitidine was again considered by the Committee at the 37th meeting on 14 December 2007, the outcome being a recommendation that ranitidine should become a general sale medicine when in packs containing 7 days' supply or less and in tablets or capsules containing not more than 150 milligrams.

The Medsafe conditions for ranitidine to be sold as a pharmacy or general sales Medicine are:-

Pack size	Not more than 14 days' supply when used at the recommended dose (7 days for GSL).
Indications	Symptomatic relief of heartburn, dyspepsia and hyperacidity OR on the recommendation of a medical practitioner.
Warning statements[1]	Do not use the medicine for any purpose other than that specified on the pack unless under the supervision of a doctor. Consult a doctor if symptoms persist, recur or worsen. Consult a doctor if new or additional symptoms occur. Do not use with non-steroidal anti-inflammatory medicines unless under the supervision of a doctor. Use with caution if over 40 years of age.

1 This information may be presented as words of similar meaning, and may be present on either the label or the package insert. Where the information is included in the package insert, the label should include a statement such as:

Read the enclosed package insert before starting to use this product.

Generally the Pharmacy Medicine strength is 300 mg ranitidine per dose form.

New Zealand has almost 10 years' experience with ranitidine for the treatment of heartburn and dyspepsia as a Pharmacy Medicine, and three years' experience as a general sales medicine for the lower strength. From 2000, consumers have demonstrated themselves well able to self-diagnose and treat these conditions safely and effectively without the input of a pharmacist at every sale, to the point where the Medicines Classification Committee was willing to entirely remove the input of a pharmacist in some instances seven years later.

Omeprazole (up to 20 mg per day) compares well with rantidine 150 mg or 300 mg in terms of efficacy and safety. In a 4-week comparison[11], omeprazole was more effective than ranitidine at 150 mg twice daily. On treatment with omeprazole, patients described a statistically significantly more marked decrease in symptoms, irrespective of dosage. Sixty-one percent and 49% of patients were asymptomatic on treatment with omeprazole 20 mg and 10 mg, respectively, compared to 40% on ranitidine at high dosage. Before treatment 61%, 62% and 58% of patients described their heartburn as moderate and 9%, 13% and 13% as severe; after treatment with omeprazole 20 mg and 10 mg or ranitidine the proportions were only 10%, 13% and 18% (moderate) and 1%, 2% and 2% (severe).

During intermittent treatment over a 12-month period, omeprazole 20 mg and 10 mg daily were again superior to ranitidine 150 mg twice daily, 55% and 40% of patients achieving freedom from symptoms after only 2 weeks, compared to 26% on ranitidine[12]. The further course of follow-up did not differ between the treatment groups. Half of all singly treated patients remained symptom-free in the follow-up period, regardless of the chosen medication. On the other hand, 27% of patients on ranitidine and 22% on omeprazole required long-term treatment with a PPI to achieve freedom from symptoms. Patients already asymptomatic after 2 rather than 4 weeks were less likely to require further treatment. Adequate symptom control after a 14-day course – the maximum treatment duration claimed in the present application for OTC use – was therefore rated as a strong prognostic factor for treatment success.

Superior improvement in quality of life for patients with heartburn and acid-related symptoms has also been demonstrated in comparison with ranitidine. After 14 days of use in patients with moderate or severe heartburn, omeprazole, at dosages of both 20 mg and 10 mg daily, was able to improve quality of life, as measured by the Psychological General Well-Being (PGWB) index, to a significantly greater extent than ranitidine 150 mg twice daily[13]. Similar results were obtained by Festen et al[14]., who used the surrogate parameter Gastrointestinal Symptom Rating Scale (GSRS) to study the effect on quality of life. Compared to ranitidine 300 mg twice daily, quality of life again improved to a significantly greater extent on omeprazole 20 mg once daily.

Armstrong et al.[15] showed in 2005 that the mean time to complete symptom relief was only 3 days on omeprazole 20 mg, but 8 days on treatment with ranitidine at a dosage of 150 mg twice daily. The distinct time advantage is attributable to the sustained effect of omeprazole on heartburn (> 24 hours) and to the resultant non-recurrence of symptoms within this period. This is particularly true after omeprazole reaches its maximum pharmacological efficacy after 3 to 5 days. This example clearly shows how important sustainability of effect and the associated duration of freedom from symptoms are in assessing efficacy.

This is of particular interest in the OTC field because marked reduction of acid suppression, consistent with habituation, has been observed during repeated administration of H_2-antagonsists for 14 days. pH metry in healthy volunteers showed comparable effects on acid suppression after the first dose of omeprazole 40 mg and ranitidine 300 mg. On repeated administration of omeprazole the acid-reducing effect increased to a maximum and thereafter remained consistently high throughout the 14-day treatment period. On ranitidine 300 mg, however, only half the initial effect was observable on days 7 and 14[16]. This explains the patient dissatisfaction reported after prolonged treatment with H_2-antagonsists.

These results demonstrate the superior efficacy, both immediate and sustained, of omeprazole compared to ranitidtine. Proton pump inhibitors are recognized as "best practice" first-line treatment of reflux and heartburn without alarm symptoms, and therefore omeprazole should be available to consumers on the same basis as other treatments such as ranitidine, unless there are compelling reasons for not doing so.

Omeprazole and H_2-antagonsists have similar tolerability profiles during short-term use. A review article summarises data on more than 19,000 patients from clinical studies, most of them comparative studies with ranitidine. The side effects of omeprazole and H_2-antagonsists occurred at incidences of the same order of magnitude and displayed similar profiles. During short-term omeprazole use, the analysis likewise showed no differences in the severity and nature of symptoms compared to the side effects of placebo[17,18]. Similar results emerged from a meta-analysis of 1057 patients conducted by Bamberg et al.[19]. The very similar side effect profiles of omeprazole and ranitidine suggest these two medicines merit the same classification.

At therapeutic doses, ranitidine has little or no influence on the effect of drugs activated by the hepatic cytochrome P450-dependent mono-oxygenase system (e.g. diazepam, warfarin, propranolol). As with omeprazole, however, interactions such as elevated plasma levels of phenytoin or an increase in the bioavailability of midazolam have been reported with ranitidine in isolated cases[20]. By raising intragastric pH, H_2-antagonsists – like proton pump inhibitors – can modify the uptake of drugs, such as itraconazole, ketoconazole or quinolones, whose absorption depends on gastric acidity. With ranitidine, unlike omeprazole, dose adjustment may be required in renal impairment as the daily dose is recommended not to exceed 150 mg in patients with severe renal impairment. Close monitoring of prothrombin time is recommended for concurrent treatment with ranitidine and warfarin (Zantac Data Sheet) – an interaction between omeprazole and warfarin is also recognized, although a need for close monitoring is not perceived (Losec tablets Data Sheet).

Omeprazole interacts with antiretrovirals and concomitant use is not recommended. However, patients on antiretroviral drugs are under the care of a specialist physician and likely to be intensively monitored.

Omeprazole and ranitidine appear relatively similar in terms of medicine-medicine interactions. Of prime importance is that neither medicine interacts with other over-the-counter medicines, and so a medicinal interaction occurring in a patient not under medical supervision is highly unlikely. Both medicines exhibit some interaction with prescription medicines, but these are relatively rare and although sometimes different are of similar severity. The most prescribed prescription medicine affected appears be warfarin (as demonstrated in the USA, see section 2.4) and both omeprazole and ranitidine are affected.

The following statement is suggested to appear on the outer packaging (carton), principally to ensure appropriate safeguards are in place for supply as a Pharmacy Medicine:

"Consult your doctor or a pharmacist before use if you are taking any other medication."

Both omeprazole and ranitidine can be used in pregnancy, and both products tend to take a conservative approach for over-the-counter availability, recommending that the advice of a doctor be taken before using the product during pregnancy or breastfeeding.

Omeprazole is characterised by marked overall superiority to H_2-antagonsists during short-term use for the treatment of heartburn and acid-related symptoms dur to its greater efficacy, while being similarly well tolerated. Since patients experience any symptom recurrence that necessitates renewed medication as a clear quality of life deficit, the primary goal of improving quality of life can be achieved particularly well by taking a long-acting proton pump inhibitor such as omeprazole. While omeprazole appears to have a greater interaction potential than ranitidine, most of the interactions described are common to both medicines. Most of these are, moreover, purely pharmacokinetic in nature, with no particular clinical relevance. Caution with use during pregnancy and lactation is recommended for both medicines.

The discussion above demonstrates that omeprazole and ranitidine are relatively similar medicines – overall, omeprazole offers superior effectiveness but with slightly more interaction potential. On all other parameters the two medicines are equivalent. With ten years of experience with ranitidine as a Pharmacy Medicine, the Medicines Classification Committee can be certain that consumers successfully manage the use of such medicines. Omeprazole 10 mg or 20 mg per day is little different to ranitidine 300 mg per day, and so is just as suitable to be classified Pharmacy Medicine.

4. International Precedents

Please refer to Section A5.1 for a complete listing of the overseas classification status for omeprazole. It can be seen that in all major reference countries except Canada, omeprazole 10 mg or 20 mg has now been switched to an over-the-counter medicine. Furthermore, in all countries except Australia omeprazole 10 mg or 20 mg is equivalent to a classification in New Zealand of Pharmacy Medicine (or less restrictive).

All major European countries and the United States have assessed omeprazole as being suitable for consumer self-selection with pharmacist supervision, but not requiring pharmacist involvement in every sale. Such international confidence in this medicine suggests the same situation would be appropriate for the New Zealand public. A classification of Pharmacy Medicine for omeprazole 10 mg would offer New Zealander's convenient access to a recognized 'best practice' medicine for first line treatment of reflux and heartburn, as currently enjoyed by most of the developed world.

5. Encouraging Self-Care

Today there is a world-wide trend encouraging consumers towards self-care when possible, promoting personal responsibility for the symptomatic treatment of short-term conditions with an aim to reducing health care expenditure for both the consumer and the Government. Reclassification of omeprazole 10 mg to Pharmacy Medicine would empower patients to address their treatment needs for reflux or heartburn by making the "best practice" first-line treatment more readily available. The demonstrated superior efficacy of omeprazole, when compared to H_2-antagonists, promotes consumer satisfaction with the treatment and adds significantly to their quality of life.

While it is true that the consumer can currently access omeprazole 10 mg relatively readily as a Pharmacist Only Medicine, this classification does raise barriers to access in that pharmacist time is limited and there is significant information recording required. Furthermore, with a common and easily identified condition such as reflux or heartburn consumers more often than not have previous experience with their symptoms and know exactly what medicine is best for them – in such cases, pharmacist involvement in every sale is unnecessary.

Pharmacists are increasingly busy professionals. The nature of retail pharmacy has undergone a profound change in the last 10 - 15 years, with pharmacists increasingly providing healthcare advice and support to their customers. Reclassification of omeprazole 10 mg to Pharmacy Medicine offers the opportunity to save pharmacists' time by not requiring their input on every sales occasion, while they are still available for referral if pharmacy assistants perceive it is required.

In December 2006 a New Zealand-wide telephone survey of 200 pharmacy assistants was undertaken, all of whom had at least 2 years' experience and were responsible for the sale of OTC medicines. As an aside to this research, the number of pharmacy assistants with less than 2 years' experience was assessed and was found to be approximately 10% of all pharmacy assistants – thus, a relatively small number would be considered "inexperienced". All pharmacy assistants were female, and tended to be a relatively mature group, with 69% being over 30 years of age and a further 28% being 21 – 29 years. Three-quarters of the sample (75%) had 5 or more years' experience. A picture emerges of pharmacy assistants as being mature females, experienced and stable in their work.

Pharmacy assistants are already responsible for dealing with customers seeking a reflux or heartburn treatment due to the classification of ranitidine in this country. Adding omeprazole 10 mg to the range of products available for the treatment of reflux or heartburn at the Pharmacy Medicine level represents only an incremental level of change from pharmacy assistant's current responsibilities in this area. Already they are responsible for screening reflux/heartburn customers - identifying alarm signals, checking for inappropriate continuous or repetitive use, checking age appropriateness and the use of other medicines – when selling ranitidine. Clearly they have performed this function competently, referring to the supervising pharmacist when necessary, as no significant problems have emerged with ranitidine over the last decade.

In order to continue this success with Losec 10 mg, pharmacy assistants would need to refresh their training in this treatment area and become more vigilant in checking for alarm signals and concurrent use of other medicines. This mature and experienced group are well-placed to take on these additional responsibilities, and Bayer would put a training programme in place to assist with this process.

5.1 Bayer Training Programme

Losec 10 mg tablets were reclassified to Pharmacist Only Medicine early in 2009. As part of the launch of this newly-classified medicine, Bayer executed an

extensive pharmacist training programme in conjunction with the New Zealand College of Pharmacists. Five major conferences, four smaller conferences and an audio-conference were held, with over 1000 attendees in all. Pharmacists unable to attend these conferences were sent information packs and a DVD of the Wellington presentation. To illustrate the high quality of this training programme, please refer to the training information pack and DVD presentation that has been provided.

Recently (July 2010) Bayer conducted an informal survey of pharmacists the company calls on to gain a snap-shot of their current attitudes towards Losec[21]. Of the 223 pharmacists that responded, 78% felt confident recommending Losec to their customers and 68% felt confident recommending Losec as a repeat purchase. This indicates that pharmacists feel well-informed about Losec, confident that they can recommend the product appropriately as a first treatment and subsequently monitor and recommend appropriately for repeat customers. Clearly the Losec training programme and Bayer's subsequent communications have been effective.

Almost half of the responding pharmacists (48%) indicated that pharmacy assistants conduct an initial discussion with customers before referring them to the pharmacist for Losec, while 33% reported their pharmacy assistants refer customers directly to the pharmacist without discussion. While these answers are open to some interpretation, it is apparent that pharmacy assistants already play a considerable role with customers for Losec. When invited to make further comment, many pharmacists spontaneously suggested that more training of pharmacy assistants would be helpful, further indicating these employees' level of involvement with Losec and that pharmacists are comfortable with their assistants dealing with customers seeking treatment for reflux or heartburn.

Bayer plans further training for pharmacy assistants on Losec, and this initiative will be scaled up when Losec 10 mg is reclassified to Pharmacy Medicine.

6. Consumer Convenience/Accessability

The efficacy and safety of omeprazole in the treatment of reflux symptoms (heartburn and acid regurgitation) is well established. The 10 mg tablets offer the flexibility to take either two tablets (2 x 10 mg) or one tablet (10 mg), in order to maintain the treatment at the lowest possible effective dose. The 10 mg strength is the most appropriate presentation of omeprazole for reclassification to Pharmacy Medicine because:-

- It is the lowest strength of omeprazole available and so intuitively represents the safest option to offer to the consumer under pharmacist supervision (but without involvement of a pharmacist at every sale)

- It is the only strength that allows maintenance of treatment at the lowest possible dose i.e. offers the possibility of dosing at 10 mg per day.

In New Zealand omeprazole 10 mg has been available over-the-counter as a Pharmacist Only Medicine since 2009. However, in other countries it has been available, effectively as a Pharmacy Medicine, for much longer - in the UK, the 10 mg tablet form has been licensed Pharmacy ('P') at a dose of 10 – 20 mg since 2004. Wider availability in New Zealand, through reclassification to Pharmacy Medicine, would be convenient to the purchaser with respect to offering greater choice and improved efficacy in the treatment of common upper gastrointestinal symptoms.

The current package carton and leaflet clearly directs the purchaser to determine whether the product is suitable for their condition and to seek medical advice if symptoms persist. This would remain unchanged for Losec 10 mg as a Pharmacy Medicine.

Consumers have demonstrated themselves well able to use omeprazole safely and effectively. A German pharmacy-based observational study investigating the use of an antacid for self-medication in more than 4,000 patients demonstrated that the symptoms "heartburn and acid regurgitation" were responsibly managed. The patients used the study product correctly, i.e. in accordance with the indications and dosage instructions[22]. In a study by Fendrick et al.[9], patients with heartburn distinguished reliably between sporadic and frequent heartburn in selecting appropriate medication. Accordingly, patients' ability to identify their symptoms as heartburn and acid regurgitation is generally rated as excellent.

After the introduction of omeprazole as an over-the-counter product in the USA, an observational trial performed there demonstrated that 97% of patients taking omeprazole for heartburn followed the recommendations of the package insert and that 86% of patients not free from symptoms after 14 days consulted a physician for further diagnosis and therapy[9]. Only 5% of subjects continued to take omeprazole for more than two weeks, whereby 85% of them consulted a doctor. Self-medication beyond the prescribed period of two weeks without any medical supervision was observed in only 1% of patients. In the choice of omeprazole for treating dyspepsia, 81% of patients fulfilled all criteria for a correct selection of the substance; every single criteria was met by 90% to 100% of subjects. Only 9.5% of patients did not pay heed to contraindications (in the sense of primary symptoms requiring clarification) initially, and none of these

patients continued the dosage for more than two weeks. On the other hand, around 65% of patients went to see a doctor before, during or after taking the test medication. In the case of 10%, this was their first visit in connection with dyspepsia.

This "actual use" study demonstrates that the majority of patients who fail to respond to treatment consult a physician, who can then institute further diagnostic and therapeutic measures. The possible delay of at most 14 days is not clinically relevant for the subsequent course, with regard to either progression of the underlying condition or a delay in diagnosis caused by the patient's own perception of the "triviality" of symptoms. The information given in the package leaflet, as shown by Fendrick et al., can also raise patients' awareness of warning symptoms and thus prompt patients who might not otherwise have sought medical attention for their symptoms to consult a physician.

Clearly, especially when taking into account that in the USA little medical consultation and advice is available from drug store personnel, consumers can responsibly use omeprazole for self-medication without the direct involvement of a pharmacist for every sale. Furthermore, it appears that less restrictive availability of omeprazole has some potential to send patients that have not already done so to their doctors for advice.

Over-the-counter experience with omeprazole in the United Kingdom appears to have been similar. McCaig et al.[10] investigated early experiences with over the counter omeprazole, surveying pharmacists approximately 6 months after the product became available without prescription (essentially a Pharmacy Medicine). They found that only 3.5% of pharmacists had refused sales on the basis that omeprazole was inappropriate for the presenting condition or due to a potential drug interaction. Given the early switch in the United Kingdom (from an international perspective), and the short time between switch and the survey, this low rate of sales refusal appears likely to be a worst case scenario and suggests that inappropriate consumer selection of omeprazole is likely to be very low. It also indicates that under the Pharmacy Medicine sales model, with pharmacist supervision but not direct involvement in every sale, pharmacists and pharmacy staff can effectively identify and prevent inappropriate selection of omeprazole by consumers.

At the moment in New Zealand there are significant barriers to customer's access to omeprazole. It is almost always true in New Zealand pharmacies that a pharmacist is not available at the counter, and must be called by the pharmacy assistant if a Pharmacist Only Medicine is to be sold. However, pharmacy assistants are naturally reluctant to interrupt the pharmacist and will instead provide the customer with a Pharmacy or General Sales Medicine if they can. Bayer's market experience is that pharmacy assistants tend to recommend and sell ranitidine rather than refer to a pharmacist for Losec – thus, the customer is

denied access to the recommended best treatment for reflux and heartburn due to pharmacy personnel dynamics. Cost is a further barrier to consumers, as margins on Pharmacist Only Medicines tend to be higher due to the greater input required.

Overall the risk of misuseof omeprazole is low[6], and the product has a well-established safety profile in terms of patient exposure[5]. The significant post marketing experience available for omeprazole as a non-prescription medicine suggests that it can be safely used with healthcare professional supervision. World-wide clinical and post-marketing experience indicates that no additional safety concerns resulting from reclassification from Pharmacist Only to Pharmacy Medicine are to be expected. All of these considerations suggest that the current barriers to access for Losec 10 mg are not warranted, and the product should be classified equivalent to other comparable treatments such as ranitidine.

APPENDICES

Appendix One

Current labelling for Losec 10 mg (14 tablet pack) as a Pharmacist Only Medicine.

Appendix Two

Current Consumer Medicine Information for Losec 10 mg as a Pharmacist Only Medicine.

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Only key references have been supplied with this submission – these have been marked with a # in the list below. All other references are available on request.

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