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

Submission to:

Medicines Classification Committee
Medsafe New Zealand

Submission from:

Nycomed Pty Ltd
2 Lyonpark Road
North Ryde NSW 2113
Australia

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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. For many years consumers in New Zealand had access to only two classes of OTC treatments for reflux symptoms: 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.

Proton pump inhibitors (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] Moreover, an international panel of gastroenterologists has concluded that the availability of PPIs in the OTC setting provides an opportunity to improve the quality of care of reflux sufferers who may be currently untreated or under-treated.[8]

The PPIs lansoprazole, pantoprazole and omeprazole have been listed as Restricted Medicines in New Zealand since 2009. Most recently at its 44th Meeting in November 2010, the Medicines Classification Committee approved the reclassification of one of these PPIs, omeprazole 20 mg, to Pharmacy Medicine. The proposal submitted by Bayer (July 2010) to reclassify omeprazole to Pharmacy Medicine status provided a comparison of that product with ranitidine, establishing that both are relatively similar medicines with omeprazole offering superior efficacy but with slightly more interaction potential.

This application seeks to reclassify pantroprazole 20 mg from Restricted Medicine to Pharmacy Only. The public health benefits that will likely result from the availability of pantoprazole 20 mg as a Pharmacy Only medicine include:

- **More effective symptom control** — Pantoprazole 20 mg 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.
- **More rationale use of medications[8]** — As the use of pantoprazole 20 mg in the Pharmacy Medicine setting will follow an on-demand strategy, patients stop

taking the PPI when they achieve adequate symptom control. This has the potential to minimise medication use (compared to a prescribed course of therapy) and related costs. 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.[9]

- **More rational use of healthcare resources[8]** — Many patients will respond quickly and completely to OTC PPI therapy, as such it acts as a filter to determine the level of further care reducing the number of patients who present for further investigation. Conversely, for those patients who do not receive adequate symptom control or in whom symptoms recur it serves as a prompt that they may need to progress to more intense therapy. Both scenarios present a favourable outcome in terms of health care utilisation.

Pantoprazole 20 mg offers superior efficacy to ranitidine (300mg/day) with no additional safety considerations[8,10] and equivalent efficacy to omeprazole (10-20mg/day)[11] with slightly less interaction potential.[12] Pantoprazole 20 mg is, therefore, just as suitable as ranitidine (300mg/day) and omeprazole (10-20mg/day) to be classified as a Pharmacy Medicine.

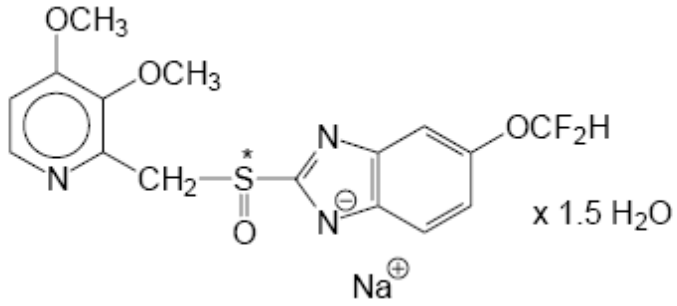
PART A

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 proprietary name is **SOMAC® Heartburn Relief**.

3. Name of company requesting reclassification

Nycomed Pty Ltd
2 Lyonpark Road
North Ryde NSW 2113
Australia

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

This submission pertains to pantoprazole 20 mg enteric coated tablets. Each tablet contains 22.6 mg pantoprazole sodium sesquihydrate (equivalent to 20 mg pantoprazole). The tablets are yellow and oval shaped, marked with "P20" on one side.

5. Pack size and other qualifications

The *New Zealand Regulatory Guidelines for Medicines* (Edition 6.13, March 2011) state that pantoprazole may be sold as a Restricted Medicine when the following conditions apply:

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

This submission seeks to reclassify the currently approved Restricted Medicine to Pharmacy Medicine. Nycomed considers that it is reasonable and appropriate that the existing dose strength (pantoprazole 20 mg), format (tablets), pack size (maximum 14 tablets), indication and warning statements (as outlined above) would continue to apply. Thus, it is proposed that pantoprazole 20 mg as a Pharmacy Medicine would be available in blister packs of 7 or 14 tablets. Each blister pack would be enclosed in a cardboard carton.

Dosage recommendation:

The proposed dosage would be one pantoprazole 20 mg tablet per day until symptoms improve. Consumers will be instructed to speak to a pharmacist or doctor if symptom control has not been achieved after 14 days' continuous treatment with one tablet per day.

The European Commission granted a marketing authorisation valid throughout the EU for non-prescription pantoprazole 20 mg to Nycomed GmbH on 12 June 2009. The proposed dosage instructions for pantoprazole 20 mg as a Pharmacy Medicine in New Zealand are the same as have been approved by the European Commission; "*The recommended dose of Pantozol Control is one tablet once a day until symptoms have stopped*."

6. Indications for which change is sought

The *New Zealand Regulatory Guidelines for Medicines* (Edition 6.13, March 2011) state that the appropriate indication for pantoprazole when sold as a Restricted Medicine is for the "*Short-term, symptomatic relief of gastric reflux-like symptoms in sufferers aged 18 years and over*".

Nycomed considers that it is reasonable and appropriate that this indication would continue to apply to the Pharmacy Medicine. Thus, it is proposed that pantoprazole 20 mg as a Pharmacy Medicine would be indicated for the short-term, symptomatic relief of heartburn, acid regurgitation and other gastric reflux-like symptoms in patients aged 18 years or over.

The European Commission granted a marketing authorisation valid throughout the EU for non-prescription pantoprazole 20 mg to Nycomed GmbH on 12 June 2009. The proposed indication for pantoprazole 20 mg as a Pharmacy Medicine in New Zealand is similar to that which has been approved by the European Commission for non-prescription pantoprazole 20 mg; this being "*Short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults*."[*]

7. Present classification of medicine

The current classification of pantoprazole in New Zealand is as follows:[†]

Ingredient	Conditions (if any)	Classification
Pantoprazole	except when specified elsewhere in this schedule	Prescription
Pantoprazole	in tablets or capsules containing 20 milligrams or less of pantoprazole when sold in a pack approved by the Minister or the Director-General for distribution as a restricted medicine	Restricted

8. Classification sought

This submission seeks to reclassify the current Restricted Medicine to Pharmacy medicine whilst retaining all of the current restrictions for the non-prescription sale of pantoprazole 20 mg.

It is of relevance to the present submission that at its 44th Meeting in November 2010, the Medicines Classification Committee approved the reclassification of another PPI, omeprazole 20 mg, to Pharmacy Medicine.

[*] Data sourced from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/001013/human_med_000969.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124 [accessed 15 June 2011]

[†] Data sourced from: http://www.medsafe.govt.nz/Profs/class/classification.asp [accessed 14 June 2011]

There is a long-standing safety experience with pantoprazole and its safety profile is well characterised and similar to those reported for other PPIs. In a direct comparative trial, pantoprazole 20 mg was shown to be equally as effective as omeprazole 20 mg at relieving gastric reflux-like symptoms.[11] After 14 days of treatment with either pantoprazole or omeprazole, the rate of symptom relief was similar (70% vs. 79%, respectively) and both treatments were well tolerated. Thus, pantoprazole 20 mg has similar merits to omeprazole with respect to its suitability for classification as a Pharmacy Medicine.

9. Classification status in other countries

As of 23 February 2011, pantoprazole 20 mg (as a Prescription Medicine) has marketing authorisations in 104 countries worldwide.

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

Pantoprazole 20 mg is currently approved as an OTC medicine in 35 countries, worldwide (see table below). Pantoprazole 20 mg was the first PPI to receive European wide OTC marketing authorisation, the application was granted based on "*robust clinical evidence collected over the last 15 years that demonstrates the safety of pantoprazole and shows it to be significantly efficacious in terms of providing sustainable relief of symptoms*".

Country	Marketing Authorisation Approval Date
Sweden	2000
Australia	June 2005
New Zealand	*May 2009*
All 27 member countries of the European Union	June 2009
Norway	July 2009
Iceland	September 2009
Liechtenstein	September 2009
Switzerland	December 2009
Belarus	January 2010

The above table demonstrates a world-wide trend of rescheduling pantoprazole 20 mg to OTC status. It is of direct relevance to this application that with the exception of only Australia and New Zealand, the current scheduling status of pantoprazole 20 mg in these markets is equivalent to Pharmacy Medicine.

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

Global data:

Pantoprazole was first licensed in February 1994 in South Africa. However, it was first approved in Germany on 23 August 1994, and this is considered to be its international birth date (IBD). During drug development pantoprazole sodium tablets were used in more than 250 clinical trials.

The product has been marketed in many countries around the world for over 17 years. As of 23 February 2011 marketing authorisation for pantoprazole 20 mg and 40 mg has been approved in 104 and 98 countries, respectively, and it is estimated that 984.5 million patients have been treated with pantoprazole worldwide.

OTC data:

As of 23 February 2011, OTC pantoprazole 20 mg tablets were marketed in 20 EU countries, Norway, Switzerland and Australia. Patient exposure to OTC pantoprazole 20 mg is significant.

In the 6-month period from 01 September 2010 to 28 February 2011, it is estimated that patient exposure from word-wide sales of pantoprazole can be estimated at 967.5 million defined daily doses (DDD), which corresponds to approximately 2.65 million patient years. OTC sales during this period correspond to over 10 million DDD and 27,667 patient years (see table below).

Global market experience with pantoprazole 20 mg OTC.

Data collection dates	01 Sept 2010 28 Feb 2011
No of tablets sold	10,098,368
Amount of pantoprazole (mg)	201,967,360
No of DDDs in period	10,098,368
No of treatment courses	360,656
No of patient-years	27,667

DDD = defined daily dose

Patient exposure to pantoprazole is substantial and the safety profile of pantoprazole is well established, supporting the use of pantoprazole 20 mg as a Pharmacy Medicine.

New Zealand data:

In New Zealand, pantoprazole is available as 20 mg and 40 mg oral tablets and a 40 mg powder for intravenous injection. The approval dates for these products are as follows:

- Pantoprazole 40 mg – May 1995
- Pantoprazole 20 mg – December 1998
- Pantoprazole 40 mg for iv use – October 2002
- Pantoprazole 20 mg (Restricted Medicine) – May 2009

Patient exposure to pantoprazole is substantial, during 2008 close to half a million packs (each containing 30 tablets) were sold in the New Zealand prescription market. Half of these sales were for pantoprazole 20 mg.

11. Draft labelling for the proposed new presentation

A copy of the proposed labelling for pantoprazole 20 mg as a Pharmacy Medicine is provided in Appendix 1 and the proposed Consumer Medicine Information (CMI) is provided in Appendix 2. They provide clear instructions on the use of pantoprazole 20 mg as a Pharmacy Medicine, including what the product is used for, how long it should be used and what to do if sufficient symptom relief is not achieved.

The proposed labels meet all of the requirements stipulated by the *New Zealand Regulatory Guidelines for Medicines* (Edition 6.13, March 2011) for pantoprazole 20 mg as a Restricted Medicine. In addition, they closely follow the labels that have been approved for the sale of this product as a non-prescription medicine in the European Union.

12. Proposed warning statements

The *New Zealand Regulatory Guidelines for Medicines* (Edition 6.13, March 2011) state that for pantoprazole 20 mg to be sold as a Restricted Medicine the following warning statements must be present on the labelling:

- For short-term use only, except on medical advice.
- Do not use the medicine for any purpose other than that specified on the pack, except on medical advice.
- Do not use if you are experiencing weight loss, persistent regurgitation of food or vomiting, difficulty swallowing or symptoms of gastro-intestinal bleeding, except on medical advice.
- Consult a doctor if symptoms persist, recur or worsen or if new symptoms occur.
- Consult a pharmacist or doctor before use if you are pregnant or are taking any other medicines.

In consideration of the discussion relating to warning statements that occurred when during the Medicines Classification Committee approved the reclassification of another PPI, omeprazole 20 mg, to Pharmacy Medicine, Nycomed proposes that the above warning statements be amended slightly so as to read as shown in the table below. Note that one additional statement has also been added, this conforms with the current requirements that have been established for omeprazole for sale as a Pharmacy Medicine.

Existing statements	Revised statements
For short-term use only, except on medical advice.	No change
Do not use the medicine for any purpose other than that specified on the pack, except on medical advice.	No change
Do not use if you are experiencing weight loss, persistent regurgitation of food or vomiting, difficulty swallowing or symptoms of gastro-intestinal bleeding, except on medical advice.	No change
Consult a doctor if symptoms persist, recur or worsen or if new symptoms occur.	Consult a pharmacist or doctor if symptoms persist, recur or worsen or if new symptoms occur.
Consult a pharmacist or doctor before use if you are pregnant or are taking any other medicines.	No change
	Do not take for more than 14 days; consult a doctor if symptoms persist

In addition, the proposed Consumer Medicine Information (Appendix 2) provides further explanation to the consumer on the above warnings.

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

Pantoprazole Dr Reddy (launched Q1, 2008)

PART B

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

This proposal seeks to reclassify pantoprazole 20 mg from a Restricted Medicine to Pharmacy Medicine. As has already been discussed, pantoprazole 20 mg is already approved as OTC medication for the treatment of reflux symptoms in a large number of markets. It has a regulatory status equivalent to that of a Pharmacy medicine in 33 countries, including all 27 member countries of the EU. In addition, the PPI omeprazole has recently been approved as a Pharmacy Medicine in New Zealand.

These regulatory changes are a direct reflection of the wealth of data that supports the suitability of PPIs as an option for the self-management of heartburn. Current international consensus is that PPIs are more effective than alternative OTC treatments (antacids, alginates and H2RAs), pose no additional risk and, therefore, represent an ideal class of drug for use as OTC reflux therapy for reflux symptoms.[8]

Reclassification of pantoprazole 20 mg to Pharmacy Medicine has the potential to provide a number of benefits, including improvement in the quality of care — with consumers achieving better symptom control with no additional safety concerns — and a more cost efficient use of healthcare resources.

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.

A report compiled for the Gut Foundation of Australia is supportive of the role of PPIs in OTC 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*"[9]. Moreover, an international panel of gastroenterologists has concluded that the availability of PPIs in the OTC setting provides an opportunity to improve the quality of care of reflux sufferers who may be currently untreated or under-treated.[8]

The availability of pantoprazole 20 mg as a Pharmacy Medicine would give consumers an alternative choice to antacids and H2RAs.

How will this improve patient care and enhance the use of healthcare resources?

More effective symptom control — Pantoprazole 20 mg 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.

More rationale use of medications[8] — As the use of pantoprazole 20 mg in the Pharmacy Medicine setting will follow an on-demand strategy, patients stop taking the PPI when they achieve adequate symptom control. This has the potential to minimise medication use (compared to a prescribed course of therapy) and related costs. 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.[9]

More rational use of healthcare resources[8] — Many patients will respond quickly and completely to OTC PPI therapy, as such it acts as a filter to determine the level of further care reducing the number of patients who present for further investigation. Conversely, for those patients who do not receive adequate symptom control or in whom symptoms recur it serves as a prompt that they may need to progress to more intense therapy. Both scenarios present a favourable outcome in terms of health care utilisation.

2. Ease of self-diagnosis

Given that a wide number of medications have been available OTC for symptomatic relief of heartburn for many years, Nycomed considers that the ease of self-diagnosis of this condition has already been recognised by the Medicines Classification Committee.

Treatment of reflux symptoms, e.g. heartburn and acid regurgitation, has been safely managed by OTC medications for decades. Most reflux sufferers have had their symptoms for many years and commonly have used OTC therapy for quite some time.[8] Consumers are able to self-recognize the symptoms, and safely self-treat.

With regards to the use of pantoprazole 20 mg for this condition, this issue has already been resolved by the MCC in light of the reclassification from prescription to Restricted Medicine status in 2009. This is further supported by recent experience from Australia.

Twelve months after the launch of SOMAC® Heartburn Relief in Australia, a Pharmacy-based audit was conducted amongst 153 consumers.[13] Although this audit was not designed to assess the use of the product, label comprehension was evaluated as a surrogate marker as to whether usage would be as instructed on the label. In this audit 92% of respondents were able to correctly

determine the daily dose, 86% were able to correctly determine the maximum duration of use and the customer's assessment of product suitability was in agreement with that of the Pharmacist in 86% of cases.

Low potential for indirect danger

There is a low potential for indirect danger with the use of pantoprazole 20 mg. Moreover, this low potential for indirect danger for pantoprazole 20 mg has already been recognised by the Medicines Classification Committee in light of the reclassification from prescription to Restricted Medicine status in 2009.

Typical reflux symptoms like heartburn and acid regurgitation are highly specific for GORD, are correctly self-diagnosable by patients and differ from the symptoms of serious gastrointestinal conditions such as gastric cancer. The risk of missing oesophageal and gastric cancer in patients with typical symptoms of GORD without alarm features is low.[8]

Any risk of masking/hiding an underlying condition requiring medical attention and supervision is similar to that of all other approved heartburn OTC medications. In the specific case of pantoprazole 20mg as a Pharmacy Medicine these risks are further adequately limited because the dosing instructions and the CMI for pantoprazole 20 mg will instruct the patient to seek the advice of a pharmacist of doctor if their symptoms persist for more than 14 days.

3. Relevant comparative data for like compounds

A comprehensive summary of the relevant clinical efficacy data for pantoprazole 20 mg was presented to the Medicines Classification Committee previously when the product was reclassified from prescription to Restricted Medicine status in 2009. In light of this, a summary of the relevant data is presented in this submission.

Clinical efficacy

Proof of efficacy of pantoprazole 20 mg for OTC use in the desired indication is supported by data from 17 clinical studies (available in the worldwide Nycomed pantoprazole clinical trial database) in which the treatment of symptoms in

patients with GORD was studied as a primary or secondary criterion.[‡](*see footnote below*)

In a published post-hoc analysis of two previously published studies, pantoprazole 20 mg was shown to provide fast and effective relief from heartburn and acid regurgitation.[10] Full relief of heartburn and acid reflux was observed in a significantly higher proportion of patients who took pantoprazole compared with nizatidine or ranitidine. Relief occurred as fast as, and in some cases, even faster than that seen with these H2RAs.

OTC use of PPIs

Treatment of reflux symptoms has been safely managed by OTC medications for decades and consumers are able to self-recognize the symptoms. Antacids and H2RAs are established OTC medications for the treatment of reflux symptoms and have been shown to be effective in self-treatment.[14] 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.[15] 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 effective than alternative OTC treatments (antacids, alginates and H2RAs) and therefore represent an ideal class of drug for use as OTC reflux therapy for reflux symptoms.[8] 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, with PPIs has been shown to be safe and effective.[16, 17] Real world investigation has shown that consumers are able to self-treat reflux symptoms with PPIs, which have been shown to be safe and effective.[18, 19]

PPIs are therefore considered the most effective therapy for patients with heartburn and acid regurgitation. Published guidance for the management of reflux symptoms with OTC PPIs concludes: *"OTC treatment of typical reflux symptoms (acid regurgitation, heartburn) with antacids and H2RAs is now*

[‡] A comprehensive summary of the relevant study that data was submitted to the European Medicines Evaluation Agency as part of the EU submission for the OTC rescheduling of pantoprazole 20 mg and can be supplied upon request.

accepted as safe and results in short-term relief of symptoms. There is no evidence of additional risk with OTC PPIs compared to these existing OTC therapies and PPIs are significantly more efficacious."[8]

PPIs are the gold standard for reflux symptom control and present an ideal class of drug for use as OTC reflux therapy.[8] The availability of pantoprazole 20 mg as a Pharmacy Medicine will enable consumers to have convenient, direct access to this established "ideal" treatment for heartburn relief.

4. Local data or special considerations relating to NZ

It is already established that heartburn is a suitable condition for self-management and that consumers have for many years been using OTC medications to manage this condition.

Until relatively recently, there were only two classes of OTC treatments for the self-management of reflux symptoms: antacids and H2RAs. Both have their limitations:

- Antacids: Antacids work by neutralising acid secretion.[20] 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.[21] Therefore H2RAs do not totally block acid secretion from the parietal cell.[20] The utility of H2RAs is also limited by the development of tolerance, which may occur in as little as 5 days of therapy.[22]

More recently, PPIs have been recognised as a suitable alternative to antacids and H2RAs in the OTC setting; lansoprazole, pantoprazole and omeprazole have been listed as Restricted Medicines in New Zealand since 2009. Most recently at its 44th Meeting in November 2010, the Medicines Classification Committee approved the reclassification of one of these PPIs, omeprazole 20 mg, to Pharmacy Medicine.

The proposal submitted by Bayer (July 2010) to reclassify omeprazole to Pharmacy Medicine status provided a comparison of that product with ranitidine, establishing that both are relatively similar medicines with omeprazole offering superior efficacy but with slightly more interaction potential.

Pantoprazole 20 mg been shown to improve acid reflux-related symptoms, heal esophagitis, and improve health-related quality of life more effectively than H2RAs.[23].

Van Zyl et al, 2000[24]: This multicentre, randomized, double-blind, parallel-group compared pantoprazole (20 mg once daily) with ranitidine (300 mg once daily). Relief from key symptoms (heartburn, acid regurgitation, pain on swallowing) was assessed after 2, 4, and if applicable, 8 weeks. Complete relief from key symptoms was noted after 2 weeks in 70/88 (80%) patients treated with pantoprazole vs 45/89 (51%) patients treated with ranitidine ('per-protocol and key-point available' populations, P < 0.001); the corresponding results after 4 weeks were 77/88 (88%) vs 51/88 (58%); p<0.001. Compared to ranitidine 300 mg, pantoprazole 20 mg provides faster relief from symptoms and is significantly more effective in healing of oesophageal lesions in patients with mild reflux-oesophagitis. Thus, the low dose of pantoprazole offers a treatment approach which minimizes drug exposure and costs while retaining high efficacy.

Kaspari et al, 2001[25]: This randomized double-blind study compared pantoprazole (20mg/day) to ranitidine (150 mg twice daily) in patients with mild GERD. Outcome was assessed after 2 and 4 weeks; the primary criterion was relief of leading symptoms (heartburn, acid eructation and pain on swallowing), after 4 weeks of treatment. According to the per-protocol analysis, 69% (100/144) and 80% (115/144) of patients in the pantoprazole group were relieved of leading symptoms after 2 and 4 weeks, respectively. The rates in the ranitidine group were 47% (62/133) and 65% (86/133). Quality-of-life parameters improved more in the pantoprazole group and patients' assessment of treatment was more favourable. Pantoprazole 20 mg demonstrated superior efficacy with faster relief of reflux symptoms and similar tolerability compared to ranitidine 150 mg.

Haag et al, 2010[10]: This paper reports the results of a post-hoc analysis of the data collected in the study by Kaspari et al[25] (summarised above). The intent of the post-hoc analysis was to evaluate the time interval to complete symptom relief from heartburn and acid regurgitation during the first 7 days of treatment with pantoprazole and ranitidine. Compared to patients receiving ranitidine, on day 7, more patients in the pantoprazole group experienced complete relief from heartburn (57.2% vs 41.2%, p<0.01) and more patients were symptom free (45.6% vs 36.3%, p=NS).

Pantoprazole 20 mg has an excellent safety profile, is as efficacious as other PPIs, and has a low incidence of drug interactions.[23]

Bardhan et al, 2001[11]: This randomized, open, parallel-group, multicentre study compared the efficacy and safety of once-daily doses of pantoprazole (20 mg) and omeprazole (20 mg) with respect to symptom relief and healing of patients with grade I reflux oesophagitis. After 2 and 4 weeks of treatment with either pantoprazole or omeprazole, the rate of symptom relief was similar (70% vs. 79% and 77% vs. 84%, respectively). High healing rates were observed after 4 and 8 weeks (pantoprazole: 84% and 90%, respectively; omeprazole: 89% and 95%, respectively). Both treatments were well tolerated. After 4 and 8 weeks of treatment with pantoprazole (20 mg) or omeprazole (20 mg), patients with mild gastro-oesophageal reflux disease (grade I) showed comparably high rates of symptom relief and healing.

Unlike omeprazole, which recently has been shown to decrease the antiplatelet activity of clopidogrel, and which is also metabolized by CYP450, pantoprazole does not affect clopidogrel efficacy.[12]

Based on the above data, pantoprazole 20 mg offers superior efficacy to ranitidine (300mg/day) with no additional safety considerations and equivalent efficacy to omeprazole (10-20mg/day) with slightly less interaction potential. Pantoprazole 20 mg is just as suitable as ranitidine (300mg/day) and omeprazole (10-20mg/day) to be classified as a Pharmacy Medicine.

5. Interactions with other medicines

The risk:benefit profile of pantoprazole 20 mg is highly favourable. Pantoprazole 20 mg tablets have been demonstrated to be very effective whilst not presenting any significant direct danger when used correctly without medical supervision. Moreover, there have been a few reported significant adverse drug interactions between pantoprazole and other medications metabolized through the CYP450 system.[23]

Pantoprazole is metabolized in the liver via the cytochrome P450 enzyme system. A study using human liver microsomes suggested that the P450 enzymes CYP2C19 and CYP3A4 are involved in its metabolism. In addition, CYP2D6 and CYP2C9-10 were implicated in another study. An interaction of pantoprazole with other drugs or compounds which are metabolised using the same enzyme system cannot be excluded. However, 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.

Treatment of dogs with IV famotidine shortened the duration of the pH elevation effect 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. Four cross-over pharmacokinetic studies designed to examine any interactions between pantoprazole and the drugs clarithromycin, amoxicillin and metronidazole, conducted in 66 healthy volunteers, showed no interactions.

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).

Concerns have been raised about the potential for an interaction between PPIs and clopidogrel. The most likely mechanism for the drug-drug interaction between clopidogrel and PPIs is competitive inhibition of CYP2C19. Individual PPIs have differences in their metabolism profiles.[26] Several studies have compared the degree of CYP2C19 inhibition by currently used PPIs. Li et al have shown that lanzoprazole is the most potent inhibitor of this enzyme whilst pantoprazole and rabeprazole were the least inhibitory.[27] It has been reported that “omeprazole appears to have the highest potential for overall drug-drug interactions among PPIs, and rabeprazole and pantoprazole appear to have the least interaction risk.”[28]

The current consensus of opinion on this issue, taking into account the U.S. Food and Drug Administration and European Medicines Agency position statements, suggests the use of pantoprazole instead of omeprazole as it may be the safest PPI to use from a biochemical perspective.[12]

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.

7. Possible resistance

In the current application, pantoprazole is indicated for the short-term treatment of reflux symptoms. Consequently, the assessment of persistence of efficacy and tolerance effects is not applicable. However, in long-term trials with pantoprazole and other PPIs, no indication regarding any development of tolerance was observed.

8. Adverse events

Pantoprazole has a well-established safety profile and low potential for drug-drug interactions.[10, 29] The Medicines Classification Committee has already recognised that pantoprazole 20 mg is substantially safe in use per the decision to reclassify it from a Prescription Medicine to a Restricted Medicine.

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. In the course of 94 safety-relevant clinical trials, a total of 26,615 patients have been exposed to pantoprazole sodium tablets. Pantoprazole was generally well tolerated and the incidence and type of adverse events consistently resembled those reported with placebo.

The favourable safety profile is further confirmed by a wealth of post-marketing surveillance data; based on a total cumulative exposure (which includes both prescription and OTC use) from an estimated total of 984.5 million patients exposed approximately one in 32,000 patients experienced adverse reactions to pantoprazole (see Appendix 3). 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.

Low incidence of adverse events with extensive OTC use

As has already been discussed in Part A of this submission, patient exposure to OTC pantoprazole 20 mg is significant. In the 6-month period from 01 September 2010 to 28 February 2011, there were an estimated 360,656 treatment courses of OTC pantoprazole. Correspondingly, during this same time period, Nycomed received only 15 adverse drug reaction reports from OTC pantoprazole users (approximately 0.004%). Cumulatively, since the OTC launch of pantoprazole 20 mg in the EU in June 2009 there have been only 36 reports (20 by healthcare professionals and 16 by non-healthcare professionals). A

review of these reports does not raise any safety concerns and does not change the current knowledge as to the excellent safety profile of pantoprazole.

9. Potential for abuse or misuse

There is a low potential for misuse or abuse of pantoprazole 20 mg. The sponsor has not received any reports of overdose with pantoprazole since it has been available as an OTC medicine.

The risk to patient's health is very low if the patient exceeds the recommended dosage of pantoprazole 20 mg daily for 14 days. Results of toxicity studies show that in acute toxicity studies (single dose administration), lethality occurs only at very high doses of over 700 mg/kg in animals. By extrapolation from these animal studies, a patient would have to ingest over 1000 tablets of pantoprazole 20 mg at once in order to obtain a systemic exposure that would reach that found in animals. As the pack sizes will only contain enough tablets for a short-term treatment (7 to 14 tablets), poisoning due to drug overdose is highly unlikely.

The direct risk to the patient's health is also very low if the patient exceeds the recommended duration of treatment as pantoprazole 20 mg has been shown to be safe in long-term treatment.

The only contraindications for the use of pantoprazole 20 mg OTC (hypersensitivity to the active substance or to any of the excipients, and coadministration with atazanavir) have a low incidence in the general population and therefore the risk of incorrect use is low. There is a potential risk to health if the patient does not observe the contraindications or warnings/precautions. However, these risks are minimised by restriction to short-term treatment, small pack sizes and supply through pharmacies only.

There is no evidence of any abuse or direct addictive effects of pantoprazole.

CONCLUDING COMMENTS

- 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.

- 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]

- For many years consumers in New Zealand had access to only two classes of OTC treatments for reflux symptoms: antacids and H2RAs.

- An international panel of gastroenterologists has concluded that the availability of PPIs in the OTC setting provides an opportunity to improve the quality of care of reflux sufferers who may be currently untreated or under-treated.[8]

- The public health benefits that will likely result from the availability of pantoprazole 20 mg as a Pharmacy Only medicine include more effective symptom control, more rationale use of medications[8] and more rational use of healthcare resources[8]

- Pantoprazole 20 mg offers superior efficacy to ranitidine (300mg/day) with no additional safety considerations and equivalent efficacy to omeprazole (10-20mg/day) with slightly less interaction potential.

- Pantoprazole 20 mg is, therefore, just as suitable as ranitidine (300mg/day) and omeprazole (10-20mg/day) to be classified as a Pharmacy Medicine.

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