AstraZeneca

Re-submission for Reclassification from

Prescription Medicine to Restricted Medicine

Losec (omeprazole) MUPS 20 mg

AstraZeneca Limited
PO Box 1301
Auckland

30 July 2002

Contents

PART A

1. International Non-proprietary Name of the Medicine

Omeprazole magnesium

2. Proprietary Name(s)

Losec MUPS

3. Company Requesting Reclassification

AstraZeneca Limited
PO Box 1301
Auckland
NEW ZEALAND

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

Dose form: Tablet

Strength: 20 mg.

5. Pack Size and Other Qualifications

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

6. Indications for which Change is Sought

Losec MUPS provides 24 hour prevention of the symptoms of frequent heartburn and indigestion.

7. Present Classification of Medicine

Prescription Only Medicine

8. Classification Sought

Restricted Medicine

9. Classification Status in Other Countries

Sweden: 10 mg and 20 mg are reclassified OTC in Sweden.

USA: Two US FDA advisory panels recommended the approval of OTC omeprazole for the prevention of frequent heartburn symptoms at a joint meeting on 21 June 2002. The proposed US label recommends taking one omeprazole 20 mg tablet each morning for 14 days to prevent the symptoms of frequent heartburn.

Rest of the world: Prescription.

With the exception of Sweden, AstraZeneca's international business strategy does not include a switch to Losec OTC, but rather a focus on innovative prescription medicines, in particular esomeprazole. In the USA Proctor and Gamble have the OTC licence for Losec MUPS.

10. Extent of Usage in NZ and Elsewhere

As of May 2002, a total of 23,143 million Losec tablets/capsules have been sold worldwide which equates to 648 million patient treatments. Losec has been available in New Zealand as a Prescription Medicine since December 1990. Since that time sales have equated to a total of over 120 million treatment-days (treatment-days have been calculated using an average daily dose of 1.2 as per New Zealand HBL data), with Losec 20 mg use since 1990 representing 109 million treatment days. During this period, Losec has only been available in capsule form in New Zealand. However, the tablet formulation, known as MUPS, has been approved in New Zealand since February 2001, and is bioequivalent with Losec capsules. Losec MUPS is approved in 48 countries world-wide.

11. Proposed Labelling and CMI

See Appendix 1 (Commercially sensitive).

12. Proposed Warning Statements

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

- If you are allergic to omeprazole or any of the ingredients of Losec MUPS listed under 'product description' in this leaflet.

- Do not use Losec MUPS for any purpose other than that specified on the pack unless under the supervision of a doctor.

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

- have symptoms including: unintended weight loss associated with indigestion, difficulty swallowing, recurrent vomiting, vomiting of blood or passage of stools stained with blood, persistent stomach pain, or
- have been told you have an ulcer, or
- have kidney or liver problems, or
- are over 40 years old and have indigestion symptoms for the first time or have symptoms that have recently changed, or
- have any allergies to any medicines, foods, dyes or preservatives, or
- have any other medical condition, or
- are taking any other medicine

While taking Losec MUPS patients will be advised to seek advice if

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

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

Not applicable.

PART B

Background

At the 26th Meeting of the Medicines Classification Committee held on 11 December 2001, the committee considered AstraZeneca's application to reclassify 10 mg omeprazole tablets from prescription medicine to pharmacy-only medicine for the symptomatic relief and short-term prevention of the recurrence of heartburn and indigestion [1].

The committee:

- agreed that the medicine had a sufficiently favourable safety profile for it to qualify for OTC sale. As such no further safety data (including interactions, contraindications, adverse events and potential for abuse or misuse) has been supplied with this submission;

- agreed that they would be willing to consider a submission for reclassification to restricted medicine at a later date should the company wish to make such a submission.

However, the Committee raised several issues that would need to be clarified if a further submission was made:

- Dose instructions
- Suitability of short-term prevention of recurrence for self medication
- Consent to market of short term prevention indication not obtained
- Clinical data to support OTC indication.

In light if the issues raised, this submission seeks approval to change the current legal classification of Losec MUPS 20 mg from Prescription Medicine to Restricted Medicine for the indication of 24 hour prevention of frequent heartburn and indigestion.

The proposed indications, dosage recommendation and pack sizes for Losec MUPS 20 mg as Restricted Medicine are as follows:

- 24 hour prevention of the symptoms of frequent heartburn and indigestion.
- One tablet to be taken once a day for fourteen days
- Pack size will be limited to 14 tablets

Proposed packaging including the pack insert is attached in Appendix 1.

Worldwide OTC Status

As noted in our previous reclassification submission Losec 10 mg and 20 mg were approved for non-prescription use in Sweden in December 1999 for the temporary relief of heartburn and reflux oesophagitis [2]. The recommended dose for both indications is one to two tablets per day when needed for a maximum of 14 days. The label recommends taking a 20 mg tablet each morning for 14 days to prevent the symptoms of frequent heartburn.

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

The reclassification of omeprazole in the USA was initially discussed on October 20, 2000 at a joint advisory committee (Gastrointestinal and Non Prescription Drug Advisory Committees). The sponsor (Proctor and Gamble) sought to market omeprazole for the same indication as OTC antacids and H2 antagonists. The committee felt that adequate data had not been presented to support the indication for omeprazole OTC and approval was not recommended. However, the committee indicated that the safety profile was such that omeprazole could be switched to OTC if a suitable population could be identified that could use this product safely and effectively [4].

Based on the committee opinion, as well as subsequent discussions with the FDA, Proctor and Gamble submitted a response stating that the target population is those suffering from “frequent heartburn”. As such, the modified the indication to “for the prevention of frequent heartburn”, “intended for those who suffer heartburn two or more days a week. The proposed dose was changed to 20 mg with a duration of treatment of 14 consecutive days.

On June 21 2002, the two joint committees met again and recommended approval of omeprazole for OTC use for the prevention of frequent heartburn symptoms [3].

Clarification of indication and dosage

In line with the approved Swedish and US OTC indications we propose the following indication and a change in the dosage from 10-20 mg to 20 mg only:

> *Losec MUPS provides 24 hour prevention of the symptoms of frequent heartburn and indigestion.*
>
> *Take 1 tablet (20 mg) once daily in the morning for 14 days*

The indication now reflects the condition of frequent heartburn which is defined as occurring two or more days a week.

The dose instructions now clearly state that treatment is for 14 days with no "as required" dosing.

Consent to market - Indication

Medsafe are currently evaluating a Changed Medicine Notification to amend the Losec prescription datasheet to include uninvestigated dyspepsia with a treatment duration of 14-28 days. Approval is expected before the next MCC meeting.

The amended dyspepsia indication in the prescription datasheet for which we seek approval is:

"Dyspepsia
For the 24-hour prevention of symptoms in patients with epigastric pain/discomfort with or without heartburn and indigestion, 20 mg Losec MUPS once daily in the morning for 14 –28 days*. If symptom control has not been achieved after 4 weeks treatment with Losec MUPS 20 mg daily, further investigation is recommended.

*Patients may respond adequately to 10 mg daily and this dose could be considered as a starting dose."

Data included in the CMN is summarised in the Supportive Clinical Data section below.

Chronic indication suitable for self-medication

The committee questioned whether the indication “short term prevention” was suitable for OTC reclassification.

AstraZeneca submit that prevention of frequent heartburn with a 14 day treatment course is suitable for OTC reclassification. This is supported by:

- international guidelines for the treatment of dyspepsia;
- The recent FDA reclassification decision
- Studies 171 and 183
- Precedent in New Zealand for products such as nasal steroids

Frequent heartburn / indigestion is described as occurring two or more days a week. The British Society of Gastroenterology Dyspepsia management guidelines 1996, recommend “it is acceptable to institute a single course of anti-secretory agent for 2-4 weeks in patients under 45 with troublesome symptoms but without alarm symptoms”. They also recommend that blood should be sent for *H. pylori* serology testing. However the value of widespread testing for *H. pylori* infection is an issue that has been widely debated within the literature. As indicated by the Genval Guidelines [5], testing is important in a small subset of patients suspected of peptic ulcer disease, as eradication of *H. pylori* infection does not heal or prevent reflux disease. New Zealand gastroenterologists and IPAs do not recommend routine *H. pylori* testing of the dyspepsia population. Hence *Hp* testing is not recommended prior to initiation of treatment with Losec MUPS for uninvestigated dyspepsia.

The FDA has recently recommended OTC reclassification for Losec MUPS 20 mg as a 14 day treatment for the prevention of frequent heartburn. Procter & Gamble provided several studies in support of this reclassification that demonstrated efficacy in the OTC setting where patients were self-selected on the basis of a history of heartburn symptoms two or more days per week.

The reclassification from Prescription Medicine to Pharmacy medicine of a short-term treatment course for a chronic/relapsing condition has ample precedent in New Zealand. For example, OTC nasal steroids, such as budesonide, beclomethasone and fluticasone, are indicated for short-term prophylaxis or treatment of seasonal allergic rhinitis (hayfever). As with heartburn, hayfever is effectively a chronic/relapsing condition.

Neither nasal steroids nor Losec represent cures. Both are intended to provide short-term prevention of symptoms. Over time both heartburn sufferers and seasonal rhinitis sufferers would be expected to relapse and require a further short course of treatment.

It was noted in the MCC minutes that a condition that is suitable for self-medication, is one that is usually capable of rapid and spontaneous relief. Nasal steroids do not provide rapid or spontaneous relief of rhinitis as it usually takes two to three days for full effect. The data provided by Procter & Gamble to the FDA similarly demonstrate a greater percentage of patients with days heartburn free at 14 days than the percent of subjects heartburn free at Day 1.

OTC nasal steroids warn patients to seek medical advice if symptoms are not relieved after 7 days. A similar warning is proposed for Losec in that patients should seek medical advise if symptoms have not improved or become worse after 14 days treatment. In both situations this warning alerts patients to medical attention to rule out a more serious underling condition.

Clinical Data to Support Indication

Losec 20 mg has been widely studied in the treatment of dyspepsia patients with symptoms of epigastric pain and /or heartburn. These studies demonstrated superior efficacy compared with both antacid-alginates as well as H2-antagonists.

The table below summarises the proposed OTC with the corresponding studies presented below.

Uninvestigated Dyspepsia • FDA Studies 171 & 183 [7] • Study DC-OMD-002 [9]
Losec MUPS* • FDA Studies 171 & 183 [7] • Study DC-OMD-002 [9] • *Note: Losec MUPS (omeprazole magnesium) is bioequivalent to Losec capsules (omeprazole sodium) but not interchangeable.
14 days therapy • Study I-1602a [8] • Bardhan et al [6] • FDA Studies 171 & 183 [7]

Some of the studies listed above are performed with Losec capsules (omeprazole sodium), however this application seeks approval for Losec MUPS tablets (omeprazole magnesium) only. It should be noted that Losec MUPS tablets and Losec capsules are bioequivalent but not interchangeable.

Comparative Data for Losec 20 mg

Bardhan et al [6] – 14 days / Relapse

Bardhan et al randomised 677 patients to either Losec 20 mg once daily, Losec 10 mg once daily or ranitidine 150 mg twice daily for two weeks.

At week two, the proportion of patients without symptoms were: 55% for Losec 20 mg, 40% for Losec 10 mg and 26% for ranitidine 150 mg *bid* ($p<0.001$). This corresponds to an incremental benefit of 19% for Losec 20 mg over and above ranitidine 150mg *bid*.

Table 1 – Summary of results

	Omeprazole 20 mg od (n=221)	Omeprazole 10 mg od (n=227)	Ranitidine 150 mg *bid* (n=229)
Asymptomatic at 2 weeks	122 (55%)	91 (40%)	60 (26%)

Thus, significantly more subjects treated with Losec 10 and 20 mg had symptom resolution at 2 weeks compared with ranitidine 150 mg *bid*. These subjects remained off therapy for a median of 281 days. Those patients not responding to initial therapy could be readily self-identified because of on-going symptoms and would be candidates for further investigation.

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

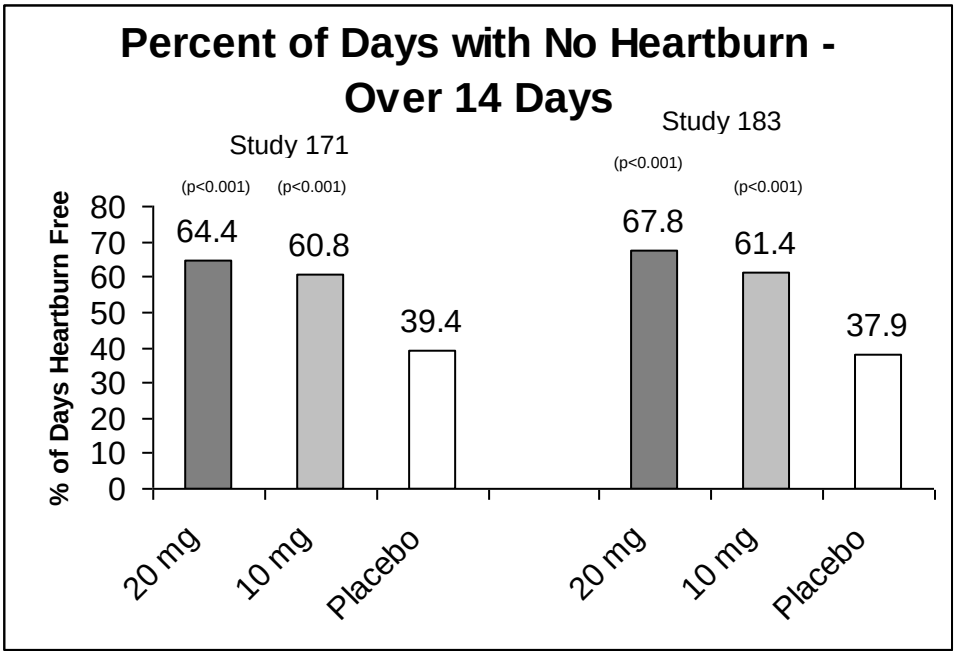
Losec 20 mg therefore allows a greater proportion of patients to remain symptom free for longer compared with ranitidine at maximum doses.

Studies 171 & 183 submitted to FDA [7]– Losec MUPS / 14 days / Uninvestigated

Proctor and Gamble submitted clinical material to the FDA to seek a change in prescription status of omeprazole magnesium (Losec MUPS) to OTC. Their studies were presented to the FDA and discussed at a Joint Meeting of the Non-prescription Drugs and Gastrointestinal Advisory Committees on October 20, 2000. The attached briefing document (X2) submitted to the FDA contains summaries of studies that investigated Losec MUPS effectiveness in preventing heartburn.

Studies 171 and 183 evaluated uninvestigated patients suffering from heartburn and were administered Losec MUPS for 14 days. Patient selection mimicked an OTC setting as they were self-selected on the basis of a history of heartburn symptoms two or more days per week These were both randomised, multicentre, parallel double blind/double dummy studies evaluating the efficacy and safety of Losec MUPS in the prevention of heartburn symptoms over a 24-hour period over 14 days. Collectively 3,162 patients were randomised to receive Losec MUPS 20 mg, Losec MUPS 10 mg or placebo. The results are summarised in the graph below.

Figure. 1



p-values vs. placebo

With consecutive daily dosing, Losec MUPS treated patients had significantly (p=0.001) greater percentage of heartburn-free days than placebo treated patients. In addition Losec MUPS treated patients had a greater percentage of nights with no nocturnal heartburn symptoms. Consecutive daily dosing with Losec MUPS also resulted in a greater percentage of days with “no more than mild heartburn” verses placebo. For all outcomes Losec MUPS provided significantly greater protection against heartburn than placebo in both studies.

It should be noted that the primary outcome measure in studies submitted by GSK to reclassify Zantac 75 mg tablets was “success rates per daily dose” [11]. This was defined as adequate pain relief within 60 minutes and sustained for at least two hours where the studies 171 and 183 have a more stringent outcome measure of “days heartburn free” defined as no heartburn over 24 hours [7].

Study I-1602a [8] – 14 days

I-1602a is a randomised, double blind multicentre study in UK general practice with a parallel group design. Nine hundred and ninety seven patients with heartburn as the predominant symptom of GORD were randomised to be treated with either omeprazole (Losec capsules) 20 mg once daily, omeprazole 10 mg once daily or ranitidine 150 mg twice daily. The primary objective was to compare the efficacy of the above 3 treatments over 4 weeks in respect to relief of heartburn.

Heartburn was the main inclusion criteria to be experienced by all patients at randomisation. The next most common symptom of GORD at presentation was regurgitation (approx. 75% of patients). Epigastric pain was reported by 63% of patients, nausea by 43%, dysphasia by 22% and vomiting by 11%.

The proportion of patients reporting these symptoms was reduced in all three treatment groups after 2 and 4 weeks. The most pronounced, and statistically significant differences between treatments were in the relief of heartburn. Tables 2 and 3 below summarise the results.

Table 2 – % of patients with no heartburn at randomisation (Day 0), 14 and 28 days.

	Day 0	Day 14	Day 28
Ome 20 mg	0%	40%	52%*
Ome 10 mg	0%	30%	38%*
Raniditine 150 mg	0%	20%	32%*

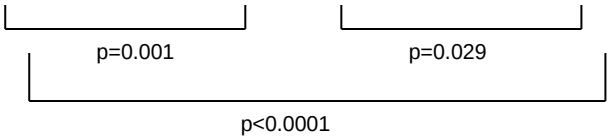
*Ome 20 mg vs 10 mg: p=0.001

Ome 20 mg vs ranitidine: p<0.0001

Note no statistical analyses were performed on Day 14 results.

Table 3 – Proportion of patients experiencing sufficient control of heartburn (per protocol analysis)

	Ome 20 mg	Ome 10 mg	Ranitidine
Sufficient relief*	64%	51%	42.3%



* Sufficient relief of heartburn was defined as no heartburn or no more than one day with no more than mild heartburn in the 7 days prior to clinic visit 3 (day 28). Hence omeprazole 20 mg was superior to omeprazole 10 mg and raniditine 150 mg in providing sufficient control of heartburn.

The results of this study demonstrate that treatment with omeprazole 20 mg once daily was superior to omeprazole 10 mg once daily or raniditine 150 mg twice daily in providing complete relief of heartburn after 4 weeks of treatment. Although no statistical analyses were performed on data collected at visit 2 (14 days), results at 14 days (refer Table 2) indicate considerable symptom improvement.

DC-OMD-002 [9] – Uninvestigated / Losec MUPS

A study in Canada measured the proportion of *Hp*-negative patients who were successfully treated in terms of global overall dyspepsia symptom severity score at six months following administration with either omeprazole magnesium (Losec® MUPS®), ranitidine, cisapride or placebo.

Five hundred and ten uninvestigated dyspepsia patients were randomised from 35 physician centres across Canada. Patients who proved to be *Hp*-negative received omeprazole, ranitidine, cisapride or placebo for a 4 week continuous treatment phase, followed by a five month follow up on-demand treatment period with the same medications. Patients in the study were treated with either omeprazole 20 mg once daily, ranitidine 150 mg twice daily, or cisapride 20 mg twice daily (10 mg bid during the on-demand phase). Following warnings issued by the FDA in January 2000, the cisapride treatment arm was terminated early.

Table 4 – Efficacy results

	Omep. 20 mg n= 135	Ranit. 150 mg bid n=139	Cisa. 20 mg bid (10 mg bid prn phase) n=105	Placebo n=133
Proportion of patients with treatment success at 4 weeks	51%	36%*	31%*	23%*

* = significantly different from omeprazole ($p<0.05$)

In uninvestigated, *Hp*-negative patients, a four-week continuous therapeutic treatment course with omeprazole resulted in a higher proportion of patients reporting relief of dyspepsia symptoms compared with ranitidine, cisipride and placebo treatment. By sub classifying dyspepsia, better response rates were observed for omeprazole compared with ranitidine, cisipride and placebo for patients with ulcer-like and reflux-like dyspepsia.

The British Society of Gastroenterology Dyspepsia management guidelines 1996, recommend “it is acceptable to institute a single course of anti-secretory agent for 2-4 weeks in patients under 45 with troublesome symptoms but without alarm symptoms”. They also recommend that blood should be sent for *H. pylori* serology testing. However the value of widespread testing for *H. pylori* infection is an issue that has been widely debated within the literature. As indicated by the Genval Guidelines [5], testing is important in a small subset of patients suspected of peptic ulcer disease, as eradication of *H. pylori* infection does not heal or prevent reflux disease. New Zealand gastroenterologists and IPAs do not recommend routine *H. pylori* testing of the dyspepsia population. Hence *Hp* testing is not recommended prior to initiation of treatment with Losec MUPS for uninvestigated dyspepsia.

Justification of Maximum Treatment Period and Dose

As demonstrated in the studies above 14 days is an effective treatment duration. In addition the studies show that Losec 20 mg once daily for 14 days is superior to ranitidine twice daily that is currently available OTC treatment regimen. The proposed dosage and duration of treatment has also been recommended approval by the FDA for OTC use.

The proposed dosage regimen is in line with The British Society of Gastroenterology Dyspepsia management guidelines 1996, which recommend “it is acceptable to institute a single course of anti-secretory agent for 2-4 weeks in patients under 45 with troublesome symptoms but without alarm symptoms”[5].

Special Precautions

Special Precautions Related to the Indications

Due to the low risk associated with masking underlying diseases, consumers with heartburn and symptoms related to gastric hyperacidity need to be clearly told under what circumstances they should seek further advice. This advice is provided in the CMI for Losec 20 mg, as is the case for H2-antagonists.

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

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

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

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

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

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

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

In line with the Medsafe evaluator's report for initial our submission, we have deleted the warning statements of pregnancy and breastfeeding as the current Losec datasheet states that Losec can be used during pregnancy and although it is excreted in breast milk it is not likely to influence the child when therapeutic doses are used [10].

Special Precautions Related to the Product

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

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

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

In line with the Medsafe evaluator's report for our initial submission, we have deleted the warning statement to ask your doctor or pharmacists if you have been told you have an ulcer [10].

Appendix 1

- Proposed labelling and pack insert

References

1. Minutes from the 26th Meeting of the Medicines Classification Committee Meeting.
2. Losec MUPS 10mg and 20mg OTC Assessment, Sweden.
3. Scrip, Article S00760194, 25 June 2002
4. Memorandum, Department of Health & Human Services (FDA), 23 May 2002.
5. Dent, J. *et al*., An evidence-based appraisal of reflux disease management – the Genval Workshop Report, Gut, 1999, 44 (Suppl. 2), S1-S13.
6. Bardhan, K.D. et al., Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine, Brit. Med. J., 1999,318, 502-507.
7. Proctor and Gamble and Company NDA No 21-229. Non-prescription Drugs and Gastrointestional Drugs Advisory Committee Briefing Document. October 20, 2000. (Sourced from FDA website).
8. I-1602a
   Reflux symptoms: Omeprazole evaluated in general practice (RESOLVE)
   24 May 1995.
9. DC-OMD-0002
   The CADET-HN study (Canadian Adult Dyspepsia Empirical therapy: *Helicobacter pylori (Hp)* – Negative): Evaluation of symptom relief provided by empirical therapy with omeprazole, ranitidine, or cisapride, in *Hp*-negative adults with uninvestigated dyspepsia: a placebo controlled randomised trial. 15 October 2001.
10. Medsafe evaluation report of initial submission.
11. Application to Schedule Zantac 75 Tablets as a Pharmacy Medicine – GSK submission (not enclosed).