Reclassification of pantoprazole 20 mg
From: Prescription Medicine
To: Pharmacist Only Medicine

Submission to:

Medicines Classification Committee
Medsafe New Zealand

Submission from:

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Australia

31 January 2009

CONTENTS

EXECUTIVE SUMMARY

Gastro-oesophageal reflux disease (GORD) is the most common peptic acid disease in the western world and is the commonest indication for acid suppression therapy. In New Zealand, the prevalence is estimated to be 34.2% for dyspepsia, 30% for reflux and 45.2% for both symptoms combined.[1] Importantly, **1 in 4 have frequent symptoms**, suffering either daily or several times each week. The majority (69%) of heartburn sufferers use over-the-counter (OTC) medicines for symptomatic relief and only 17% have consulted a medical practitioner about their condition.[1]

Heartburn and acid regurgitation are the typical symptoms of GORD[2]. Therapy is focused on symptom control using acid-neutralizing or acid-inhibiting drugs in combination with general measures like weight loss and lifestyle changes. As such, the vast majority of patients with reflux symptoms can be managed at the self-care and primary care levels.[3]

In New Zealand, at the time of writing this submission, there are only two classes of OTC treatments for reflux symptoms like heartburn and acid regurgitation: antacids and histamine-2-receptor antagonists (H2RAs). These medications are well established in the market, with many of them being available in supermarkets and other general sales outlets. Yet, both have their limitations, particularly in people who suffer from frequent heartburn symptoms. Thus for sufferers of frequent heartburn without other atypical gastro-oesophageal reflux symptoms, a better treatment option is needed. Proton pump inhibitors (PPIs) have dramatically improved the management of GORD and are regarded as the mainstay of medical therapy today.[3, 4, 5, 6] PPIs are more potent acid suppressors than H2RAs and have been shown to be superior to H2RAs in the short-term relief of heartburn.[7]

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[1] Haque M, Wyeth JW, Stace NH, Talley NJ, Green R. Prevalence, severity and associated features of gastro-oesophageal reflux and dyspepsia: a population-based study. *N Z Med J* 2000 May 26;113(1110):178-181.

[2] Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006 August;101(8):1900-1920.

[3] Tytgat GN, McColl K, Tack J, Holtmann G, Hunt RH, Malfertheiner P, Hungin AP, Batchelor HK. New algorithm for the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2008 February 1;27(3):249-256.

[4] Galmiche JP, Stephenson K. Treatment of gastroesophageal reflux disease in adults: an individualized approach. *Dig Dis* 2004;22(2):148-160.

[5] Richter JE. The many manifestations of gastroesophageal reflux disease: presentation, evaluation, and treatment. *Gastroenterol Clin North Am* 2007 September;36(3):577-5ix.

[6] National Institute for Clinical Excellence. NICE Guideline - Dyspepsia: management of dyspepsia in adults inprimary care. www.nice.org.uk . 2004.
Ref Type: Internet Communication

[7] Triadafilopoulos G. Gastroesophageal reflux. *Curr Opin Gastroenterol* 2004 July;20(4):369-374.

This application seeks to reclassify the PPI pantroprazole 20 mg oral dosage form in packs of 14 dosage units from Prescription Only to Pharmacist Only. Pantoprazole is an established chemical entity for the treatment of acid related gastrointestinal disorders. Pantoprazole 20 mg has marketing authorisations as a Prescription Medicine in 79 countries (status as of 8 January 2009) worldwide. Pantoprazole 20 mg has been available OTC (equivalent to Pharmacy Only Medicine) in Sweden since 2000. Pantoprazole 20 mg was approved as a Schedule 3 (equivalent to Pharmacy Only Medicine) in Australia in June 2005. This was made effective in May 2008. OTC pantoprazole 20 mg was launched in Australia in October 2008 under the brand name Somac® Heartburn Relief.

The proposed Pharmacist Only pantoprazole 20 mg product would be indicated for the symptomatic relief of heartburn, acid regurgitation and other symptoms associated with GORD in patients aged 18 years or over**. The recommended dosage would be one pantoprazole 20 mg tablet per day for at least 7 days and up to 14 days.** The provision of packs of 7 or 14 tablets facilitates this dosing regime. The labeling, consumer medicine information and package insert will reinforce the appropriate use of the product.

As such, the availability of SOMAC® Heartburn Relief is expected to provide a significant contribution to patient care in the community by allowing treatment of heartburn with a product of well-established safety and improved efficacy as compared to the available OTC antacids and H2RAs.

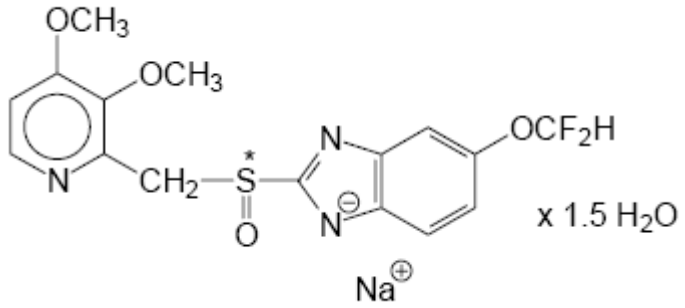
PART A

1. International non-proprietary name of the medicine

Pantoprazole sodium (as pantoprazole sodium sesquihydrate)

CAS Number: 138 786-67-1 (pantoprazole sodium)

The chemical structure of pantoprazole sodium sesquihydrate is:



2. Proprietary name

The proposed proprietary name is SOMAC® Heartburn Relief.

3. Name of company requesting reclassification

Nycomed Pty Ltd
2 Lyonpark Road
North Ryde NSW 2113
Australia

Contact person: Jennifer Connolly

Phone: (612) 9859 6932

Fax: (612) 9859 6950

Email: jennifer.connolly@nycomed.com

4. Dosage form and strength for which a change is sought

Dosage form: oral enteric-coated tablets.

SOMAC® Heartburn Relief tablets contains 22.6 mg pantoprazole sodium sesquihydrate, equivalent to 20 mg pantoprazole.

5. Pack size and other qualifications

SOMAC® Heartburn Relief tablets are available in blister packs of 2, 7 or 14 tablets. The tablets are yellow and oval shaped, marked with "P20" on one side.

6. Indications for which change is sought

This product is intended to be used for the management of frequent heartburn or other symptoms of gastro-oesophageal reflux disease (GORD).

Somac® Heartburn Relief is indicated for symptomatic relief of heartburn, acid regurgitation and other symptoms associated with GORD in patients aged 18 years or over.

7. Present classification of medicine

Pantoprazole is classified Prescription Medicine

8. Classification sought

Pharmacist Only Medicine (Restricted Medicine) for:

Pantoprazole in oral preparations containing 20 mg or less of pantoprazole for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease in packs containing not more that 14 days supply.

9. Classification status in other countries

Pantoprazole 20 mg has marketing authorisations as a Prescription Medicine in 78 countries worldwide.

Pantoprazole 20 mg has been available over-the-counter (OTC; equivalent to Pharmacy Only Medicine) in Sweden since 2000. Pantoprazole 20 mg was approved as a Schedule 3 (equivalent to Pharmacy Only Medicine) in Australia in June 2005. OTC pantoprazole 20 mg was launched in Australia in October 2008 under the brand name Somac® Heartburn Relief.

Two other low-dose proton pump inhibitors (PPIs) are approved for OTC use in a number of other markets worldwide:

PPI	Country	Year of OTC approval
Lansoprazole	Sweden	2000
Omeprazole	Sweden	2000
	UK	2004
	USA	2003
	Mexico	2003
	China	2004
	Denmark	2006

We note that there were three submissions to the MCC for the rescheduling of PPIs to Pharmacy Only Medicine status:

- Lansoprazole 15 mg modified release capsule (Solox Relief, Douglas)
- Omeprazole 10 mg modified release capsule (AstraZeneca)
- Omeprazole 10 mg modified release capsules (Omezol, Pacific)

They were reviewed by the Medicines Classification Committee in New Zealand at its 40th meeting. At the time of preparing this submission for pantoprazole 20 mg the outcome of these three earlier submissions is not known.

10. Extent of usage in NZ and elsewhere and dates of original consent to distribute

Global data:

The first international registration of pantoprazole 40 mg occurred in South Africa in February 1994. Worldwide oral dosage forms of pantoprazole (20 mg and 40 mg) are approved in 86 countries (as at 8 January 2009). As of February 2008, an estimated 665 million patients have been treated with oral pantoprazole, of whom approximately 80,500 were treated in clinical trials.

In Sweden, pantoprazole was available OTC since February 2000.

In Australia, pantoprazole OTC was launched in October 2008.

New Zealand data:

In New Zealand, pantoprazole 40 mg was registered in May 1995. Pantoprazole 20 mg tablets were approved in December 1998. Both strengths are classified prescription medicines.

11. Labelling or draft labelling for the proposed new presentation

A copy of the proposed labelling is provided in Appendix 1.

12. Proposed warning statements

The proposed packaging (Appendix 1) displays a bullet point list of warnings, alerting the consumer to the following key points:

- Use strictly as directed.
- Prolonged use without medical supervision could be harmful.
- Do not take Somac® Heartburn Relief if you have severe liver disease or cirrhosis.
- Do not take Somac® Heartburn Relief if you are taking atazanavir (an anti-viral medication).
- Check with your doctor or pharmacist before taking Somac® Heartburn Relief if you are pregnant/breastfeeding or may be pregnant/wish to start breastfeeding.
- Do not use Somac® Heartburn Relief if the foil blister is damaged.

The proposed Consumer Medicine Information (Appendix 2) provides further explanation to the consumer on the above key points.

13. Other products containing the same active ingredient that would be affected by the proposed change

Pantoprazole 20 mg tablet, enteric coated tablet 20 mg by Affordable Healthcare Ltd (launched Q1, 2008).

PART B

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

B1.1 Prevalence of GORD

GORD belongs to the most common diseases in modern civilization. In Europe and North America up to 44% of the population are reported to experience heartburn on a regular basis.[3, 12]

Figures for New Zealand are very similar. A population-based study conducted amongst 1000 subjects (aged 18 years or more) in Wellington, New Zealand has shown a 12-month prevalence of 34.2% for dyspepsia, 30% for reflux and 45.2% for both symptoms combined.[1] Whilst the majority (48%) of those who suffered reported suffering once a month, one quarter reported suffering either daily (6%) or several times a week (19%).

B1.2 Consumers' ability to self-manage heartburn

The signs, symptoms and clinical conditions associated with GORD result primarily from recurrent reflux of gastric acid into the oesophagus, which can be mediated by different mechanisms like e.g. transient lower oesophageal sphincter relaxations or reduced pressure, impaired oesophageal clearance, delayed gastric emptying, or hiatal hernia. No single predominant principle has been identified in the aetiology of GORD, and factors like hormonal and neuronal mechanisms, medications, food, and patient lifestyle can contribute to its pathophysiology.[3, 8]

Heartburn and acid regurgitation are the typical symptoms of GORD[2]. Heartburn is a symptom described as a retrosternal burning pain rising from the epigastrium which may radiate into the pharynx. Patients may experience heartburn for periods

[8] Boeckxstaens GE. Review article: the pathophysiology of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007 July 15;26(2):149-160.

ranging from less than one year (15%) to more than 10 years (29%).[3]

The therapy of uncomplicated GORD is focused on symptom control using acid-neutralizing or acid-inhibiting drugs in combination with general measures like weight loss and lifestyle changes. The vast majority of patients with reflux symptoms can be managed at the self-care and primary care levels. [3]

Treatment of reflux symptoms, e.g. heartburn and acid regurgitation, has been safely managed by OTC medications for decades. Consumers are able to self-recognize the symptoms, and safely self-treat. Antacids and histamine-2-receptor antagonists (H2RAs) are established OTC medications for the treatment of reflux symptoms and have been shown to be effective in self-treatment.[9] As the effect of antacids is short-lasting, they are primarily suitable for occasional post-prandial symptoms. H2RAs effectively inhibit gastric acid secretion, however, their efficacy diminishes over time due to the development of tolerance.[10] H2RAs were once considered standard care for the treatment of GORD, however their use has now been largely superseded with PPIs, which have greater efficacy (resulting in prolonged symptom relief) and safety.

PPIs have dramatically improved the management of GORD and are regarded as the mainstay of medical therapy today.[3-6] PPIs are more potent acid suppressors than H2RAs and have been shown to be superior to H2RAs in the short-term relief of heartburn.[7] PPIs can be used long-term without development of tolerance of the pharmacologic effect, in contrast to H2RAs. On-demand treatment of non-erosive reflux disease (NERD), as well as mild and uninvestigated forms of GORD, has been shown to be safe and effective.[11,12]

Some PPIs have already been approved as OTC medication for the treatment of reflux symptoms in some markets (refer to "Classification status in other countries", Section A, Part 9, above). Real world investigation has shown that consumers are able to self-

[9] Tran T, Lowry AM, El-Serag HB. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. *Aliment Pharmacol Ther* 2007 January 15;25(2):143-153.
[10] Lachman L, Howden CW. Twenty-four-hour intragastric pH: tolerance within 5 days of continuous ranitidine administration. *Am J Gastroenterol* 2000 January;95(1):57-61.
[11] Metz DC, Inadomi JM, Howden CW, van Zanten SJ, Bytzer P. On-demand therapy for gastroesophageal reflux disease. *Am J Gastroenterol* 2007 March;102(3):642-653.
[12] Pace F, Pallotta S, Bianchi PG. On-demand proton pump inhibitor therapy in patients with gastro-oesophageal reflux disease. *Dig Liver Dis* 2002 December;34(12):870-877.

treat reflux symptoms with PPIs, which have been shown to be safe and effective.[13],[14]

A recent report compiled for the Gut Foundation of Australia is supportive of the role of PPIs in heartburn management; stating "*It is clear from the report that many people endure symptoms that interfere with their way of life without accessing effective therapies that play a role by reducing acid secretion from the stomach, and thereby quite dramatically reduce symptoms*"[15].

B1.3 Potential to improve patient care

The New Zealand prevalence data, published in 2000, reported that 69% of heartburn sufferers used OTC medicines and that only 17% had consulted a medical practitioner about their condition.[1] Moreover, given that H2RAs have been made available in a general sales environment since this time, it is unlikely that this has changed in recent years. Thus, whilst people are self-treating they are doing so in an environment that does not give them easy access to professional advice.

The availability of a new Pharmacist Only heartburn relief medication is expected to drive more heartburn sufferers back into the Pharmacy; which in turn will positively impact public health by promoting a better use of professional expertise.

SOMAC® Heartburn Relief is expected to provide a significant contribution to patient care by allowing treatment of reflux symptoms like heartburn and acid regurgitation with a product of well-established safety and improved efficacy as compared to the available OTC antacids and H2RAs. Importantly, this access will be restricted to the Pharmacy setting, thus ensuring that the consumer has recourse to appropriate professional advice.

The availability of Pharmacist Only pantoprazole 20 mg would give consumers an alternative choice to antacids and H2RAs. By consulting their Pharmacist, consumers would be provided with timely counselling on the range of medications available to treat their condition. This will result in more appropriate medication choice, facilitated by Pharmacist recommendation, and ensure

[13] Inadomi JM, Fendrick AM. PPI use in the OTC era: who to treat, with what, and for how long? *Clin Gastroenterol Hepatol* 2005 March;3(3):208-215.
[14] Fendrick AM, Shaw M, Schachtel B, Allgood L, Allgood G, Grender J, Peura D. Self-selection and use patterns of over-the-counter omeprazole for frequent heartburn. *Clin Gastroenterol Hepatol* 2004 January;2(1):17-21.
[15] Access Economics Pty Ltd. Gut Instincts: the economic impact of GORD and PUD. 2007 May 3.

that frequent heartburn sufferers are given access to the most appropriate treatment for their symptoms rather than continuing to "*endure symptoms without accessing effective therapies*"[15] (as is thought to be the current practice for some people with frequent heartburn who self medicate with products purchased in the supermarket).

2. Ease of self-diagnosis or diagnosis by a pharmacist

A protocol and treatment algorithm, developed as part of the SOMAC® Heartburn Relief training programme (detailed below), have been based upon the understanding that Pharmacist intervention in the management of heartburn will facilitate early identification of atypical symptoms or red flags that warrant referral to a GP. Customers who seek the advice of a Pharmacist will be automatically screened using these tools and any patients with atypical symptoms or red flags will be referred to their GP. This, in turn, may lead to more timely medical consultation with resultant cost savings. One of the largest areas of cost reduction is likely to be in improved work productivity, particularly given GORD is a major contributor to productivity losses due to absenteeism, presenteeism and lower employment [15].

To facilitate the launch of SOMAC® Heartburn Relief as a Pharmacist Only medicine in Australia, Nycomed developed and implemented an extensive Pharmacy education programme to ensure that the Pharmacist is trained to provide appropriate counsel to customers concerning the symptomatic management of heartburn and the appropriate use of SOMAC® Heartburn Relief.

A similar level of commitment with regard to Pharmacy education and training will be provided in New Zealand.

3. Relevant comparative data for like compounds

A comprehensive summary of the relevant clinical efficacy data for pantoprazole 20 mg, was submitted to the NDPSC in 2005. The data was considered and documented in the minutes of the 44th Meeting in June 2005 (Appendix 3). The results convincingly show the pronounced clinical efficacy of pantoprazole 20 mg in the treatment of heartburn and acid regurgitation during a 14-day

treatment course with a substantial clinical benefit demonstrated after 7 days of treatment.

4. Local data or special considerations relating to NZ

Despite local prevalence data showing that one in four people with heartburn suffer either daily or several times a week,[1] there are currently no PPIs available OTC in New Zealand.

In New Zealand, at the time of writing this submission, there are only two classes of OTC treatments for reflux symptoms like heartburn and acid regurgitation: antacids and H2RAs. Both have their limitations (see below); thus for sufferers of frequent heartburn without other atypical gastro-oesophageal reflux symptoms, a better treatment option is needed.

- Antacids: Antacids work by neutralising acid secretion.[16] Antacids are intended for occasional use. As their effect is short-lasting, they are subject to dissatisfaction or overuse when symptoms are not sufficiently controlled.

- H2RAs: H2RAs work by blocking the H2 receptor on the parietal cell. However, other mediators (such as acetylcholine and gastrin) can activate the parietal cell by other pathways.[17] Therefore H2RAs do not totally block acid secretion from the parietal cell.[16] The utility of H2RAs is also limited by the development of tolerance, which may occur in as little as 5 days of therapy.[17]

OTC pantoprazole 20 mg would be indicated for use in patients with frequent heartburn (at least 2 times a week). It is expected to provide a significant contribution to patient care in the New Zealand community by allowing treatment of frequent heartburn with a product of well-established safety and improved efficacy as compared to the available OTC antacids and H2RAs.

5. Interactions with other medicines

[16] Sachs G. Physiology of the parietal cell and therapeutic implications. *Pharmacotherapy* 2003 October;23(10 Pt 2):68S-73S.
[17] Yeomans ND. Drugs that inhibit acid secretion. *Aust Prescr* 2000;23:57-59.

Although pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system, no clinically significant interactions were observed in specific tests with a number of such drugs or compounds, namely carbamazepine, caffeine, diazepam, diclofenac, digoxin, ethanol, glibenclamide, metoprolol, naproxen, nifedipine, phenytoin, piroxicam, theophylline, and the low dose oral contraceptive Triphasil® (levonorgestrel and ethinyloestradiol). There was also no interaction with a concomitantly administered antacid (aluminium hydroxide and magnesium hydroxide).

Although no interaction during concomitant administration of phenprocoumon or warfarin has been observed in clinical pharmacokinetic studies, a few isolated cases of changes in international normalised ratio (INR) have been reported during concomitant treatment in the post-marketing period. Therefore, in patients being treated with coumarin anticoagulants, monitoring of prothrombin time/INR is recommended after initiation, termination or during irregular use of pantoprazole.

As with all acid suppressant medications, the absorption of drugs whose bioavailability is pH dependent (e.g. ketoconazole), might be altered due to the decrease in gastric acidity.

There were no interaction between pantoprazole and clarithromycin, amoxicillin and metronidazole.

It has been shown that co-administration of atazanavir 300 mg/ritonavir 100 mg with omeprazole (40 mg once daily) or atazanavir 400 mg with lansoprazole (60 mg single dose) to healthy volunteers resulted in a substantial reduction in the bioavailability of atazanavir. The absorption of atazanavir is pH dependent. Therefore PPIs, including pantoprazole, should not be co-administered with atazanavir (see Contraindications).

For further information, please refer to the attached Product Information (Appendix 4).

6. Contraindications

Pantoprazole should not be used in cases of known hypersensitivity to any components of the formulation, or in cases of cirrhosis or severe liver disease. Pantoprazole, like other PPIs, should not be co-administered with atazanavir (see Interactions, above).

7. Possible resistance

In the current application, pantoprazole is indicated symptomatic relief of heartburn, acid regurgitation and other symptoms associated with GORD in patients aged 18 years or over.

Consequently, the assessment of persistence of efficacy and tolerance effects is not applicable. However, in long-term trials with pantoprazole and other proton-pump inhibitors, no indication regarding any development of tolerance was observed.

8. Adverse events

In general, PPI therapy is accepted to be remarkably safe[18]. Based on preclinical and clinical studies as well as extensive post-marketing experience, pantoprazole has a low general toxicity and no relevant genotoxicity, carcinogenicity nor reproductive toxicity.

The overall analysis of clinical studies comprises 94 clinical studies conducted with pantoprazole tablets in more than 26,000 patients. Pantoprazole was generally well tolerated and showed a favourable safety profile. This favourable safety profile is further confirmed by a wealth of post-marketing surveillance data, which includes 14 years of prescription use worldwide and 8 years of OTC use in Sweden, from an estimated total of 665 million patients exposed. The majority of reported adverse events has been minor and transient in nature and mostly referred to gastrointestinal and nervous system disorders such as diarrhoea, nausea, and headache. No safety concerns have been identified. Pantoprazole 20 mg has a well established, favourable safety profile and a wide therapeutic index.

B8.1 Safety data from clinical studies

During drug development more than 250 clinical studies with pantoprazole tablets have been carried out in over 80,500 patients. In most studies daily doses ranged from 20 to 80 mg; however, in particular settings higher doses up to 320 mg p.o. and 240 mg i.v. were given and well tolerated. Analysis of pooled clinical trial safety data from 26,615 patients receiving

[18] Labenz J, Leodolter A. [Medication therapeutic strategies for gastro-esophageal reflux disease]. *Z Gastroenterol* 2007 November;45(11):1169-1179.

pantoprazole tablets and 1,598 patients receiving placebo has shown that the incidence of treatment emergent adverse events with pantoprazole (21.5%) is generally comparable to that with placebo (24%). The corresponding figures for serious adverse events are 2.1% and 1.4%, respectively.

B8.2 Post-marketing surveillance data

Between first launch of pantoprazole and February 2008 approximately 733,000 treatment courses have been documented in Post-Authorisation Safety Studies (PASS). These studies, which reflect the use of the product in medical practice as compared to the scientific setting of clinical studies with strict inclusion and exclusion criteria, contribute considerable evidence to the safety profile of pantoprazole. The order of the most frequent suspected adverse drug reactions (ADRs) found in PASS matched with the results obtained in clinical studies. No new ADRs, or an increased frequency of known ADRs, or any other risk that might affect the safe use of the drug has been detected in PASS.

Analysis of post-marketing safety data has been based on a worldwide exposure, estimated on the basis of sales data, of approximately 665 million patients. Overall, 11,153 case reports have been received with 20,697 associated adverse event terms; 1,599 cases (14.3%) were regarded as serious. Based on an estimated 665 million exposed patients, the incidence of serious reports is extremely rare (<0.0002%).

B8.3 Data from Australian safety databases

There have been a total of 304 case reports of any adverse event related to the use of pantoprazole or Somac recorded in the Australian Adverse Drug Reactions Advisory Committee (ADRAC) database from 01 May 2000 to 15 September 2008. None of the adverse events reported (at any dose of pantoprazole) resulted in death. Analysis of the case details reveals that only 16 (5.26%) of these adverse event reports were related to pantoprazole 20 mg. Of these 16 case reports, only one was considered to be life threatening. This case involved dyspnoea, the patient fully recovered after ceasing to take pantoprazole. These data further affirm the excellent safety profile of pantoprazole.

9. Potential for abuse or misuse

There is a low potential for abuse from inappropriate use of pantoprazole 20 mg (SOMAC® Heartburn Relief).

Low potential for misuse: There have been only 48 post-marketing reports of misuse of pantoprazole tablets (derived from 26 periodic safety update reports collated between 1994 and February 2008). Six were serious, four of which were unrelated to pantoprazole. In one fatal case of a man who committed suicide by ingesting 560 mg pantoprazole along with unknown doses of chloroquine and zopiclone. Thus, the risk of misuse can be considered to be small.

No evidence of abuse: There is no evidence of any abuse or direct addictive effects of pantoprazole. Whereas omeprazole may be used at high doses to prolong the action of central stimulants by inhibiting their metabolism, no such report has been received for pantoprazole.

No reports of overdose in OTC use: A total of 47 overdose cases have been reported, none of which resulted in death or permanent disability. For the majority of overdose cases there were no associated symptoms and if so, those were mostly non-serious and unspecific. There have been no reports of overdose of pantoprazole in Sweden, where pantoprazole tablets have been sold OTC for 8 years.

There are no known symptoms of overdosage in humans. In individual cases, 240 mg was administered i.v or p.o. and was well tolerated.

4. REFERENCES

1 Haque M, Wyeth JW, Stace NH, Talley NJ, Green R. Prevalence, severity and associated features of gastro-oesophageal reflux and dyspepsia: a population-based study. *N Z Med J* 2000 May 26;113(1110):178-181.

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August;101(8):1900-1920.

3 Tytgat GN, McColl K, Tack J, Holtmann G, Hunt RH, Malfertheiner P, Hungin AP, Batchelor HK. New algorithm for the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2008 February 1;27(3):249-256.

4 Galmiche JP, Stephenson K. Treatment of gastroesophageal reflux disease in adults: an individualized approach. *Dig Dis* 2004;22(2):148-160.

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Ref Type: Internet Communication

7 Triadafilopoulos G. Gastroesophageal reflux. *Curr Opin Gastroenterol* 2004 July;20(4):369-374.

8 Boeckxstaens GE. Review article: the pathophysiology of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007 July 15;26(2):149-160.

9 Tran T, Lowry AM, El-Serag HB. Meta-analysis: the efficacy of over-the-counter gastro-oesophageal reflux disease therapies. *Aliment Pharmacol Ther* 2007 January 15;25(2):143-153.

10 Lachman L, Howden CW. Twenty-four-hour intragastric pH: tolerance within 5 days of continuous ranitidine administration. *Am J Gastroenterol* 2000 January;95(1):57-61.

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March;3(3):208-215.

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15 Access Economics Pty Ltd. Gut Instincts: the economic impact of GORD and PUD. 2007 May 3.

16 Sachs G. Physiology of the parietal cell and therapeutic implications. *Pharmacotherapy* 2003 October;23(10 Pt 2):68S-73S.

17 Yeomans ND. Drugs that inhibit acid secretion. *Aust Prescr* 2000;23:57-59.

18 Labenz J, Leodolter A. [Medication therapeutic strategies for gastro-esophageal reflux disease]. *Z Gastroenterol* 2007 November;45(11):1169-1179.

5. APPENDICES

Appendix 1: Proposed label

Appendix 2: Proposed CMI and Package Insert

Appendix 3: NDSC Edited Minutes of Meeting 44, June 2005

Appendix 4: Australian Approved Product Information