Investigation

1. **The proposed strength, quantity, dosage form, dose and route of administration of the medicine including indication**

10mg

Blister packs of 14

Solid dose form for oral administration. It is unclear whether the application applies solely to the MUPS tablet or includes the 10mg capsule.

Dose: One to two units to be taken once a day for no more than fourteen days. This needs to be changed to one to two tablets instead of units.

Indication: symptomatic relief and short-term prevention of the recurrence of heartburn and indigestion

2. **Approved indications**

(Omeprazole 10mg, 20mg and 40mg)
Treatment of:

- Reflux oesophagitis
- Duodenal ulcer
- Gastric ulcer
- NSAID-associated gastric and duodenal ulcers or erosions
- Acid related dyspepsia
- Zollinger-Ellison syndrome

In the treatment of peptic ulceration, the eradication of *H.pylori*, as the causative organism, must be a high priority. Accordingly, Losec should be used as part of combination therapy for the eradication of *H.pylori*.

Maintenance treatment of:

- Reflux oesophagitis
- Duodenal ulcer
- Gastric ulcer
- Zollinger-Ellison syndrome

Note starting doses recommended for omeprazole are generally 20mg daily for 2-4 weeks depending on the condition, except in the case of acid related dyspepsia where 10mg may be considered as a starting dose. 10mg daily is also recommended for long-term management of patients with healed reflux oesophagitis and for prevention of relapse in patients with duodenal ulcer disease, however durations are not given and one would assume at least 1-3 months. Other indications require higher doses.

The sponsor requests the indication “symptomatic relief and short-term prevention of the recurrence of heartburn and indigestion”. The main issue is whether this is covered or not by the currently approved indications for Losec 10mg, and if not whether a new indication must be applied for.

The most closely related of the currently approved indications is “acid related dyspepsia”. The data sheet dosing instructions for this are as follows:

Acid related dyspepsia

For relief of symptoms in patients with epigastric pain/discomfort with or without heartburn the recommended dosage is LOSEC 20 mg once daily. Patients may respond adequately to 10 mg daily and this dose could be considered as a starting dose.

If symptom control has not been achieved after 4 weeks treatment with Losec 20 mg daily, further investigation is recommended.

Note that a duration is not specifically mentioned, however it would seem unlikely that 10mg daily for 2 weeks would be sufficient and the company has certainly not provided evidence to confirm their dosage regimen.

If acid related dyspepsia is not considered to cover the indication requested in this submission then the company must supply further data supporting their claims:
i.e. efficacy in symptomatic relief (is this acute relief of symptoms after one tablet or is this relief gained after taking a course of tablets?)
And efficacy in short-term prevention of the recurrence of heartburn and indigestion (the duration of short-term needs to be given and relevant clinical trial data supplied).

3. How long has the particular product been marketed?

Omeprazole has been available as a prescription medicine in New Zealand since 1990. Losec MUPS 10mg was approved in New Zealand in February 2001.

4. Overseas regulatory status

Omeprazole is a prescription medicine in 22 countries.

Losec MUPS 10mg and 20mg were approved for non-prescription use in Sweden in December 1999 with the following indication: symptomatic short-term relief of heartburn and acid regurgitation (in pack sizes of 7 and 14 tablets).

An application for OTC status for omeprazole (Prilosec) in the United States by Proctor and Gamble was reviewed by an FDA advisory committee in October 2000.[1] The application requested approval of omeprazole in the OTC setting for the same indications as antacids and acid reducers (treatment of acute occasional heartburn symptoms) and the additional claim that applies to the acid reducers only (prevention of meal induced heartburn symptoms if ingested at specified times prior to a meal), plus a new claim of 24 hour

[1] Final minutes of the Joint Meeting of the Nonprescription Drugs & Gastrointestinal Advisory Committees. Food and Drug Administration. Center for Drug Evaluation and Research. October 20, 2000. Available on http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Gastrointestinal

prevention of heartburn. Their findings are discussed below and appended with this document.

The committee did not find in the studies submitted sufficient evidence of a clinically significant improvement of acute symptomatic heartburn (i.e. sustained complete relief of the first treated episode of heartburn) in either the 10 or 20mg omeprazole groups compared to placebo. Whereas, in the studies with the primary endpoint for efficacy being the complete prevention of heartburn between the first two doses of therapy, the committee did find clinically significant improvement in heartburn symptoms compared to placebo.

The committee was divided on whether the safety concerns could be addressed in the label (they considered anaphylaxis/angiodoedema/urticaria, liver toxicity, white blood cell disorders and severe skin reactions). The majority of members considered that other safety concerns (such as rebound hyperacidity, hypergastrinaemia, tumorigenicity) did not affect acceptability of the OTC marketing of omeprazole.

The committee were divided over whether the treatment of chronic heartburn or gastro-esophageal reflux (GERD) was an acceptable OTC indication. It appears that the application was turned down although confirmation of this was unable to be found on the FDA web site.

5. Demonstrated efficacy (i.e. its ability to produce a wanted pharmacological effect at the proposed dosage)

The AstraZeneca submission to Medsafe claims that its "present application to Medsafe is able to provide a wealth of additional trial data addressing Losec's efficacy in relieving heartburn." However, none of the studies provided demonstrate the efficacy of omeprazole in *rapid* symptomatic relief of heartburn after a single dose. This is contrary to the company consumer medicine information leaflet, which says, "Losec begins to relieve symptoms rapidly and after treatment with Losec, most patients find that symptoms do not return as frequently."

Furthermore, apart from one study which compared 10mg omeprazole with antacid/alginate over 2 and 4 weeks[2] there is an absence of efficacy data for either omeprazole 10mg daily for 14 days or 20mg daily for 7 days in the prevention of heartburn and indigestion. The studies provided were in general of at least 4 weeks duration (although in one study symptoms were reviewed at 2 weeks[2]) [3,4,5]. In addition, there is large individual variability in duration of

[2] Goves J et al. First line treatment with omeprazole provides an effective and superior alternative strategy in the management of dyspepsia compare to antacid/alginate liquid: a multicentre study in general practice. *Aliment Pharmacol Ther* 1998;12:147-57.
[3] Talley NJ et al. Efficacy of omeprazole in functional dyspepsia: double-blind, randomised, placebo-controlled trials (the Bond and Opera studies). *Aliment Pharmacol Ther* 1998;12:1055-65.
[4] Savarina V et al. Variability in individual response to various doses of omeprazole Implications for antiulcer therapy. *Digestive diseases and sciences* 1994;39(1):161-8.

acid suppression in those taking omeprazole 10mg (mean 13 hours) compared with omeprazole 20mg and 40mg (means 19 and 21 hours respectively) [4] which may reduce the efficacy of the 10mg dose in particular in short courses.

In addition the studies examining the benefits of intermittent treatment all used an initial short-term course (for 2-8 weeks) followed by on-demand treatment. The intermittent therapy dose of omeprazole was either randomly selected from 10mg or 20mg[6] or was the dose that had been successful in the initial course[7,8] for a duration of 2-4 weeks[7,8] or up to 6 months.[6] Neither the efficacious omeprazole dose nor duration of treatment for the intermittent regimen for symptom relief appears to have been defined.

Most studies involved a full course of treatment. It is not clear in the company's submission whether the dose regimen for reclassification is use on an as required basis or use as a 7 or 14-day course. This confusion is reflected in a discrepancy between the dose instructions on the outside packaging and in the inside consumer information leaflet:
Outside package: 1-2 units as needed for your symptoms,
Leaflet: take 1-2 Losec tablets once daily for 7-14 days….To get the best results and to prevent your symptoms returning as frequently, you should continue your treatment with Losec for 7-14 days even if your symptoms show signs of improvement.

6. Is the product intended for treatment of a minor ailment or symptom readily identifiable by the user, which is capable of rapid spontaneous resolution and for which a medical consultation is not necessary?

The British Society of Gastroenterology[9] defines dyspepsia as "a group of symptoms which alerts doctors to consider disease of the upper gastrointestinal tract. It is not a diagnosis and includes symptoms of upper abdominal discomfort, retrosternal pain, anorexia, nausea, vomiting, bloating, fullness, early satiety and heartburn amongst others…. Many diseases cause dyspepsia and these include peptic ulcers, oesophagitis, cancer of the stomach or pancreas, and gallstones. In a large proportion of cases no clear pathological cause for a patient's symptoms can be determined." The

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[5] Mason I et al. The management of acid-related dyspspsia in general practice: a comparison of an omeprazole versus an antacid-alginate/ranitidine management strategy. *Aliment Pharmacol Ther* 1998;12:263-71.

[6] Lind T. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis – a placebo-controlled randomised trial. *Aliment Pharmacol Ther* 1999;13:907-14.

[7] Bardhan KD et al. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. *BMJ* 1999;318:502-7.

[8] Wiklund KD et al. Quality of life during acute and intermittent treatment of gastro-oesophageal reflux disease with omeprazole compared with ranitidine. Results from a multicentre clinical trial. *Ital J Gastroenterol Hepatol* 1998;30:19-27.

[9] British Society of Gastroenterology. *Dyspepsia management guidelines.* 1996. Available on http://www.bsg.org.uk/clinical_prac/guidelines/dyspepisia.htm

prevalence of dyspepsia is high in Western societies (20-40%)[9,10] and the majority of sufferers do not consult a doctor.[9]

Episodic or short-lived heartburn and indigestion related to food and drink are conditions easily recognisable by the user and the condition will not be serious. In these cases immediate symptom relief will be sought not a course of treatment. More serious or chronic problems will usually need medical input. The British Society of Gastroenterology[9] advises that "it is acceptable to institute a single course of treatment with an anti-secretory agent for 2-4 weeks in patients under 45 with troublesome symptoms but without alarm symptoms". However they also recommend that blood should be sent for *H.pylori* serology testing.

The above symptoms are easily recognised by the patient, although not all will understand the word heartburn. The submission includes a paper which examined the efficacy of language in identifying patients with GERD; they found that a word picture was better than just saying "heartburn".[10] The proposed OTC omeprazole package describes heartburn as a burning feeling rising from the stomach or lower chest up towards the neck.

7. Likelihood of mis-diagnosing, masking or compromising the appropriate medical management of a disease

The British Society of Gastroenterologists state that a diagnostic endoscopy is appropriate when alarm symptoms or signs are present (weight loss, iron deficiency anaemia, GI bleeding, dysphagia, previous gastric surgery, persistent vomiting, vomiting, previous ulcer, severe pain), or any patient over the age of 45 with recent onset dyspepsia, or patients under the age of 45 with troublesome dyspepsia who are positive for *H.pylori* on non-invasive testing.

The major concern is masking gastric cancer. However, according to the British Society of Gastroenterology *Dyspepsia Management Guidelines*[9] the majority of patients with gastric cancer will present with characteristic symptoms (dysphagia, weight loss) and the *Guidelines* quote a rate of less than 3% of gastric cancers occur in those aged under 45. This product is for short-term use and a delay of 2 weeks is unlikely to affect prognosis of more serious conditions. The proposed warning statements appear appropriate.

8. Requirement for professional advice from a medical practitioner, dentist or pharmacist

From the submission it would appear that intermittent therapy should be used only after successful initial treatment from a doctor. In addition *H.pylori* testing requires a visit to a doctor. Hence it may not be appropriate for people to self medicate, in particular for the initial treatment.

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[10] Carlsson R et al. The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. *Scand J Gastroenterol* 1998;33:1023-29.

9. Requirement for supervision of sale by a pharmacist

There may be a need for an explanation regarding the difference between OTC H2antagonists (which have been demonstrated to give rapid relief of symptoms and could conceivably be used singly on an as required basis) and omeprazole (which works to suppress acid secretion over a matter of days and requires a full course to be taken) to ensure that the product is used appropriately.

Safety concerns seem to be mostly satisfied by the warnings, however the NZ Society of Gastroenterology imply that a pharmacist should be involved in the sale of OTC omeprazole because they request “inclusion of warnings relating to possible drug interactions be included with the package inserts and that pharmacists bring these to the attention of patients when the[y] dispense Omeprazole over the counter.”

10. Proposed labelling and warning statements

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

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

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

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

While taking Losec patients will be advised to seek advice if

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

Given that the efficacy evidence provided for intermittent treatment include those with ulcers who have been treated then the warning statement “have been told you have an ulcer” should be modified or deleted.

See 11. for comment on the statement “are taking any other medicine”. Should be more specific and include in the consumer leaflet the particular medicines involved.

The current omeprazole data sheet says that Losec can be used during pregnancy and that although it is excreted in breast milk it is not likely to influence the child when therapeutic doses are used. Also no dose adjustment is needed in renal impairment. Hence consideration should be given to whether these warning statements are necessary.

The points about having *any* allergies or *any other* medical condition seem excessive.

[Note warning statements for OTC H2 antagonists, which must be contained in the consumer information, are as follows:
a warning not to use the medicine for any purpose other than that specified on the pack unless under the supervision of a doctor
the need to consult a doctor if symptoms persist
the need to consult a doctor if symptoms recur
the need to consult a doctor if symptoms become worse
the need to consult a doctor if new or additional related symptoms occur
a warning against use with non-steroidal anti-inflammatory medicines unless under the supervision of a doctor
a warning to use with caution if over 40 years of age
a warning not to use without medical supervision if warfarin, phenytoin or theophylline are being taken (for cimetidine only).]

11. Hazard potential, including likelihood for any adverse effects

Omeprazole has been used extensively and has an excellent safety record. It has highly specific activity, rapid clearance and activation only in acidic channels. The most common side effects in short term studies were headache, nausea, diarrhoea (dose-related[11], overall incidence <5%), abdominal pain, constipation, and dizziness.[12]

Drug interactions (see also pharmacokinetics section on metabolism and abstract provided by the NZ society of Gastroenterology). There are three mechanisms by which omeprazole can cause interactions:

(a) pH dependent drug absorption – affecting low gastric pH dependent medicines, e.g. ketoconazole, itraconazole (concentration in plasma reduced[13]), digoxin (10% reduction in absorption[11]), ampicillin, iron salts. Aspirin and NSAIDs have other sites of absorption and are not considered to be affected. Increases the absorption of nifedipine by

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[11] Reilly JP. Safety profile of the proton-pump inhibitors. *Am J Health-Syst Pharm* 1999;56(supp4):s11-17.

[12] Bate CM et al. Evaluation of omeprazole as a cost-effective diagnostic test for gastro-esophageal reflux disease. *Aliment Pharmacol Ther* 1999;13:59-66.

[13] Jaruratanasirikul S et Sriwiriyajan S. Effect of omeprazole on the pharmacokinetics of itraconazole. *Eur J Clin Pharmacol* 1998;54:159-61.

26%.[11] The co administration with antacids does not lead to additional clinically significant interactions.

(b) Inhibition of CYP450 enzyme metabolism – omeprazole reduces diazepam clearance by 25%, reduces carbamazepine clearance, increases the concentration of Rwarfarin (may not influence coagulation[14] except at high dose[11] as the Swarfarin, which is more potent, is unaltered[12]), reduces the absorption of vitamin B12,[12] reduces phenytoin clearance[11]. According to an abstract submitted from the NZ Society of Gastroenterolgy, "most of these interactions [via CYP2C19 inhibition] are not clinically significant although reductions in the clearance of phenytoin, warfarin and diazepam may be important in some individuals".

(c) Induces CYP450 system. This may be via CYP1A/1A2 induction, which can result in possible theophylline clearance although this is not well proven according to the above abstract.

Hence the interaction potential with phenytoin, warfarin, and theophylline seems to be the most clinically relevant.[11] It is interesting to note that pantoprazole and rabeprazole are weaker substrates for CYP3A4/2C19 and have fewer drug interactions than omeprazole.[12]

Hypochlorhydria may result in malabsorption of fat, vitamin B12 and iron. In the vast majority this has not been found to be of clinical relevance, however a small percentage of patients on long-term treatment have been found to have reduced serum B12 levels, and there has only been one report of overt deficiency.[12] Hypochlorhydria has also been thought to weaken the stomach's defence and cause bacterial overgrowth and enteric infection, the significance of this has not been confirmed.[12]

Atrophic gastritis appears to be more related to *H.pylori* infection although it is still possible that PPI treatment may accelerate the course of *H.pylori* gastritis.[12]

Rebound hyperacidity occurs in patients treated long term and its average duration is not known. It may be related to parietal cell hyperplasia but the long-term significance of this is uncertain.[12]

All PPIs raise gastrin levels to at most four times baseline.[11] These levels are higher with PPIs than H2 antagonists. Secondary hypergastrinaemia has led to concerns about risks of gastric cancer and carcinoid tumours, plus also parietal cell hyperplasia, colonic adenomas, and adenocarcinoma. Hypergastrinaemia and ECL cell hyperplasia leading to carcinoid was seen in rats,[12] and in humans ECL changes have been seen but not causing carcinoids.[15] Gastrin returns to normal within one week of stopping treatment.[12]

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[14] Svedberg et al. A study of the interaction of omeprazole and warfarin in anticoagulated patients. *Br J Clin Pharmac* 1992;34:509-12.

[15] Klinkenberg-Knol EC et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. *Gastroenterology* 2000;118:661-9.

The above adverse effects are rare but serious. Expansion of the market into OTC is likely to produce an increase in incidence of these adverse effects and these may be difficult to address in the labelling. However most of the serious adverse effects are related to long-term treatment, therefore reassurance that consumers would use this medicine only in the short-term (i.e. follow the labelling) would be useful.

12. Any relevant data on post-marketing experience

Omeprazole was monitored on the IMMP from 1990-1996, achieving a cohort of 22,050. It had a very low reaction rate compared to other monitored medicines. Gastric polyps, carcinoid, hyponatraemia, polymyositis, vitamin B12 deficiency and interstitial nephritis were rare but generated signals.
The Centre for Adverse Reactions Monitoring wrote an article for *Prescriber Update* on omeprazole and interstitial nephritis after 7 reports of acute renal failure were received plus 2 on the IMMP.

A long-term safety study[15] over a mean of 6.5 years in subjects taking at least 20mg of omeprazole daily showed the incidence per year of gastric corpus mucosal atrophy was higher in *H.pylori* positive patients. In both groups the atrophy occurred in patients with moderate to severe gastritis, if these patients were analysed separately the incidences were similar regardless of *H.pylori* status. Gastrin levels were measured, the majority of the increase occurred during the first year with only slight further increases thereafter. A few patients had unusually high levels of gastrin. After 11 years of treatment there were no cases of dysplasia or neoplasia.

13. Potential for inappropriate use of the medicine

Given the large number of people with dyspepsia and heartburn who self-medicate and do not see a doctor, there is a potentially large risk of prolonged use of omeprazole OTC. However one could argue that this risk is present for use of OTC H2antagonists, although providing another therapeutic option may exacerbate the potential problem. The company submission provides no data on this risk.

14. Potential for abuse of the medicine (e.g. non-therapeutic use of the medicine for self-gratification)

Nil

15. Current availability of other products with similar benefits

Antacids that are general sale medicines are also available. These produce a short-lived effect on gastric pH. They can cause problems with diarrhoea and constipation and reduced absorption of some medicines due to change in pH.

H2 antagonists available pharmacy only are ranitidine 75mg and famotidine 10mg. Other strengths plus cimetidine and nizatidine are restricted medicines. All are restricted to 14 days supply. OTC H2 antagonists are approved for

short-term symptomatic relief of heartburn, dyspepsia, excess acid (hyperacidity), or on recommendation of a doctor. Doses for the H2 antagonists are on an as required basis, rather than a full course.

16. Any public health advantage associated with the availability of these medicines

No. May be a disadvantage if *H.pylori* in the community is not being treated. However the majority of people with these conditions self-medicate currently.

17. Patient convenience including geographical factors

Not relevant, patients can obtain H2 antagonists from pharmacy.

18. Monitoring

Not required.

19. Education

As alluded to above the public would need extensive education regarding the manner of use of these products, i.e. a course not single doses as required.

20. Comments from other interested parties

Letter from NZ Gastroenterology Society
Comments from GlaxoSmithKline
Comments from Pharmaceutical Society and Pharmaceutical Guild

21. Pharmacokinetics

Bioavailability of omeprazole is 35% after the first dose and 60% after repeated daily oral administration[12].

PPIs cause irreversible inhibition of the proton pump. Therefore duration of acid suppression after one oral dose (30-40mg) is similar for all, as duration of effect is a function of resynthesis rate of proton pumps rather than the half-life of the drug. I.e. full restoration takes 96 hours, half-life of the PPI is 1-2 hours, and duration of acid suppression is 24-36 hours. Degree of acid suppression is a function of bioavailability. Acid secretion is required for PPI activation, and therefore the best effect occurs if taken half an hour before food, there is also increased absorption in the morning. 75-80% of the proton pumps are stimulated by a meal and therefore available for inhibition. However 20-25% of pumps will not be inhibited so acid suppression is not complete.

Omeprazole undergoes first pass metabolism by the liver, it is highly protein bound (>95%). It is extensively metabolised by the CYP450 system. Omeprazole in particular of the PPIs, is metabolised by CYP2C19 and CYP3A4. CYP2C19 has genetic polymorphism and hence a small proportion

of the population (3% of Caucasians, 15% of Asians[16]) will be poor metabolisers of PPIs. This increases the AUC but has not been thought to be clinically relevant as omeprazole is well tolerated and safe.[15] None of the PPIs are known to interact significantly with CYP3A4 dependent drug metabolism.

Cirrhosis increases the AUC and the elimination half-life by 100%, but omeprazole is usually very quickly eliminated and has once daily dosing so therefore there is minimal accumulation. This is true for the elderly also[12,15] where dose change is also not needed.[12] In addition no change in dose is needed in renal insufficiency, as it is completely metabolised before excretion in urine.[15]

Conclusion

Reclassification of omeprazole 10mg from prescription only to pharmacy only is not recommended. AstraZeneca need to clarify the indication for OTC omeprazole and supply sufficient efficacy data. That is, is this product for use in the treatment of acid related dyspepsia, if so there needs to be more data on the efficacious dose and duration; or is this product for *immediate* symptomatic relief (which is likely to be what consumers are wanting from an OTC product) or relief *after a course of treatment;* or if the indication is the prevention of short-term recurrence then efficacy data is required as to what length of time short-term refers to (i.e. hours or days or months?).

More consideration is required of whether chronic diseases such as dyspepsia and heartburn are appropriate to be treated OTC and specifically whether they are amenable to intermittent courses of treatment without an initial course.

The safety of omeprazole has been well established, although rare but serious side effects do occur, in particular with long-term use. Drug interaction information should be included in the consumer leaflet.

Reclassification to restricted medicine could also be considered if the above problems with efficacy data and dosage instructions were addressed and additional advice provided to the consumer about appropriate use of the product.

ATTACHMENTS

Final minutes from the joint meeting of the non-prescription drugs & Gastrointestinal Advisory Committees, FDA

[16] Anderson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. *Clin Pharmacokinet* 1996;31(1):9-28.