Bayer HealthCare Consumer Care

Proposal for Reclassification

of

Losec®
MUPS Tablets
Omeprazole 20 mg

to

Pharmacist Only Medicine

July 2009

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PART A

At its 40th meeting in 2008 the Medicines Classification Committee recommended:-

> That tablets or capsules containing 10 milligrams or less of omeprazole should be reclassified from prescription medicine to restricted medicine when sold in packs which have received the consent of the Minister or the Director-General to their sale as restricted medicines and are sold in the manufacturer's original pack.

This recommendation, which included a maximum dosage per day of 20 mg omeprazole, was subsequently accepted, and effected by Gazette notice on 19 March 2009.

This submission to the New Zealand Medicines Classification Committee now proposes extension of this recommendation to:-

> That tablets or capsules containing ***20 milligrams or less*** of omeprazole should be reclassified from prescription medicine to restricted medicine when sold in packs which have received the consent of the Minister or the Director-General to their sale as restricted medicines and are sold in the manufacturer's original pack.

Bayer's reasons for proposing the reclassification of Losec 20 mg tablets are:-

Consumer convenience – for those consumers that require 20 mg per day, the availability of a 20 mg tablet will offer them the convenience of a one tablet dosage regime.

Consumer compliance – the dosage instructions for Losec 20 mg tablets are simpler and easier to understand than the current instructions for 10 mg. Thus, compliance with the dosage regime will be improved.

Cost effectiveness – for those consumers that require 20 mg per day, Losec 20 mg tablets will offer a more cost effective option that taking two Losec 10 mg tablets per day.

International precedence – the recent evaluation of and approval for reclassification of omeprazole 20 mg tablets to OTC in Germany represents a significant change in a large international market, recognised by Medsafe as having one of the leading regulatory agencies.

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 MUPS tablets dosage form, containing omeprazole magnesium.

A2. Name of the Company

This submission is made by:-

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Bayer Consumer Care has completed an international agreement with AstraZeneca regarding the marketing of omeprazole (Losec) as an over-the-counter medicine. The effect of this agreement in New Zealand is that Bayer New Zealand Limited, Consumer Care Business Group (hereafter referred to as Bayer) is responsible for any Losec 10 mg or 20 mg products classified as non-prescription medicines, and is responsible for all commercial and registration activities associated with these products.

Under this agreement Bayer is responsible for the labeling, distribution, marketing, selling and any other associated activities for Losec products entering the non-prescription market.

A3. Dose Forms, Strengths and Pack Sizes

As stated above, the MCC has previously recommended:-

> That tablets or capsules containing 10 milligrams or less of omeprazole should be reclassified from prescription medicine to restricted medicine when sold in packs which have received the consent of the Minister or the Director-General to their sale as restricted medicines and are sold in the manufacturer's original pack.

As part of this recommendation, restrictions were placed upon the strength of the dose units (to a maximum of 10 mg omeprazole), the dosage (doses should not exceed 20 milligrams and this should be reduced to 10 milligrams once symptomatic relief has been attained) and on the pack size (to a maximum of 14 dose units).

Bayer proposes that these restrictions should now be modified to:-

- dose units should not exceed 20 milligrams
- doses should not exceed 20 milligrams
- packs should not contain more than 14 dose units

The Medicines Classification Committee also recommended a number of labelling requirements for the 10 mg presentation – namely:-

> The indication should be the same as that required in the UK for OTC sale, that is, for the short-term, symptomatic relief of reflux-like symptoms in sufferers aged 18 years and over.
>
> The following should be required on the label
>
> - use should not be prolonged except on medical advice
> - the 4 main alarm symptoms as in the GORD guidelines:
>   - weight loss
>   - persistent regurgitation of food or vomiting
>   - dysphagia
>   - symptoms of GI bleeding

- an instruction to inform the pharmacist about use of other medicines (may be included on the package insert if there is insufficient space on the label)
- a statement instructing consumers to inform the pharmacist if pregnant (may be included on the package insert if there is insufficient space on the label)
- the interactions on the package insert should be the same as those on the data sheet.

These requirements are considered to apply equally to the 20 mg presentation and no changes are proposed.

Clearly, Bayer's proposal is a relatively modest change from the current restrictions controlling omeprazole as a Pharmacist Only Medicine – while the strength is proposed to increase, the maximum daily dose and pack size restrictions are unchanged.

A4. Indications

In terms of appropriate indications for omeprazole 10 mg as a Pharmacist Only Medicine, the Medicines Classification Committee recommended:-

> The indication should be the same as that required in the UK for OTC sale, that is, for the short-term relief of reflux-like symptoms in sufferers aged 18 years and over.

The indication statement approved by Medsafe for Losec tablets 10 mg sold as a Pharmacist Only Medicine in New Zealand has been expanded slightly to:-

> Losec tablets are for the short-term relief of reflux-like symptoms. These symptoms may include a burning feeling rising up from the stomach or chest (heartburn), or acid regurgitation.

See Attachment One for the currently approved Losec 10 mg labels. Further explanation of the indication was considered necessary to put the purpose of the medicine into language consumers are familiar with.

Losec 20 mg tablets as a Pharmacist Only Medicine are proposed to have the same application as the 10 mg presentation, and the indication statement above is considered equally appropriate for the higher strength.

A4.1 Dosage Recommendation

The current dosage instructions on the carton label for Losec 10 mg tablets approved by Medsafe 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.

The proposed instructions on the carton label for Losec tablets 20 mg would be:-

> Take 1 tablet once daily.

The dosage wording on the current approved data sheet is slightly different – viz:-

> 20 mg (2 tablets) once daily until symptoms improve, then reduce the dose to 10 mg (1 tablet) once daily. If symptoms return the dose may be increased to 2 tablets once daily.
>
> The lowest dose that controls symptoms should be used.

See Attachment Two for the proposed data sheet and Attachment Three for the proposed Consumer Medicine Information covering both strengths of omeprazole. The dosage instructions in the data sheet have been modified to:-

> **10 mg tablets:** 20 mg (2 tablets) once daily until symptoms improve, then reduce the dose to 10 mg (1

tablet) once daily. If symptoms return the dose may be increased to 2 tablets once daily.

20 mg tablets: one tablet once daily.

The lowest dose that controls symptoms should be used.

The proposed 20 mg dosage instructions have the advantage of being very simple and easy to follow. The initial daily dosage remains the same (20 mg) and consumers are still instructed to use the lowest dose that controls symptoms. While it is acknowledged the opportunity to reduce dosage is unavailable if Losec 20 mg tablets have been purchased, the pack size limitation and the availability of a 7 tablet pack means this situation would only exist for a short time. At the next purchase, consumers can try the lower dose to see if it is effective for them.

In terms of differentiating between the two strengths, Bayer envisages that for first time users of OTC omeprazole pharmacists would recommend the 20 mg tablets, as:-

- if the consumer has, in the past, unsuccessfully treated with other remedies (the most likely scenario), it makes sense to try the higher dose in order to gain rapid and profound resolution of symptoms
- if it is the first time the consumer has had heartburn, the pharmacist would only consider treatment with Losec for a severe attack.

The 20 mg presentation is intended as a convenient and economical option for those consumers seeking greater control of their symptoms or for whom reduction to 10 mg during treatment was unsuccessful.

Anecdotal evidence from the United Kingdom, where omeprazole 10 mg tablets have been available without prescription since 2004, and where similar dosage instructions are in use to those currently approved in New Zealand, suggests that consumers find the dosage reduction/escalation concept highly confusing and difficult to follow. Compliance with the dosage recommendations is known to be poor. Non-compliance with the dosage instructions may result in poorly controlled symptoms, if the consumer does not comprehend the dosage can be increased again in this situation, and perceptions of lack of efficacy may result. The very simple dosage regime proposed for the 20 mg tablets address this issue.

A5. Classification

The current classification of omeprazole, taken from the Medsafe Web site on 15 July 2009, is:-

Omeprazole, except when specified elsewhere in this Schedule	Prescription
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 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 — ***Restricted***

Essentially, this submission encompasses all of the current restrictions for the OTC sale of omeprazole, the only change being the strength of the presentation allowed.

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.

Switch Status of Omeprazole Oral Presentations

Country	Current Classification	Year of Switch from Prescription
Sweden	Omeprazole 10 mg, 20 mg – classification	April 2000

	equivalent to Pharmacy Only Medicine	
United States of America	Omeprazole 20 mg – classification equivalent to Pharmacy Only Medicine (available in drug stores)	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	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	2008
Poland	Omeprazole 10 mg	2009
Germany	Omeprazole 20 mg - classification equivalent to Pharmacy Only Medicine	August 2009

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

These figures demonstrate that since 1990 there has been a world-wide trend towards less restriction of omeprazole. In many instances this trend has embraced OTC classification of 20 mg presentations – significantly the recent German reclassification is for a 20 mg presentation.

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 1997 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.

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.

A7. Labelling

See Attachment One for the currently approved labelling (7 and 14 tablet packs) 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 20 mg packs, apart from the strength of the tablet and the dosage instructions as discussed above. Additionally, the shade of the packaging would be different, so that pharmacists and consumers can easily differentiate the two different strengths of tablet.

The pack insert would be a copy of the proposed Consumer Medicine Information as provided in Attachment 3.

A8. Proposed Warnings

The required warnings for omeprazole have already been established by the Medicines Classification Committee in the minutes of the 40th Meeting. These are:-

The following should be required on the label:

- use should not be prolonged except on medical advice
- the 4 main alarm symptoms as in the GORD guidelines:
  - weight loss
  - persistent regurgitation of food or vomiting
  - dysphagia
  - symptoms of GI bleeding
- an instruction to inform the pharmacist about use of other medicines (may be included on the package insert if there is insufficient space on the label)
- a statement instructing consumers to inform the pharmacist if pregnant (may be included on the package insert if there is insufficient space on the label)
- the interactions on the package insert should be the same as those on the data sheet.

These warnings are equally applicable to the 20 mg strength. Additional warnings are not considered necessary for the 20 mg tablet as the indication is identical and the safety profile of this higher strength tablet is virtually identical to that of the 10 mg tablet (see Section B).

A9. Other Products

In addition to the Losec tablets that are the subject of this submission, there are a number of other omeprazole products currently sold in the New Zealand market. These are:-

Brand Name	Strength and Pack Size	Sponsor Company
Losec	Capsules 10 mg, 20mg	AstraZeneca Limited
DP - Omeprazole	Capsules 20mg	Douglas Pharmaceuticals Ltd.
Omeprazole	Capsules 10 mg, 20mg	Dr. Reddy's New Zealand Limited
Omezol	Capsules 10 mg, 20mg	Mylan New Zealand Limited
Probitor	Capsules 20mg	Novartis New Zealand Limited

At the time of writing all of the products above are classified Prescription Medicine (including the 10 mg presentations) by virtue of the pack sizes registered. The medicines above would be relatively unaffected by any change in classification, in that the companies can choose what classification they wish to market products under according to the pack size marketed.

PART B

Bayer's proposal to reclassify omeprazole 20 mg capsules or tablets to Pharmacist Only Medicine, including the restrictions as outlined in Part A, is based on and essentially similar to the current conditions for omeprazole 10 mg as a Pharmacist Only Medicine. The proposal extends the current situation in three key areas:-

- the maximum strength of the dose form is proposed to increase from 10 mg to 20 mg. While this may appear a significant change, it must be viewed within the context that the maximum daily dose is not proposed to increase – the maximum daily dose allowed for omeprazole as a Pharmacist Only Medicine is currently 20 mg per day.
  Furthermore, the current dose recommendations allow continuous treatment with 20 mg per day if symptoms do not improve or if symptoms return. Thus, treatment with 20 mg omeprazole per day is already established as a Pharmacist Only Medicine dose.

  In this section, Bayer will demonstrate that
  the proposed increase in strength to 20 mg is justified due to the greater efficacy of this strength, and the greater potential for consumer compliance and convenience that this strength of tablet offers.

- the duration of therapy may be extended slightly. Currently a maximum pack size of 14 tablets is allowed, and this maximum pack size is retained in Bayer's proposal. However, currently dosage recommendations are to take 2 tablets per day initially, reducing to 10 mg per day once symptoms are controlled. Ideally, patients are likely to take 2 tablets per day for 2 – 3 days, and so a 14 tablet pack is effectively up to 11 – 12 days therapy, but could be as much as 14 days. In contrast, a 14 tablet pack of Losec 20 mg (the maximum pack size proposed) represents up to 14 days of omeprazole therapy.

  In this section, Bayer will demonstrate that
  14 days is an appropriate maximum treatment timeframe for reflux-like symptoms that has already been accepted in New Zealand for other products in this treatment category.

- the total amount of omeprazole offered in one pack, and by implication available for a course of treatment, is increased from 140 mg to 280 mg. This increase is recognised as sizeable –

however:-

In this section, Bayer will demonstrate that
this increase in the amount of omeprazole available for a course of treatment represents virtually no increase in the risk to the patient.

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

Reclassification of Losec 20 mg tablets to Pharmacist Only Medicine has the potential to offer consumers significantly improved efficacy, convenience and cost utility with virtually no increase in the risk of unwanted side effects, medicinal interactions or masking of serious disease.

1. Efficacy of Losec 20 mg Tablets

The term “efficacy” in the treatment of heartburn and acid-related symptoms subsumes a variety of parameters. While the term is interpreted in the pharmacological or pharmacodynamic sense on the basis of the surrogate parameter “pH increase”, clinical interpretation from the patient’s viewpoint involves, primarily, the degree of relief or complete freedom from symptoms and, secondarily, the associated improvement in quality of life. pH metric studies thus provide objective information on the dynamics of pH changes, whereas clinical efficacy assessment focuses on aspects such as the subjectively experienced time of onset of action and treatment response in the form of reduced or absent symptoms over a given period.

The development of proton pump inhibitors for the symptomatic treatment of GORD introduced a class of compounds capable of increasing gastric pH within 24 hours to values above 4 for a longer period than was possible with the hitherto most effective treatment option, H_2 receptor antagonists *(Bell 1992)*. Since symptom intensity closely correlates with oesophageal acid exposure, the achievement within 24 hours of sustained acid suppression over as long a period as possible is a decisive factor for improved control of symptoms *(Robinson 2004)*.

With regard to pharmacological efficacy, Williams et al. showed in 1998 that intragastric acidity measured in healthy subjects over 24 hours was already reduced by 35% after the first of eight consecutive doses of 20 mg omeprazole and that gastric pH was raised to values above 3 and 4, respectively, for 36% and 25% of the day. After the last dose, acid exposure in the stomach was actually reduced by 76% and pH values above 3 and 4 were achieved for approximately 59% and 51%, respectively, of a 24 hour interval *(Williams 1998)*. Similar results were obtained by Geus et al. *(Geus 1998)*. In addition, a study by Miner et al showed that, after five days of use, omeprazole 20 mg daily maintains gastric pH above 4 for almost 12 hours *(Miner 2003)*. In a current study, Calabrese et al. monitored pH over four days after ingestion of omeprazole 20 mg daily. As early as day 2, acid exposure returned to normal in 75% of patients receiving omeprazole. In keeping with this finding, their reflux-related symptoms were also reduced at that time point *(Calabrese 2008)*.

These results demonstrate that 20 mg omeprazole once a day is an effective dose providing rapid resolution of reflux-like symptoms.

Numerous studies with clinically relevant endpoints such as “relief or freedom from symptoms” or “improved quality of life” document the clinical efficacy of omeprazole 20 mg in the treatment of heart burn and acid reflux, and the superior efficacy of 20 mg daily compared to the lower dose of 10 mg daily: Richter et al. *(Richter 2000)* compared the efficacy of omeprazole at doses of 10 mg and 20 mg with placebo in the treatment of NERD patients with moderate to severe heartburn of more than 12 months duration. Efficacy was evaluated by subjective assessment of symptoms by the patients after 2 and 4 weeks of treatment. As early as day 7 of treatment, 62% of patients receiving omeprazole 20 mg were completely asymptomatic, compared to only 14% on placebo. After 2 weeks of treatment this proportion had increased to 67% vs. 23% on placebo, thus achieving in the first two treatment weeks almost the same efficacy as that seen at the end of the four-week treatment cycle (74% vs. 23%). On treatment with 10 mg omeprazole, by contrast, 41%, 46% and 49% of patients were completely asymptomatic after 7, 14 and 28 days, respectively. Complete freedom from symptoms throughout the week was achieved in the last week of treatment by 48% of the 20 mg omeprazole group vs. 27% of the 10 mg omeprazole group vs. 5% of the placebo group. Omeprazole therapy was thus shown to be clearly superior to placebo, with omeprazole 20 mg consistently more effective than 10 mg.

As long ago as 1997, Lind et al. compared the efficacy of omeprazole at doses of 10 mg and 20 mg with that of placebo in patients with endoscopically negative heartburn. The study, which investigated the number of completely asymptomatic days on treatment, showed a clear dose-response relationship. Omeprazole 20 mg was significantly superior to both placebo and the 10 mg dose. After a 4-week treatment, 46.3% of patients treated with omeprazole 20 mg were completely asymptomatic in the 7 days preceding the study visit. The corresponding figure on placebo was only 13%. This efficacy was also

reflected in patient satisfaction with treatment, 66% receiving omeprazole 20 mg being satisfied with their treatment, compared to only 31% on placebo. Similarly high satisfaction was already present two weeks after the start of treatment (64% on omeprazole 20 mg vs. 32% on placebo). By comparison, the proportion of completely asymptomatic patients in the 7 days before the study visit on treatment with omeprazole 10 mg was 31.1%, and the degree of satisfaction after 4 and 2 weeks of treatment was 57% and 59%, respectively. Since the patients kept a symptom diary, it was also possible to show rapid onset of action. Within the first few days of the start of treatment, most patients no longer reported any heartburn at all. The subjective improvement in symptoms correlated well with the increase in pH shown by 24-h pH metry. Symptom relief was achieved in patients both with and without pre-existing oesophageal acid exposure *(Lind 1997)*. These results were confirmed in a further study in which the proportion of completely asymptomatic patients after 4 weeks of treatment was 41% and 35% on omeprazole 20 mg and 10 mg, respectively, and 19% on placebo. The proportion with adequate symptom control was 73% with omeprazole 20 mg and 62% with omeprazole 10 mg *(Carlsson 1998)*.

Apart from studies on the efficacy of omeprazole compared to placebo, there are also comparative studies with H_2 receptor antagonists (H2RAs). In a 4-week comparison, omeprazole was more effective than the H2RA ranitidine at a dosage of 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). This study too showed the therapeutic superiority of omeprazole at a 20 mg dosage compared to a 10 mg dosage. After 4 weeks of treatment with omeprazole 20 mg, symptoms improved significantly more than on treatment at lower dosage (*Venables 1997*).

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. 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 (*Bardhan 1999*).

Two comparative US studies on the efficacy of omeprazole over a 14-day OTC treatment period in over 3000 patients with frequent heartburn showed that omeprazole dosages of 20 mg and 10 mg daily are superior to placebo. On the last day of treatment, 69.7% of patients taking omeprazole 20 mg in the first study (73.0% in the second study) and 71.7% (66.4%) of those taking omeprazole 10 mg were completely symptom-free, compared to 42.7% (43.0%) taking placebo. Assessed over the entire 14 treatment days, 64.4% (67.8%) and 60.8% (61.4%) of patients were completely symptom-free on omeprazole 20 mg and 10 mg, respectively, but only 39.4% (37.9%) on placebo. Overall, omeprazole was consistently more effective at the 20 mg dosage than at 10 mg. The proportion of heartburn-free patients on the first day of treatment with omeprazole 20 mg (49.7%) was significantly higher than on treatment with 10 mg (41.5%). In the second study, the 20 mg omeprazole dosage was superior to the 10 mg dosage with regard to the proportion of heartburn-free patients after 14 days and over the entire 14-day treatment period *(Allgood 2005)*.

Comparative studies on improvement in quality of life on treatment of heartburn with omeprazole 10 mg or 20 mg or placebo demonstrate that quality of life is markedly improved by the decrease in symptoms and, on successful treatment, is again comparable with quality of life in the healthy. In a 4-week study, Havelund et al. observed no differences between omeprazole 10 mg and 20 mg in their effect on general well-being, but the higher dosage performed significantly better in terms of the reflux-related dimension, as measured by the Gastrointestinal Symptom Rating Scale (GSRS) *(Havelund 1999)*. Lind et al. obtained similar results in NERD patients after 4 weeks of treatment with omeprazole 20 mg and 10 mg daily, reporting improved quality of life comparable with that in the healthy. Omeprazole in a 20 mg dosage also showed superiority in the reflux dimension *(Lind 1995)*. In patients with known reflux oesophagitis and frequent heartburn it was proved that disease-related impairment in quality of life decreased markedly on treatment with omeprazole 20 mg twice daily; only the response to symptomatic treatment – but not the course of oesophageal mucosal healing – was predictive of improved quality of life *(McDougall 1998)*.

Superior improvement in quality of life for patients with heartburn and acid-related symptoms has also been demonstrated in comparison with H2RAs. 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 a dosage of ranitidine 150 mg twice daily *(Wiklund 1998)*. Similar results were obtained by Festen et al., 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 *(Festen 1999)*.

Onset and Duration of Action

With regard to clinical onset of action it is necessary to distinguish between relief onset in acute heartburn (e.g. sporadic heartburn due to dietary and/or nicotine excess) and relief over a defined period, measured as “heartburn-free days”. A key factor in the treatment of frequent heartburn is the ability to prevent the occurrence of heartburn, acid reflux and epigastric pain for a longer period. Only this lasting symptomatic relief brings the desired improvement in quality of life, whereas every recurrence of symptoms is associated with renewed deterioration in quality of life.

The pharmacological onset of action of omeprazole is marked by the start of H+/K+ ATPase inhibition and subsequent rise in gastric pH. In pH metric studies in healthy volunteers the acid-reducing effect of omeprazole was shown to commence as early as 1.5 hours after a single 20 mg dose (*Pantoflickova 2003*). By contrast, the maximum acid-suppressant effect is reached only after some 3 to 5 days of use, since about a third of proton pumps are newly synthesised each day and PPIs mainly inhibit only pumps activated by food intake *(Rösch 2005)*. The degree of acid inhibition also appears to correlate with the bioavailability of omeprazole *(Prichard 1985, Miner 2006)*, which increases with consecutive dosing.

Bytzer et al. used frequent symptom enquiry to demonstrate early onset of action after omeprazole 20 mg in patients with erosive oesophagitis and heartburn. After an average of 1.5 days the patients gained control of heartburn and acid reflux *(Bytzer 2006)*. Ten years earlier Bate et al. had already obtained a similar result with omeprazole 20 mg. The treatment time to the first day with complete freedom from symptoms – i.e. from any attacks of heartburn – was 2 days *(Bate 1996)*.

In order to draw conclusions on the possible use of PPIs in a short-term treatment of 14 days, McQuaid studied the early effect of PPIs on heartburn in a systemic meta-analysis. Subgroup analysis of the pooled results showed that as early as the first day, 29% of patients treated with omeprazole 20 mg were already completely symptom-free, a lasting effect that persisted for the next 7 days in 19% of patients. Twenty-six to 37% of the maximum possible therapeutic effect after a 4-week treatment with PPIs is achievable after only 24 h. This proven early effect increases still further on the second day of treatment *(McQuaid 2005)*. Similar findings are also reported by Carlsson et al., patient diary entries showing 34% and 30% symptom-free as early as the first day of treatment with omeprazole 20 mg and 10 mg, respectively, compared to 22% of patients on placebo *(Carlsson 1998)*. Two studies compared the effect of a “single” and “double dose” (omeprazole 10 mg vs. 20 mg or esomeprazole 20 mg vs. 40 mg) on symptom relief within 24 hours of first administration. The “single dose” strategy was less effective in terms of

early effect (RR 0.82; 95% CI 0.74–0.92) *(McQuaid 2005)*. Rapid onset of action is an important contributor to patient compliance and quality of life, and is the underlying rationale for the current "loading dose" dosage instructions for omeprazole 10 mg as an OTC medicine. However, sustained efficacy is equally important, and it is in this area that omeprazole 20 mg has the potential to provide superior results, generating improved compliance and greater customer satisfaction with minimal risk.

Armstrong et al. 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 h) 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 *(Armstrong 2005)*.

The two studies conducted by Allgood et al. on the efficacy of low-dose omeprazole in short-term therapy in over 3000 patients with frequent heartburn likewise provide information on the time of onset of action and on the duration of effect. After only the first dose of omeprazole 20 mg, 49.7% of patients were completely symptom-free in the first study and 46.8% in the second. The corresponding proportions with omeprazole 10 mg were 41.5% and 45.2% of patients. Those mainly symptom-free apart from mild heartburn, and hence satisfied with the treatment response, after the first dose comprised 81.0% (81.8%) of patients on omeprazole 20 mg and 79.0% (78.0%) on omeprazole 10 mg, compared to 71.6% (70.8%) on placebo. With tablets taken in the morning, the occurrence of nocturnal heartburn may be informative about the duration of therapeutic effect. After the first dose, 78.4% and 77.7% of patients taking omeprazole 20 mg reported absence of nocturnal heartburn. Over the entire 14-day treatment duration, significantly more patients had no nocturnal heartburn with omeprazole 20 mg (84.1% and 86.3%) and 10 mg (82.9% and 82.8%) than with placebo (73.8% and 75.7%). The sustained clinical effect of omeprazole over 24 h was thus demonstrated after both single and repeated administration *(Allgood 2005)*.

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 H2RAs 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. This explains the patient dissatisfaction reported after prolonged treatment with H2RAs *(Hurlimann 1994)*.

In summary, it is clear that the efficacy of omeprazole in the treatment of heartburn and acid reflux has been well demonstrated. For short-term OTC use, the 20 mg omeprazole dose is to be preferred, comparative studies having shown it to be consistently more effective than omeprazole 10 mg, with comparable tolerability (notwithstanding omeprazole 10 mg demonstrating adequate efficacy in its own right). This superior efficacy encompasses the onset of action, the degree of symptom relief and the proportion of completely asymptomatic patients at the start, during and after the end of treatment. The pharmacological onset of action of omeprazole 20 mg, as evidenced by a pH increase, is rapid and comparable with the effect of H2RAs.

Adequate symptom control was observed a mere 1.5 days after the first dose. Rapid and effective relief of symptoms is of particular importance for correct OTC use, since inadequate symptom relief can lead to faulty compliance (patients taking supplementary doses and thereby exceeding the maximum daily dose). This can be avoided by offering omeprazole 20 mg as an OTC alternative treatment. Moreover, continuous omeprazole use generally leads after no more than 3 – 5 days to sustained symptom relief with maximum acid suppression achieved through the carryover effect thanks to irreversible blockade of the proton pump. The associated lasting therapeutic effect can contribute decisively to minimising the risk of treatment beyond the proposed duration of use of a maximum of 14 days.

2. Treatment Timeframe

The currently approved maximum treatment timeframe (as effected by limiting pack size) for omeprazole in New Zealand is 10 – 12 days, depending on how many days the consumer takes the loading dose of 20 mg per day. This submission proposed to extend that maximum treatment time frame slightly to 14 days.

Two weeks is already an accepted time frame in New Zealand for the treatment of acid-related symptoms, as evidenced by the current classification of H_2 antagonists. In New Zealand ranitidine is classified as a Pharmacy Medicine when sold in the manufacturer's original pack containing not more than 14 days supply. Likewise, cimetidine is classified as a Pharmacist Only Medicine when sold in the manufacturer's original pack containing not more than 14 days supply. Thus, the concept of a maximum two week treatment period is well-established for self-medication of acid-related problems – even for medicines that do not require the input of a pharmacist. The OTC indication is essentially the same for omeprazole and H_2 antagonists, and the safety profiles comparable – thus, there seems no reason why the maximum duration of treatment currently applied to H_2 antagonists cannot be equally applied to omeprazole.

The situation is similar in other countries. Pantoprazole 20 mg as a Pharmacist Only Medicine in Australia has a treatment duration of 2 weeks, and omeprazole 10 mg as an OTC medicine in the UK has a treatment duration of up to 4 weeks. The recent reclassification of omeprazole 20 mg in Germany also allows for a treatment time frame of 2 weeks. The current maximum treatment duration in New Zealand for omeprazole 10 mg (10 – 12 days) is relatively conservative, and an extension of this maximum treatment duration to 14 days would be completely consistent with international practice for OTC PPIs.

An actual use study in the United States (*Fendrick et al. 2004*), conducted on 758 consumers with frequent heartburn in an OTC setting, found that three months after taking one 14-day treatment course of omeprazole 20 mg, 43% of subjects had no recurrence of their frequent heartburn.

Bardhan et al, showed that omeprazole used for 14 days decreases the occurrence of symptoms and relapse. Omeprazole 20 mg was used for 14 days and patients with relief from symptoms after this period of time were deemed in remission. When symptoms recurred, omeprazole was available as intermittent therapy for a 14 day treatment. After the initial treatment period, 33% of patients had no relapse in the entire 12-month follow-up period and needed no intermittent therapy. Of those on intermittent therapy (67%), 26.8% had no further relapses while 20.1% had only one. 80% of patients were able to effectively manage their symptoms with only three short-term treatments over 12 months. The authors concluded that after treatment with omeprazole, relapses were infrequent and control was gained rapidly with an additional short course of treatment.

A potential benefit of treatment with omeprazole, secondary to symptom resolution, is a reduced likelihood of symptom recurrence upon treatment cessation, so that treatment is required only intermittently as is intended for OTC medications.

3. Unwanted Effects

3.1 Side Effects

The side effects that occur with omeprazole therapy are mostly mild, self-limiting and independent of the patient's age. *Dose-finding studies found no correlation between the dose administered and the incidence of side effects.*

Less than 2% of patients stated the occurrence of side effects during treatment with omeprazole as a reason for terminating the trial *(Wilde 1994).*

The side effect profile for short-term therapy (2 to 12 weeks) with omeprazole did not differ from that for the H2RA or placebos used in a number of comparative studies (*McTavish 1991, Simon 1991*). Likewise, the side effect profile for long-term use (up to 4 years) did not differ from that for short-term therapy (< 12 weeks) (*Wilde 1994*), which is why the observations from clinical studies and post-marketing observations are presented together here.

The following side effects were described for oral therapy with omeprazole (*Martindale 2007*):

Frequently (>1 / 100; <1 / 10)

- diarrhoea, obstipation, flatulence (in some cases with abdominal pain), nausea and vomiting, tiredness, drowsiness, insomnia, headache and dizziness. In the majority of cases these complaints subsided over the course of treatment.

Occasionally (>1 / 1000; <1 / 100)

- impaired vision (blurred vision, impaired visual acuity and loss of visual field), defective hearing (e.g. tinnitus), changes in taste, changes in liver enzyme values. These conditions are usually reversible.
- itching, skin rash, dermatitis, alopecia, erythema multiforme, photosensitivity and hyperhidrosis
- paraesthesia and light-headedness
- urticaria
- illness
- peripheral oedema (usually subsided after treatment)

Rarely (>1 / 10,000; <1 / 1,000)

- brownish-black discoloration of the tongue with concomitant use of clarithromycin (drug for certain bacterial infections) and benign glandular cysts. Both reactions subsided after the end of the treatment.
- Stevens-Johnson Syndrome and toxic epidermal necrolysis
- amyasthenia, muscular pain and joint pain
- aggressive reactions, dementia and hallucinations, usually in seriously ill or elderly patients.

Very rarely (<1 / 10,000)

- dryness of the mouth, stomatitis, thrush and pancreatitis
- hepatitis with and without jaundice, liver failure and encephalopathy in patients with previous severe liver disease
- changes in blood picture, reversible thrombocytopenia, leucopoenia, pantocytopenia and agranulocytosis,
- interstitial nephritis

- agitation and depression primarily in seriously ill or elderly patients
- elevated body temperature, angioneurotic oedema, constriction of the airways or anaphylactic shock, allergic vasculitis and fever.
- hyponatraemia and gynaecomastia

On the whole, the side effects occurring most frequently during treatment with omeprazole affect the gastrointestinal tract or are general, non-specific symptoms which subside during the course of treatment or when treatment has ended. In comparative studies the side effect profile of omeprazole was comparable with that for H_2 receptor antagonists and placebos. Serious side effects are rare or very rare. In order to minimize the risk, the signs of possible side effects are described in layman's terms in the Consumer Medicine Information and they come with the advice to inform a doctor or pharmacist should such symptoms occur.

In summary, the side effects of omeprazole therapy are usually slight, self-limiting and independent of the age of the patient. There is no correlation between the administered dosage and the incidence of side effects as seen in dosage finding studies *(Sölvell 1990, Wilde 1994)*. Omeprazole has been in clinical use for 20 years in various dosages (most commonly 20 mg), and there is now sufficient post-marketing experience in various dosages and pharmaceutical forms (450 million prescribed patient treatment cycles[1] to 2002 including 217 million oral treatment cycles from 2003 to 2008) *(Procter & Gamble Company, AstraZeneca LP 2002, AstraZeneca PSUR 2008)* to confirm this finding. On the basis of data from preliminary clinical studies on OTC introduction (Omeprazole (MUPS tablets) 10 mg: n = 3139; Omeprazole 20 mg: n = 5040; placebo: n = 3120; 1 – 45 days) as well as from studies on prescription drugs (Omeprazole (capsules) 10, 20, 40 mg: n = 5757; placebo: n = 1125) and post-marketing experience, there is no dosage dependent increase of side effects. The side effects profile is comparable to that of placebo. Severe undesirable effects are rare and not more common in patients under treatment of acid related complaints in general *(Procter & Gamble Company, AstraZeneca LP 2002)*.

The current PSUR from AZ (time period 2003 – 2008) contains n = 2609 case reports with a total of 4792 recorded side effects under oral pharmaceutical forms employing up to 40 mg. Regarding the approximately 217 million oral patient treatment cycles performed during this time, this corresponds to a side effects rate of approx. 0.02% *(AstraZeneca PSUR 2008)*.

[1] One patient treatment cycle is defined as an average treatment period with an average dosage. This is calculated from the number of quantities sold with the assumption of an average daily dosage ranging from 20 to 40 mg throughout an average time period of 3 to 4 weeks.

3.2 Medicinal Interactions

In terms of over-the-counter use, interactions with widely used drugs are particularly important. This relates to both non-prescription products and products prescribed by the doctor. The top-selling products in the over-the-counter market are cough and cold remedies, gastrointestinal products, cardiovascular products and products for treating veins, pain killers and products for treating rheumatism and muscular pain. This is also reflected in a survey of the best-selling monosubstances in the over-the-counter market. The best-selling substances include xylometazoline, ibuprofen, paracetamol, acetylsalicylic acid, dexpanthenol, diclofenac and magnesium. There is no evidence of interactions between omeprazole and diclofenac, naproxen or antacids. In addition, the available literature does not document any interactions with the over-the-counter substances available for treating colds, gastrointestinal complaints or cardiovascular complaints.

The most frequently medically prescribed substances include angiotensin inhibitors, beta receptor blockers, lipid-lowering agents, diuretics, antidiabetics, calcium antagonists, therapeutic agents for ulcers, antiasthmatics, sex hormones, and antithrombotics. There is no evidence of interactions with the beta receptor blockers propranolol and metoprolol (*Andersson 1991*). The potential interactions of omeprazole with the coagulation inhibitor warfarin is explicitly referred to in the labeling for the over-the-counter market. No other interactions with the substances most frequently prescribed are reported in the literature.

Interactions with food ingredients (alcohol, caffeine) are not known.

On the whole, the majority of the interactions described in the literature between omeprazole and other drugs are exclusively pharmacokinetic in nature and no clinical relevance has been proven to date. The package insert provides detailed, easy-to-understand descriptions of possible drug interactions in order to reduce their risk. Serious side effects due to drug interactions when using over-the-counter omeprazole are therefore not expected.

3.3 Risk of Masking Serious Disease

Heartburn and other acid-related complaints are generally not in themselves the dominant symptoms of serious disorders of the gastrointestinal tract such as gastric or duodenal ulcers, stomach or oesophageal cancer, or Barrett's oesophagus. Clinically relevant lesions rarely occur in the absence of alarm symptoms such as involuntary weight loss, persistent vomiting, dysphagia, loss of appetite, fever, jaundice or anaemia. Nonetheless, it must be taken

into consideration that medical diagnosis and treatment could possibly be delayed as a result of self-medication with omeprazole (*Tytgat 2008, Armstrong 2005*, *DeVault 2005*).

The risk of disease progression in terms of increased inflammatory changes is low. In more than 60% of patients with heartburn or other acid-related complaints, no or no relevant pathological abnormalities of the oesophageal and gastric mucosa are detected endoscopically (*Koop 2005*). In a long-term study of 4,633 patients with GORD receiving symptomatic treatment over a period of 20 years, increasing mucosal abnormalities were only observed in 11% of cases. The incidence of strictures was 0.08% in patients with NERD and 1.9% in patients with ERD (*Sontag 2006*). Evaluation of the ProGERD study showed that symptomatic GORD develops into Barrett's oesophagus in less than 1% of cases, and that this development is not influenced by treatment with PPIs. Over a 2-year period, the majority of patients receiving a wide variety of treatments remained in endoscopically negative GORD stages (*Labenz 2006*). A cohort study on the incidence of Barrett's oesophagus in GORD patients showed that none of the patients with NERD and only 1% of those with ERD developed Barrett's oesophagus over an average period of 3.4 years (*Stoltey 2007*).

The incidence of stomach cancer has been declining for decades. Although the pathogenesis is multifactorial, colonisation of the gastric mucosa by *H. pylori* is of particular importance. Malignant abnormalities of the gastric mucosa occur as a consequence of chronic inflammation associated with atrophy and intestinal metaplasia, which in turn is generally triggered by *H. pylori* infection. The severity of the inflammatory changes is determined by the virulence of the microorganism, the genetic predisposition of the patient, bile acid reflux, dietary factors and reduced gastric acidity (*Ng 2007, Axon 2002*). A long-term study over a period of 6.5 years in 230 patients with resistant GORD showed a low risk for the development of intestinal metaplasia during treatment with omeprazole. The incidence of atrophic changes in the corpus mucosa was 4.7% and 0.7% per year for *H. pylori*-positive and *H. pylori*-negative patients respectively; these abnormalities were mainly observed in older patients with pre-existing gastritis. Dysplasia or neoplasia was not detected in any cases (*Klinkenberg-Knol 2000*).

With regard to possible masking of symptoms, it should also be noted that the occurrence of stomach cancer is associated with non-specific complaints, rather than with acid-related symptoms such as heartburn. Patients with early-stage cancer are asymptomatic or complain of ulcer-like symptoms. Signs of advanced cancer are abdominal pain, loss of appetite, weight loss, and weakness. Dysphagia, nausea and recurrent vomiting may indicate a stenosing carcinoma. (*Riemann 2008).*

In the case of malignant tumours of the oesophagus, squamous cell carcinoma and adenocarcinoma are to be distinguished with regard to epidemiology, pathogenesis and risk factors. The cardinal symptom of

oesophageal cancer is dysphagia. While the incidence of squamous cell carcinoma (mainly caused by exogenous noxae such as alcohol and tobacco use) is constant, the incidence of adenocarcinoma is rising, especially in Western countries. (*Riemann 2008, Varadhachary 2005).* The precursor to adenocarcinoma is Barrett's oesophagus, which is of interest on account of the potential risk of malignant degeneration. In patients examined endoscopically, the prevalence of Barrett's oesophagus varies from study to study between 1% and 4% (*Cook 2005*). A Swedish study involving 3,000 people showed a prevalence of 1.6% in the general population (*Ronkainen 2005*). Although chronic GORD is a risk factor for the development of Barrett's oesophagus, the causal relationship between chronic GORD and Barrett's oesophagus is called into question by recent epidemiological studies (*Riemann 2008, Pondugula 2007*). While Barrett's oesophagus is more frequently diagnosed in patients with reflux disorders, no typical symptom profile can be observed (*Avidan 2002*). In some cases, the course is asymptomatic. One study found a prevalence of 25.0% in asymptomatic individuals (*Gerson 2002*). The risk of malignant degeneration of Barrett's oesophagus is, however, lower than has been assumed in the past. A meta-analysis by Shaheen showed that the risk of carcinomatous degeneration – 0.5% per year – is markedly lower than previously assumed (*Shaheen 2000*).

The incidence of peptic ulcers and lesions is now mainly determined by the frequency of *H. pylori* infections and the use of non-steroidal anti-inflammatory drugs. Around 90% of all peptic ulcers can be attributed to *H. pylori* infections or the intake of non-steroidal anti-inflammatory drugs (NSAIDs). In Germany and Western Europe, the prevalence of gastric ulcers is 0.2–0.3%, and that of duodenal ulcers 1.0–1.5%. About 10% of patients receiving NSAID therapy develop gastroduodenal ulcers, and of these patients, 10% develop gastrointestinal bleeding in the course of treatment. The "typical" clinical picture consists of recurrent upper abdominal symptoms during or after eating (gastric ulcer) or fasting pain (duodenal ulcer); however, this only applies to a minority of cases. Indeed, up to 50% of cases are asymptomatic (*Riemann 2008, Ramakrishnan 2007, Vergara 2005, Langman 1994*).

For initial assessment, therefore, instead of endoscopy, empirical treatment with a PPI is recommended, which is then both diagnostically suggestive and causally effective as a treatment. In patients whose symptoms are caused by manifest oesophagitis, the best possible chance of a cure is provided by the earliest possible treatment with a PPI, possibly also in the form of self-medication. A meta-analysis published in 2008 concerning treatment options for previously undiagnosed heartburn confirms the value of this therapeutic approach and shows that primary endoscopy for low-risk patients is less sensitive and specific than empirical treatment (*Delaney 2008*).

As shown by the "actual use" study of Fendrick et al. (*Fendrick 2004*), 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. At the same time, 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.

Overall, it can be noted that heartburn or other acid-related complaints do not usually occur as cardinal symptoms of serious diseases of the gastrointestinal tract. As a rule, such diseases are associated with so-called alarm symptoms such as involuntary weight loss, loss of appetite, dysphagia or persistent vomiting, or run an asymptomatic course. Even with recurrent symptoms, the risk of developing mucosal changes is low, given the non-progressive course of GORD. The prevalence of serious conditions that could possibly be masked by self-medication is low, and in some cases even declining. The limitation of the period of use to a maximum of 14 days does not lead to any clinically relevant delay in the treatment of serious diseases, as patients do not initially regard acid-related complaints as requiring medical attention and only consult a physician if their symptoms are not controlled. In the event of 14 days' self-treatment with omeprazole, the prescription of initial empirical treatment would be pre-empted, but if symptom control is not achieved the physician can then immediately institute further diagnostic measures. The informational texts prepared for self-medication (Consumer Medicine Information, pack insert) are designed to reduce the risk of serious diseases being masked by including a description in layman's terms of the alarm symptoms (e.g. weight loss, swallowing disorders, persistent gastrointestinal symptoms, chronic vomiting or blood in vomit). Patients with such symptoms are advised to consult a doctor before using the product. To emphasise its importance, this information could be highlighted by, for example, printing it on a coloured background. The already very low risk of serious conditions being masked is thereby further minimised.

In summary, omeprazole 20 mg per day has already been approved in New Zealand as an OTC dose. The current proposal is to extend treatment at this dosage level for a maximum of 14 days, thereby increasing total treatment from a maximum of 140 mg omeprazole to 280 mg. The discussion above demonstrates that:-

There is little evidence to suggest that a total treatment of 140 mg omeprazole over 10 – 12 days is somehow safer or presents less risk for the patient that a total treatment of 280 mg over 14 days. There is no correlation between side effects experienced and the dose administered. The majority of drug interactions are pharmacokinetic in nature with questionable clinical relevance, and there is little

evidence that drug interactions or the risk of masking serious disease would be increased with the short-term use of this higher dose.

A number of leading health authorities in the world (primarily the United States and Germany) have accepted the safety and clinical appropriateness of omeprazole 20 mg as an OTC medicine – in particular, the recent switch of omeprazole from prescription to OTC in Germany was approved by a leading Health Authority assessing the product to the most modern standards, and it is enlightening that BfArm chose to switch the 20 mg presentation, bypassing the possibility of a 10 mg presentation switch.

Omeprazole 10 mg was reclassified to OTC in the United Kingdom early in 2004. As of 2008, the OTC availability of omeprazole in the UK has not raised any new safety concerns. The situation is the same in those countries that switched omeprazole 20 mg some time ago (United States, Sweden), confirming the trends observed in clinical trials that the incidence of adverse events is not dose-dependent. The risk to patient safety of relatively low-dose omeprazole (up to 20 mg per day) being available OTC is considered to be very low, and the additional risk of a 20 mg presentation being available OTC over that of a 10 mg OTC presentation is practically undetectable.

4. Assessing the Risk/Benefit Ratio

For more than 20 years, omeprazole has proved its tolerability in a wide range of clinical applications and has stood out as a substance with an excellent safety record. Omeprazole 20 mg is the most common dosage worldwide. The general toxicity can be graded as low; potential side effects during a short-term therapy are in general mild and self-limiting. Interactions with other drugs are predominantly pharmacokinetic in nature and hitherto without proven clinical relevance. Likewise, there is no evidence of interaction with substances most commonly used in self-medication

In spite of its comparatively short plasma half-time, the acid-suppressing effect lasts over 24 hours owing to irreversible proton pump inhibition. In short-term therapy, omeprazole is superior to H_2 receptor antagonists, thanks to its significantly better efficacy at comparative tolerability. Its long-term action helps improve the overall quality of life.

In view of the risk/benefit aspect of the therapy, a dosage of 20 mg omeprazole once a day and a maximum daily dosage of 20 mg omeprazole – provided that the maximum treatment period does not exceed two weeks – is a fruitful treatment strategy employed in self-medication. At this dose, owing to its swift and effective action, Losec 20 mg provides for a significant improvement of the patient's condition. A treatment period of maximum two weeks is sufficient for effectively controlling the symptoms. However, it is very unlikely to delay the diagnosis and treatment of serious disorders or diseases.

> *Losec 20 mg tablets demonstrate a highly favourable risk/benefit ratio, at least as good as (if not better than) comparable OTC medicines such as ranitidine and cimetidine. Losec 20 mg is perfectly suited for short-term self-medication in treating acid-related disorders such as heartburn, regurgitation and acid reflux.*

5. Introduction of Losec 20 mg Tablets as a Pharmacist Only Medicine

At the time of writing, Bayer New Zealand Limited is about to embark on the launch of Losec 10 mg tablets as the first OTC PPI into the New Zealand marketplace. Bayer has committed to, and is in the process of executing, a thorough training programme designed to introduce all pharmacists to this new class of OTC medicine.

Bayer is working closely with the New Zealand College of Pharmacists to ensure this training programme is of the highest industry standard and will be available to all pharmacists. The training programme developed contributes to pharmacist's Continued Professional Education as it is part of the College of Pharmacist's quality accredited continuing education programmes to assist pharmacists maintain and upgrade their professional knowledge and skills.

When it is available, Bayer will provide the Medicines Classification Committee with a complete copy of all the training materials developed for Losec 10 mg tablets.

Bayer has discussed the possibility of reclassification of omeprazole 20 mg with the College of Pharmacists also. The College agreed with the company that, given the extensive training programme being provided for the 10 mg presentation, a full training programme for the 20 mg presentation is not necessary. However, the two organisations would work together to provide an abbreviated programme for the new strength of tablet, with emphasis on the differences compared to Losec 10 mg tablets.

APPENDICES

Appendix 1

Current labelling for Losec 10 mg as a Pharmacist Only Medicine

Appendix 2

Proposed data sheet for Losec 10 mg and 20 mg as Pharmacist Only Medicines

Appendix 3

Proposed Consumer Medicine Information for Losec 10 mg and 20 mg as Pharmacist Only Medicines

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

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