Reclassification of Ranitidine HCl (Zantac Relief) 150 mg in packs containing no more than 7 days supply

Present Classification:	Pharmacy Only medicine
Sought Classification:	Unscheduled

Submission to:
Medicines Classification Committee
Medsafe New Zealand

Submission from:

GlaxoSmithKline New Zealand Ltd
trading as GlaxoSmithKline Consumer Healthcare

29 January 2007

SPONSOR INFORMATION

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1. EXECUTIVE SUMMARY

1.1 Purpose of the application

This application seeks to change the scheduling status of ranitidine HCl 150mg (Zantac Relief), with a maximum dose of 300 mg/day, for the effective long lasting relief of heartburn and acid indigestion in packs containing no more than 7 days supply from Pharmacy Only (Schedule 2) to unscheduled.

1.2 Justification for reclassification

1.2.1 The burden of dyspepsia (heartburn and indigestion) in the community

Heartburn and other symptoms of indigestion related to gastric hyperacidity, such as indigestion and acid indigestion, are extremely common in the community. Prevalence data from New Zealand is limited. However, Haque and colleagues have conducted a population-based study, the objective of which was to describe the prevalence and severity of dyspepsia and gastro-oesophageal reflux in the community, to investigate their association with lifestyle factors and to evaluate the consultation pattern for these conditions.[1] Their research revealed a prevalence of 34.2% for dyspepsia, 30% for reflux and 45.2% for both symptom groups combined over the past 12 months. Most subjects had multiple symptoms — the results indicated 63% of subjects with reflux also had symptoms of dyspepsia and 56% of subjects with dyspepsia showed symptoms of reflux. Importantly, although 69% of subjects with heartburn used over-the-counter medications, only 17% consulted medical practitioners.

These data are similar to those from other countries. For example, in an Australian community survey over half (56%) of respondents reported that they had suffered from heartburn at some time in the past and 37% had symptoms at least once every 4-6 months.[2] Almost half the individuals experienced mild pain or discomfort, one-third had moderate discomfort and 15% reported severe pain or discomfort. More than half the respondents relied on antacids to control symptoms, 20% used prescription medications and a similar number did not use any medication.

A number of studies have shown an association between dyspepsia and reduced quality of life. In general, people with functional dyspepsia score higher on measures of anxiety, neuroticism, depression and hypochondriasis compared with healthy controls.[3-6] Wilhelmsen et al compared 100 people with functional dyspepsia, 100 with duodenal ulcer, and 100 controls, 18 and found that those with functional dyspepsia had more anxiety and depression, and a lower general level of functioning than people in the other two groups.[7] In addition, those with functional dyspepsia had more frequent dyspepsia symptoms and longer duration of symptoms than those with duodenal ulcer.

1.2.2 Extensive market experience with ranitidine HCl

Ranitidine was first approved in June 1981 in Italy. It was approved as a prescription product in New Zealand in December 1989 and has been available as a Pharmacy Only product in New Zealand since May 2000.

Ranitidine is available as a non-prescription product in a vast number of markets around the world, including Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Netherlands, Spain, Sweden, USA, UK, Czech Republic, Hungary, Lithuania, Norway, Poland, Slovak Republic, Slovenia, and Switzerland. Moreover, there is extensive market experience with ranitidine as an unscheduled product in other markets:

- In the USA it was first made available as an unscheduled medicine in 1995 at a dose of 75 mg. In 2004, the 150 mg dose was also approved as an unscheduled product.
- In Canada the 75 mg strength is currently available as an unscheduled medicine and there is a current application under review for the 150 mg strength to also be available unscheduled.
- In the UK the 75 mg strength has been available since the mid 1990's as an unscheduled medicine with a restriction on pack six to 12 tablets and a maximum daily dose of 300mg.

1.2.3 Ranitidine HCl has excellent efficacy and tolerability profiles

Ranitidine belongs to the class of H_2 antagonists which work by blocking the action of histamine on parietal cells in the stomach, thereby decreasing acid production by these cells.

Ranitidine is one of the most extensively studied and widely used drugs of all time. Worldwide, the clinical experience with H_2 antagonists spans almost 30 years and includes a number of careful post-marketing surveillance studies. A review of data from 189 controlled clinical trials (in which more than 26,000 patients received daily doses of ranitidine for 4 weeks or more; 80% of patients were treated with up to 300 mg ranitidine daily and the remaining patients received doses of up to 1200 mg daily) as well as analyses of post-marketing surveillance studies and spontaneously reported adverse events has confirmed the excellent safety profile of ranitidine.[8] The net result of the available information is that ranitidine generation is one of the safest drugs known.[9]

There are no clinically significant interactions between ranitidine and commonly prescribed medications.[10] There has been extensive experience with millions of people using ranitidine as a non-prescription product over the last 12 years.

Ranitidine 300mg per day, given in divided doses, is well established as an efficacious treatment for the relief of heartburn, dyspepsia and hyperacidity.[11] A number of studies have demonstrated that the use of low-dose ranitidine is superior to placebo in the relief of heartburn and related symptoms.[12-14]

1.2.4 Indication

Zantac Relief 150mg is indicated for the effective long lasting relief from heartburn and indigestion.

Zantac Relief 150 will be available for oral use, with a maximum of 2 tablets (300mg) to be taken in any 24 hour period. To provide long lasting relief from heartburn and indigestion one tablet of Zantac Relief 150mg should be swallowed whole with water as soon as symptoms appear. A second tablet may be taken 1 hour later if needed. However, the consumer should not take more than one 150 mg tablet at a time and not more than two tablets in 24 hours (i.e., 300 mg maximum in 24 hours). Zantac Relief 150mg should not be taken for more than 7 days consecutively without seeking the advice of a healthcare professional.

1.3 Public health benefits

In the current unscheduled environment, antacids and antacid/alginate products are the only treatment options available for relieving the symptoms of gastro-oesophageal reflux. Many individuals with heartburn and indigestion self-medicate with antacids and although these products are fast acting they provide only short term relief from symptoms (up to 4 hours).[15;16] Consequently, antacids need to be administered three to four times a day in order to provide all day relief from heartburn and indigestion.

Despite their widespread use, it is noteworthy that in recent systematic reviews investigating pharmacological interventions for non-ulcer dyspepsia, antacids were found to be no more effective than placebo.[17;18] A Cochrane Collaboration Review included only one small trial of antacids and this trial did not show any statistically significant benefit compared to placebo (total 109 patients; Relative Risk Reduction [RRR] = -2%; 95% CI = -36% to 24%).[18] In contrast, 11 eligible trials with H_2 antagonists were reviewed and these results were statistically significant compared to placebo (total 2,164 patients; RRR = 22%; 95% CI = 7% to 35%).[18]

Moreover, although they are generally well tolerated antacids do have the potential to cause side effects in susceptible patients.[19] Antacids containing aluminium salts are constipating, whereas magnesium-containing antacids can cause diarrhoea. Many products contain a combination of the aluminium and magnesium salts to balance these two effects, but many individuals do experience some effect on gastrointestinal motility with combination antacids.[20]

Antacids containing sodium bicarbonate deliver significant amounts of sodium, which can be a problem for individuals with cardiovascular disorders who need to restrict sodium intake. Calcium-containing antacids can cause increased gastric acid secretion, which can lead to acid rebound. All antacids may cause problems for individuals with severe renal impairment.[20;21] Another consideration in the use of antacids is the potential for interfering with, or altering the absorption of, concomitantly administered oral medications.[20]

Despite this well-documented adverse event profile, most individuals use these products in an unsupervised general sale environment with apparently few reported problems. However, there appears to be a need for broader access to a more effective, longer lasting and safe alternative for the treatment of heartburn and related symptoms.

The availability of ranitidine 150mg, in pack sizes limited to a maximum of 7 days supply as an unscheduled product would therefore meet the current need in the grocery environment by providing consumers with access to a more efficacious, longer lasting and safe medication with which to relieve heartburn and indigestion. The suggested limit to packs of no more than 7 days supply is in line with the current unscheduled pack sizes for antacids and antacid/alginate combination products.

1.4 Minimal potential for misuse of the product

There is no evidence that ranitidine has any euphoric effect or any potential for abuse. Moreover, the available data indicates that in the decade that ranitidine has been available as a non-prescription product there is limited — if any — evidence of abuse or overuse of this product.

In a recent US actual use study, conducted to determine how well unsupervised consumers understand and comply with the labeling of an unscheduled ranitidine preparation (Zantac 75), 90% of participants adhered to the direction to take one tablet per dose, 90% followed the instructions to take no more than two tablets in 24 hours, and 96% complied with the direction not to take the maximum daily dose for more than 14 consecutive days. This demonstrates that US consumers can safely use ranitidine in an unsupervised environment and fully comply with the package directions by not exceeding the maximum daily dosage and length of use.[22]

It is of note that, as with all of GSK's major consumer healthcare brands, the labeling for unscheduled Zantac 150mg in New Zealand will undergo label comprehension testing to optimize its performance prior to being launched.

In the USA, where H_2 antagonists have been available OTC (similar to unscheduled in New Zealand) two cross sectional community surveys, were performed to examine whether switching H_2 antagonists to an OTC environment affected the frequency of physician visits by individuals with dyspepsia.[23] Analysis of the surveys indicated that the OTC availability of H_2 antagonists has not affected the number of physician visits by dyspeptic individuals (presentation frequency for dyspepsia was 22% in 1993

versus 23.5% in 1997). Thus, it would seem that dyspeptic patients will visit a physician when (despite self directed treatment) symptomatic relief is not achieved. Moreover, the vast majority of respondents reported using a H_2 antagonist for the approved indication and in recommended doses.

There are high rates of diagnostic investigation amongst dyspeptics who consult doctors, however, in contrast many individuals with dyspepsia decide to self-medicate with antacids regardless of whether or not they have consulted a doctor or are taking prescriptions.[24] For example, in a New Zealand based population study Haque and colleagues have shown that 69% of people with heartburn used over-the-counter medications and only 17% consulted a medical practitioner.[1] A community survey conducted in Europe and North America has also shown that of those with clinically relevant symptoms, 49% had taken an over-the-counter medication, and 27% prescription medication during the period studied.[25] In addition, Australian data have shown that more than half of the people that reported having heartburn rely on antacids to control symptoms, 20% used prescription medications and a similar number did not use any medication.[2] This demonstrates that the potential unscheduled availability of products to treat heartburn and indigestion is independent of consultation behaviour.

2 PART A

2.1 International non-proprietary name of the medicine

Ranitidine hydrochloride

Chemical name:
(E)-N-(2-((5-((dimethylaminomethyl)furan-2-yl)methylthio)ethyl)-N'-methyl-2-nitroethene-1,1-diamine, hydrochloride.

2.2 Proprietary name

Zantac Relief 150mg tablets

2.3 Name of company requesting reclassification

GlaxoSmithKline Consumer Healthcare
82 Hughes Avenue
Ermington NSW
Australia 2115

2.4 Dosage form and strength for which a change is sought

Zantac Relief 150mg tablets will be marketed as white, film-coated oral tablets.

Each Zantac Relief 150mg tablet contains 168mg of ranitidine hydrochloride (150mg ranitidine anhydrous free base).

2.5 Pack size and other qualifications

Zantac Relief 150mg will be available for oral use, with a maximum of 2 tablets (300mg) to be taken in any 24 hour period.

Zantac Relief 150mg will be supplied in packs containing no more than 7 days' supply in foil blisters contained in a cardboard carton. Two pack sizes will be made available containing either 7 or 14 tablets.

2.6 Indications for which change is sought

Zantac Relief 150mg is indicated for the effective long lasting relief from heartburn and indigestion.

2.7 Present classification of medicine

Pharmacy Only Medicine (also known as Schedule 2 medicine).

2.8 Classification sought

Unscheduled Medicine (also referred to as general sales or open sale).

2.9 Classification status in other countries

Ranitidine was first marketed as a prescription product 25 years ago (launch year: 1981). Since this time it has become available as a non-prescription product in a number of markets around the world, including Australia, New Zealand, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Netherlands, Spain, Sweden, USA, UK, Czech Republic, Hungary, Lithuania, Norway, Poland, Slovak Republic, Slovenia, and Switzerland.

In Australia, ranitidine has been a Schedule 2 (Pharmacy Only) medicine since November 2000. An application to the National Drugs and Poisons Scheduling Committee to reclassify Zantac relief 150mg tablets from schedule 2 to unscheduled was made in 2006. This application will be considered at the February 2007 meeting.

Ranitidine is already available as an unscheduled (general sales) product in a number of major markets as shown below.

- **USA:** In 1995, Ranitidine 75mg was approved for OTC sale (equivalent to unscheduled in New Zealand) for use as an acid reducer with adult dosing limited to 75mg twice a day (i.e., 150mg total daily dose). In August 2004, the US FDA approved the 150 mg strength of ranitidine HCl for unscheduled OTC use.

  OTC (equivalent to unscheduled in New Zealand) Zantac 150mg was subsequently launched in January 2005, and is indicated for the relief of heartburn associated with acid indigestion and sour stomach and the prevention of heartburn associated with acid indigestion and sour stomach brought on by certain foods and beverages when taken 30-60 minutes before eating or drinking.

  In the USA, unscheduled Zantac 150mg tablets can be taken up to twice daily (giving a maximum daily dose of 300mg ranitidine) and is available in blister packs in boxes of 3, 8, and 24 tablets and in bottles of 50, 65 and 80 tablets.

- **Canada:** Ranitidine 75mg (maximum daily dose of 150mg) has been available as an unscheduled product in Canada since 1998. There is a current proposal to switch the 150 mg dose (maximum daily dose of 300mg) to unscheduled on the grounds that it has an established high margin of safety and would provide convenient access to an appropriate dose option to those heartburn sufferers who

find that a 75mg dose is not sufficiently effective. [See attached Notice of Intent distributed by the Canadian Therapeutic Products Directorate in July 2006.]

- **UK:** Ranitidine 75mg has been available as a non-prescription product in the UK since 1994. It is currently available as a Pharmacy Only (equivalent to Pharmacy Only in New Zealand) and an unscheduled product; the differences between the two relate to maximum daily dose and indications. The Pharmacy Only packs are indicated for short-term symptomatic relief of heartburn, dyspepsia, indigestion, acid indigestion and hyperacidity or for the prevention of these symptoms when associated with consuming food or drink and a maximum daily dose of 300mg can be taken for up to 14 days (i.e., the equivalent of the current New Zealand situation). Whilst the unscheduled packs are restricted to a maximum pack size of 12 tablets and a maximum daily dose of 150mg for the symptomatic relief of heartburn, dyspepsia, indigestion, acid indigestion and hyperacidity.

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

Ranitidine was first approved as a Prescription Only (Schedule 4) product in New Zealand in December 1989 and was then reclassified to Pharmacy Only (Schedule 2) in May 2000. Sales volume, by year, of ranitidine tablets in New Zealand for the last 5 years are shown in the table below:

Net Sales Value

SKU	Launch month	2003	2004	2005	2006	2007
ZANTAC RELIEF 150mg 14s NZ	Jan	87,721	119,725	120,718	134,751	1,397
ZANTAC RELIEF 150mg 28s NZ	Jan	260,560	297,709	258,595	290,322	5,723
ZANTAC RELIEF EXTRA 300mg 14s	Nov				41,776	2,093
ZANTAC RELIEF 150mg 4PK TOWER	Nov				11,890	44

Sales Volume (packs)

SKU	Launch month	2003	2004	2005	2006	2007
ZANTAC RELIEF 150mg 14s NZ	Jan	11,915	15,929	15,918	17,847	180
ZANTAC RELIEF 150mg 28s NZ	Jan	26,667	30,002	25,748	28,757	560
ZANTAC RELIEF EXTRA 300mg 14s	Nov				4,330	200
ZANTAC RELIEF 150mg 4PK TOWER	Nov				283	1

Data source: IMS audited units for ranitidine sold in New Zealand.

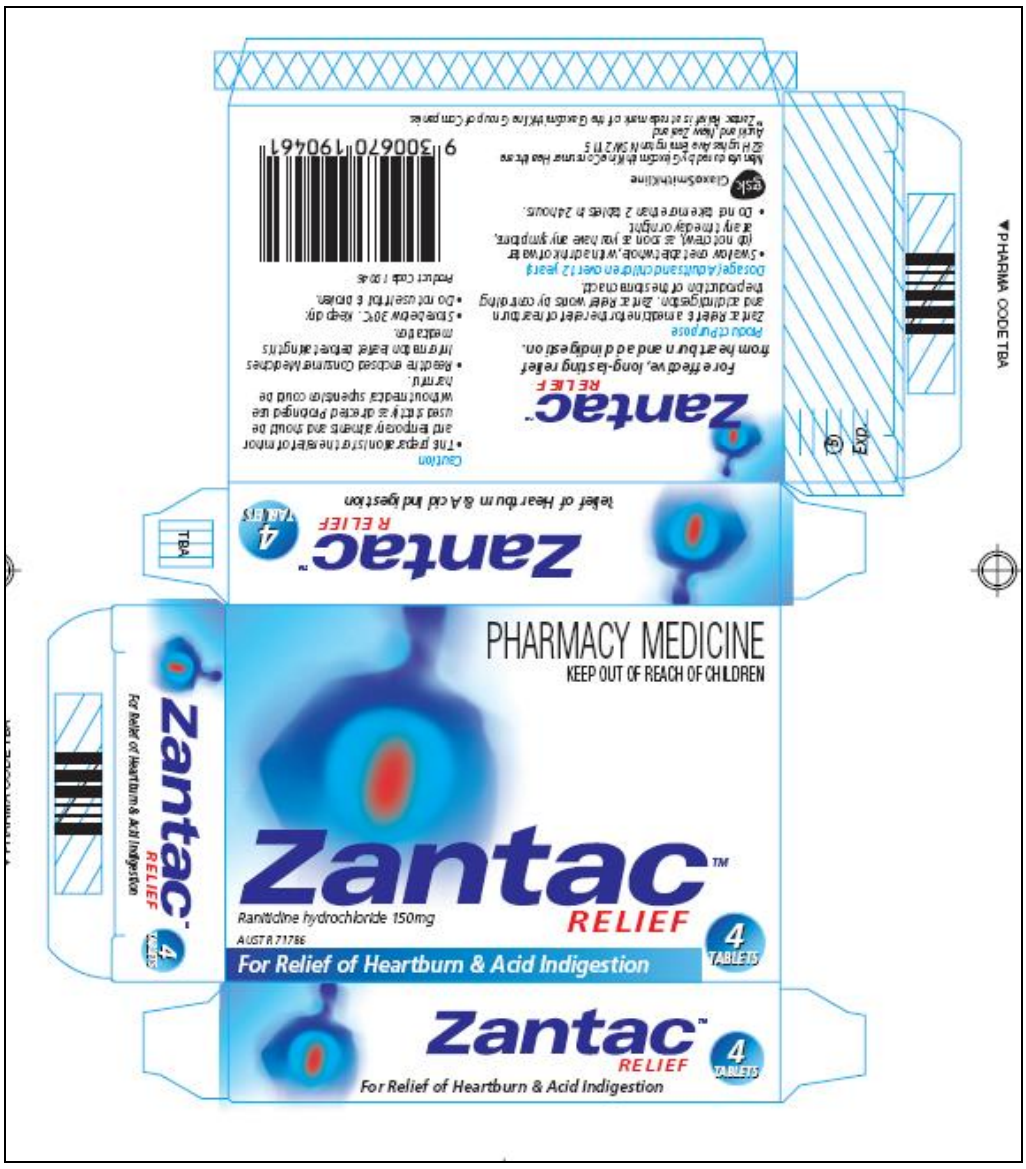
2.11 Labelling or draft labelling for the proposed new presentation

- Blister foil (primary packaging)
- Carton label (secondary packaging)
- Pack insert (to be contained in the carton)

[Refer to Attachment 2 for the draft text]

2.12 Proposed warning statements

- **Proposed pack insert** : A copy of the proposed pack insert is included in Appendix 2. It will contain relevant information under the following sub-headings:
  - What is in this leaflet?
  - What is Zantac Relief used for?
  - Before you take Zantac Relief
  - How to take Zantac Relief
  - While you are taking Zantac Relief
  - Side-Effects
  - Storage
  - Avoiding Heartburn & Acid Indigestion
- **Proposed label**: The proposed **Zantac Relief 150 mg** carton labelling will be largely similar to that for the current Pharmacy Only product, which is shown below. The only warning statement will be to not take more than the stated dose (ie 2 tablets in 24 hours). The consumer will also be directed to the pack insert for other information.



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

Gavilast 12 hour action

Apo ranitidine

3 Part B

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

This submission contains relevant data to support a change in the scheduling status of ranitidine 150mg tablets from Pharmacy Only to unscheduled.

3.1.1 Public health benefits

Dyspepsia (heartburn and indigestion) or gastro-oesophageal reflux refers to a symptom complex of epigastric pain or discomfort rather than a specific disease; as such there is no single, accepted definition.[15]

Dyspepsia is very common. Estimates of its prevalence in the community have varied between studies, primarily because of differences in the definitions used. However, roughly speaking, 15-20% of the general population will report recurrent upper abdominal pain over the course of a year.[26] Estimates of the number of new dyspepsia sufferers per year are difficult to gauge, but it has been estimated that 5 – 10% of the adult population who did not previously have dyspepsia will develop the symptom in any one year.[26]

The following chart summarises prevalence data from selected countries around the world.

Country	Data
Western countries	♦ Gastro-oesophageal reflux has been reported to affect up to 20% of the population of Western countries and account for around 5% of a primary-care physician's workload;[27] ♦ A community survey of 5581 subjects from ten European and North American populations found that 28% of the total sample was defined as having clinically relevant upper gastrointestinal symptoms (i.e. symptoms of at least moderate severity and with a frequency of at least once per week in the previous 3 months).[25]
USA	♦ In the general population roughly 7% suffer from heartburn daily, 13% once a week and 24% at least once a month.[9]
UK	♦ Surveys in the UK have shown a six month prevalence of 38-41%.[28;29]
Australia	♦ In a community survey over half (56%) of respondents reported that they had suffered from heartburn at some time in the past and 37% had symptoms at least once

	every 4-6 months.[2] ♦ Almost half the individuals experienced mild pain or discomfort, one-third had moderate discomfort and 15% reported severe pain or discomfort.
New Zealand	♦ A recent population-based study has revealed a prevalence of 34.2% for dyspepsia, 30% for reflux and 45.2% for both symptom groups combined over the past 12 months.[1] ♦ Most subjects had multiple symptoms — the results indicated 63% of subjects with reflux also had symptoms of dyspepsia and 56% of subjects with dyspepsia showed symptoms of reflux. ♦ The majority (48%) of those who suffered reported suffering once a month, with 27% suffering weekly.

Importantly, most of those people suffering from dyspepsia do not seek medical advice for their symptoms, often accepting them as a natural consequence of their diet or lifestyle. Mild to moderate intermittent symptoms are typically self-managed by avoiding triggers (which may relate to certain foods or behaviours) and using over-the-counter products such as antacids/alginate combinations or H_2 antagonists.[30]

Australian data have shown that more than half of the people that reported having heartburn rely on antacids to control symptoms, 20% used prescription medications and a similar number did not use any medication.[2] Similarly, in New Zealand it has been shown that 69% of people with heartburn used over-the-counter medications and only 17% consulted a medical practitioner.[1] A community survey conducted in Europe and North America has also shown that of those with clinically relevant symptoms, 49% had taken an over-the-counter medication, and 27% prescription medication during the period studied.[25]

Antacids and antacid/alginate products are currently the only options available in the unscheduled environment to relieve the symptoms of gastro-oesophageal reflux. Many individuals with heartburn and indigestion self-medicate with antacids and although these products are fast acting they provide only short term relief from symptoms (up to 4 hours).[15;16] Consequently, antacids need to be administered three to four times a day in order to provide all day relief from heartburn and indigestion.

It is noteworthy, however, that in recent systematic reviews investigating pharmacological interventions for non-ulcer dyspepsia, antacids were found to be no more effective than placebo.[17;18] A Cochrane Collaboration Review included only one small trial of antacids and this trial did not show any statistically significant benefit compared to placebo (total 109 patients; Relative Risk Reduction [RRR] = -2%; 95% CI = -36% to 24%).[18] In contrast, 11 eligible trials with H_2 antagonists were reviewed and these results were statistically significant compared to placebo (total 2,164 patients; RRR = 22%; 95% CI = 7% to 35%).[18]

Moreover, although they are generally well tolerated antacids do have the potential to cause side effects in susceptible patients.[19] Antacids containing aluminium salts are constipating, whereas magnesium-containing antacids can cause diarrhoea. Many products contain a combination of the aluminium and magnesium salts to balance these two effects, but many individuals do experience some effect on gastrointestinal motility with combination antacids.[20]

Antacids containing sodium bicarbonate deliver significant amounts of sodium, which can be a problem for individuals with cardiovascular disorders who need to restrict sodium intake. Calcium-containing antacids can cause increased gastric acid secretion, which can lead to acid rebound. All antacids may cause problems for individuals with severe renal impairment.[20;21] Another consideration in the use of antacids is the potential for interfering with, or altering the absorption of, concomitantly administered oral medications.[20]

Despite this well-documented adverse event profile, most individuals use these products in an unsupervised general sale environment with apparently few reported problems. However, there appears to be a need for broader access to a more effective, longer lasting and safe alternative for the treatment of heartburn and related symptoms.

Ranitidine is one of the most extensively studied and widely used drugs of all time. Worldwide, the clinical experience with H_2 antagonists spans almost 30 years and includes a number of careful post-marketing surveillance studies. A review of data from 189 controlled clinical trials (in which more than 26,000 patients received daily doses of ranitidine for 4 weeks or more; 80% of patients were treated with up to 300 mg ranitidine daily and the remaining patients received doses of up to 1200 mg daily.) as well as analyses of postmarketing surveillance studies and spontaneously reported adverse events has confirmed the excellent safety profile of ranitidine.[8]

There are no clinically significant interactions between ranitidine and commonly prescribed medications.[10] There has been extensive experience with millions of people using ranitidine as a non-prescription product over the last 12 years.

A number of studies have demonstrated that the use of low-dose ranitidine is superior to placebo in the relief of heartburn and related symptoms.[12-14] The overall conclusion from these studies is that single doses of ranitidine (up to 125mg) provide prompt relief of heartburn that lasts for up to 12 hours, has a safety profile comparable to that of placebo, and has the potential to reduce antacid consumption.

A review of data from 189 controlled clinical trials (in which more than 26,000 patients received daily doses of ranitidine for 4 weeks or more; 80% of patients were treated with up to 300 mg ranitidine daily and the remaining patients received doses of up to 1200 mg daily) as well as analyses of postmarketing surveillance studies and spontaneously reported adverse events has confirmed the excellent safety profile of ranitidine.[8] The net result of the available information is that ranitidine is one of the safest drugs known.[9]

The availability of ranitidine 150mg, in pack sizes limited to a maximum of 7 days supply as an unscheduled product would therefore meet the current need in the grocery

environment by providing consumers with access to a more efficacious, longer lasting and safe medication with which to relieve heartburn and indigestion. The suggested limit to packs of no more than 7 days supply is in line with the current unscheduled pack sizes for antacids and antacid/alginate combination products.

3.1.2 Potential social benefits

Dyspepsia is not life-threatening and it has not been shown to be associated with any increase in morbidity.[31] However, the impact of this condition on patients and health care services has been shown to be considerable.

A number of studies have also shown an association between dyspepsia and reduced quality of life. In general, people with functional dyspepsia score higher on measures of anxiety, neuroticism, depression and hypochondriasis compared with healthy controls.[3-6] Haug et al compared 100 people with functional dyspepsia,100 with duodenal ulcer, and 100 controls, and found that those with functional dyspepsia had more anxiety and depression, and a lower general level of functioning than people in the other two groups.[7]

Importantly, in a large community survey of 5581 subjects from ten European and North American populations, almost 3 out of every 10 people with dyspepsia reported taking days off work or school because of their symptoms.[25]

Self-medication is common amongst people with dyspepsia and there is widespread consumption of readily available antacids. The value of these products are however hampered by the short term relief they provide, issues surrounding efficacy[15-18] and the potential for a number of drug interactions.[16;32]

Wider availability of ranitidine has potential societal benefits for dyspepsia sufferers and economic benefits for employees by providing access to a product which has proven efficacy benefits over antacids and a superior safety profile to antacids.

3.1.3 Potential to improve appropriate treatment choices

The Australian National Prescribing Service recommends H_2 receptor antagonists as the first line treatment in a step up approach to managing the symptoms of dyspepsia or gastro-oesophageal reflux disease.[15] Similarly the New Zealand guidelines group recommends the use of H_2 receptor antagonists before that of antacids for the management of dyspepsia.[33]

Despite these guidelines, and the documented evidence that ranitidine provides clinically significant efficacy compared to placebo (RRR = 22%; 95% CI = 7% to 35%)[18] whereas antacids do not [17;18], many consumers still opt to use antacids to manage their symptoms.

The availability of ranitidine alongside antacids in a general sales environment would provide consumers with an efficacious, longer lasting and convenient treatment alternative with which to manage their symptoms. This is of particular importance given that as many as 1 in 5 do not seek the advice of their GP until their symptoms become more severe or more frequent.[1] Consumers who have previously used antacids and found them of little or minimal benefit would be able to self select ranitidine.

In direct contrast to antacids, ranitidine is available in a convenient once (or twice if required) daily dose. One tablet of ranitidine provides 12 hours of relief providing a much longer duration of action than antacids[32]. Importantly, ranitidine has been proven to be effective[17;18] and is amongst the safest drugs known.[9] Thus its wider availability would enhance treatment options available to consumers for the relief of heartburn and indigestion.

3.2 Evidence and rationale for reclassification

3.2.1 Treatment of dyspepsia (heartburn and indigestion)

The recently published New Zealand evidence based guidelines on the management of dyspepsia and heartburn offer the following advice with regards to the current treatment options for dyspepsia:[33]

"The range of management options is great, particularly if it is accepted that dyspepsia has a wide variety of causes. In addition, many people with dyspepsia will decide that their symptoms are minor or transient enough to ignore, or they will prefer to treat themselves with proprietary antacids or over-the-counter acid inhibitors rather than consult general practitioners. A wide variety of psychosocial factors often affect this decision.

When consulted, the general practitioner must decide whether the person requires reassurance only, empiric treatment, simple investigation, or referral to a gastroenterologist for definitive diagnosis. Appropriate treatment includes the care of the whole person. It is an opportunity to review personal and lifestyle factors (eg, diet, weight control, smoking, alcohol abuse, drug use) and, in a number of cases, this may be all that is required. Most people can be treated by simple medical means with satisfactory outcomes. However, symptomatic recurrence is common, so that repeated courses and sometimes continuous medication may be required.

Once a definitive diagnosis has been made, further follow-up can be defined more precisely. However, for functional dyspepsia, follow-up is often dictated by symptoms. Long-term continuing medication for functional dyspepsia is discouraged. Care needs to be exercised to achieve a balance between not 'overmedicalising' and offering rational long-term follow-up when necessary."

The New Zealand guidelines advocate the use of H_2 receptor antagonists before that of antacids in the management of dyspepsia recommending.[33]

3.2.2 Rationale for unscheduled status

The rationale for reclassifying ranitidine 150mg from a Pharmacy Only to an unscheduled medicine is based on the following key points:

- Dyspepsia (heartburn and indigestion) is a self-limiting, self-recognisable condition.

- Antacids and antacid/alginate products are currently the only options available in the unscheduled environment, despite the fact they have been shown to be no more effective than placebo.[17;18]

- Ranitidine is available in a convenient once (or twice if required) daily dose, it has been proven to be effective[17;18], has a longer duration of action than antacids[32] and is amongst the safest drugs known.[9]

Given the extensive market experience with ranitidine and its excellent safety profile, an alteration of its scheduling status from Pharmacy Only to unscheduled is appropriate. The availability of ranitidine as an unscheduled product would provide consumers with access to an alternative to antacids to treat the symptoms of heartburn and indigestion. The unscheduled availability of Zantac Relief 150mg would provide heartburn and indigestion sufferers with a treatment that is effective, longer lasting , safe and more convenient to take than the currently available unscheduled options. The suggested pack size limit of 7 days supply is in line with the current unscheduled pack sizes for antacids and antacid/alginate combination products.

It is considered that Zantac Relief 150mg meets the regulatory requirements for re-classification, details of which are provided in subsequent sections of this document.

3.2.3 Overview of efficacy of ranitidine

Ranitidine belongs to the H_2 antagonists class of medicines. H_2 antagonists block the action of histamine on parietal cells in the stomach, thereby decreasing acid production by these cells. These drugs are used for the symptomatic relief of gastro-oesophagea reflux. Since their initial introduction as ulcer healing treatments, H_2 antagonists have been one of the most widely prescribed groups of medicines worldwide. This almost unprecedented level of usage reflects the efficacy of these agents across the range of gastric acid-related diseases, as well as the excellent safety profile, which characterises this pharmacological group.

Ranitidine was developed as a result of a rational drug-design process utilising quantitative structure-activity relationships (QSAR) — the imidazole-ring of cimetidine was replaced with a furan-ring which also contained a nitrogen substituent. As a result of these structural changes, ranitidine was found to have a far-improved tolerability profile (i.e. fewer adverse drug reactions), longer-lasting action, and ten times the activity of cimetidine.

Ranitidine is well established as an effective inhibitor of gastric acid secretion in the treatment and prophylaxis of gastrointestinal lesions aggravated by gastric acid secretion.[11] A number of studies have demonstrated that the use of low-dose ranitidine is superior to placebo in the relief of heartburn and related symptoms.[12-14]

Therapeutic trials involving several thousands of patients with peptic ulcer disease confirm that ranitidine 300mg daily administered orally in single or divided doses is at least as effective as cimetidine 800 to 1000mg daily in increasing the rate of healing of duodenal and gastric ulcers.[11] Similar dosages of ranitidine have been shown to relieve the symptoms of reflux oesophagitis and heal or prevent gastrointestinal damage caused by ulcerogenic drugs. Ranitidine 150mg orally at night maintains ulcer healing in the long term.[11]

In a Cochrane Collaboration Review of pharmacological management options for dyspepsia, H2 antagonists were found to be statistically superior compared to placebo (total 2,164 patients; RRR = 22%; 95% CI = 7% to 35%).[18]

Ranitidine OTC is used at a dosage of up to 300mg per day for 14 days. In the prescription setting, it is used at different dosage levels depending upon the condition being managed:[16]

- Peptic ulcer disease (PUD):
  Oral, initially 300 mg daily as a single evening dose (or 2 divided doses) for 4–8 weeks.
  IV/IM, 50 mg every 6–8 hours. Maintenance, oral 150–300 mg daily as a single evening dose.

- Gastro-oesophageal reflux disease (GORD):
  Oral, 300 mg daily as a single evening dose, or 2 divided doses.

- Stress ulcer prophylaxis:
  Oral, 150 mg twice daily until risk factors removed.
  IV, 50 mg every 6–8 hours; or 50 mg initially, then IV infusion 125 to 250 micrograms/kg/hour until risk factors removed.

- Dyspepsia: Oral, 150 mg twice daily for 4–8 weeks.

The overall conclusion from the available data is that ranitidine provides prompt relief of heartburn that lasts for 12 hours (24 hours for the 300mg dose), has a safety profile comparable to that of placebo, and reduces antacid consumption.

3.2.4 Efficacy of low dose ranitidine

Clinical studies have also shown that doses of ranitidine up to 300mg/day are effective in both treating and preventing episodic heartburn. [22;34;35] The following text provides a brief review of clinical data.

- Adults with at least a 3-month history of heartburn were eligible and were randomized to receive treatment with one tablet of either ranitidine 75 mg (n = 491), ranitidine 25 mg (n = 504), or placebo (n = 494), to be taken as needed up to four times daily for 2 weeks for the relief of heartburn. The ranitidine 75 mg regimen (in which patients were able to take up to 300 mg per day) was clinically (> 10 percentage points) and statistically (P < 0.05) significantly more effective than placebo for all measured efficacy end-points in relieving heartburn and reducing antacid consumption. In addition, the ranitidine 75 mg regimen was superior to placebo in providing heartburn relief within 30 min of dosing that lasted for up to 12 h. The authors concluded that: "***All treatments were well tolerated and adverse events occurred no more frequently with the ranitidine regimens than with placebo.***"[34]

- In another study of the same design, subjects were randomly assigned to receive treatment with one tablet of either ranitidine, 75 mg (n = 537); ranitidine, 25 mg (n = 539); or placebo (n = 544), to be taken as needed up to four times daily for 2 weeks for the relief of heartburn. The ranitidine 75 mg regimen was statistically (P < 0.05) and clinically (as defined a priori as > or =10% improvement) more effective than placebo in relieving episodic heartburn and in reducing antacid consumption The authors concluded that: ***"low-dose ranitidine provides prompt and lasting relief of heartburn and has a safety profile comparable to that of placebo."***[36]

- In a dose-ranging trial of ranitidine tablets for relief of episodic heartburn, adult out-patients who reported heartburn relieved by antacids at least seven times per week were randomized to a 1-week, double-blind treatment phase during which they received ranitidine doses of 25, 75 or 125 mg, or placebo. Of 577 patients randomized, 566 had at least one evaluable heartburn episode and were included in the intention-to-treat analysis. All three ranitidine doses were statistically significantly superior to placebo in providing overall episodic heartburn relief for the first episode (P < 0.002), last episode (P</=0.004), and all episodes combined (P < 0.001). The ranitidine 75 mg and 125 mg doses provided sustained relief (relief within 60 min of dosing that lasted throughout the 4-h evaluation period) to a greater proportion of patients for each individual episode (43-56% for 75 mg and 42-57% for 125 mg) than the ranitidine 25 mg dose (35-50%) or placebo (21-29%). The incidence of adverse events was similar in all treatment groups. Patients treated with ranitidine 75 mg and 125 mg consumed statistically fewer rescue antacids than placebo-treated patients for the first episode. All three doses were well tolerated, with adverse event profiles similar to those of placebo.[37]

3.3 Ease of self-diagnosis for the condition indicated

The natural history of dyspepsia (heartburn and indigestion) or gastro-oesophageal reflux is one of persisting or frequently recurring symptoms; in many people, these are of short duration or mild severity.[15] Mild to moderate intermittent symptoms can be self-managed — strategies include avoiding triggers (which may relate to certain foods

or behaviours) and using over-the-counter products such as antacids/alginate or H_2 antagonists.[30]

Medsafe and the Medicines Classicfication Committee (MCC) have already accepted that members of the general population are able to self-diagnose and self-manage heartburn and indigestion without recourse to a healthcare professional by virtue of the fact that antacids are already available as unscheduled medicines.

Furthermore, MCC approved ranitidine as a Pharmacy Only medicine in New Zealand in 2000. The rescheduling proposal was supported on the grounds that the safety data justified a Pharmacy Only classification and the indications met the Schedule 2 classification criteria. The pack insert that accompanied the launch of this product was designed to advise the consumer to consult their doctor or pharmacist should their symptoms worsen or not improve. This approach has ensured the appropriate and safe use of ranitidine in a Pharmacy Only environment.

Data from a recent US actual use study has demonstrated that consumers can safely use unscheduled ranitidine without medical supervision and that the vast majority of unsupervised consumers understand the package label and fully comply with the package directions by not exceeding the maximum daily dosage and length of use.[22]

Given the excellent safety profile of ranitidine and the extent to which it has been safely used in a number of unsupervised markets, rescheduling ranitidine to unscheduled in limited pack sizes will not impose any greater risk to the population than from the currently available Pharmacy Only schedule.

3.4 Risk of masking a serious disease or compromising medical management of a disease that can be managed by a Pharmacist

The risk of masking a significant underlying condition is small. Early concerns that the use of H_2 antagonists might mask the symptoms of gastric cancer have not been borne out in the literature.[9]

- A US case-control study has found that the crude odds ratio of gastric cancer amongst people taking cimetidine versus non-users was 2.1 (95%CI 0.7 to 6.3) and was similar to that for antacids (1.9, 95%CI 1.0 to 3.7).[38]

- Endoscopy was performed in almost the whole population of one Norwegian town, gastric erosive changes were found in almost equal proportions of patients with dyspepsia and controls (35% vs. 38%) and no gastric cancer was found.[39]

- In a further endoscopic study involving 562 people with dyspepsia who self medicated with OTC famotidine no cases of gastric cancer were found.[40]

It is important that the availability of products, potentially without any supervision, does not delay the diagnosis of serious underlying diseases, for which other therapy

is more appropriate. In patients with significant pathology, symptoms persist for extended periods of time. The available data indicates that despite self selection consumers do visit a physician when symptoms persist of get worse:

- In the US a study of users of H_2 receptor antagonists — where these products have been available open sale since 1995 — has demonstrated that self-medicating, dyspeptic patients will visit a physician when symptomatic relief is not achieved.[23]

- This is also reflective of data from New Zealand, which demonstrates that whilst only 1 in 5 people consult a doctor about their heartburn symptoms and people are more likely to seek advice if the symptoms are more severe than before or are becoming more frequent.[1]

Importantly any risk of masking more serious condition may be overcome by the limitation to the dose and pack size for unscheduled sale. The pack insert directs consumers to seek the advice of a doctor if symptoms do not improve or get worse.

3.5 Relevant comparative data for like compounds

Antacids are currently unscheduled in New Zealand and hence are available in a variety of general sales outlets. They work by neutralising the acid or reducing the amount of acid in the stomach. Most antacids contain aluminum, calcium or magnesium. Some antacids contain additional active ingredients, such as simethicone. Claims are made that these agents help relieve symptoms of reflux or excess gas, but there is limited evidence to support this.[16] Optimum antacid effect is achieved if these products are taken 1–3 hours after meal; and it appears that liquid preparations are more effective, but less convenient, than solid preparations. [16]

The most common side effects of antacids are constipation (with aluminum-containing antacids), diarrhoea (with magnesium-containing antacids), increased thirst and decreased appetite. Some consumers need to take extra care when selecting and taking antacids. For example, people who are on a low-sodium diet should avoid taking antacids that contain high levels of sodium. Additionally, antacids interact with many prescription drugs, the most significant drug interactions are summarised in Table 3 below.[32]

Despite their widespread use, it is noteworthy that in recent systematic reviews investigating pharmacological interventions for non-ulcer dyspepsia, antacids were found to be no more effective than placebo.[17;18] A Cochrane Collaboration Review included only one small trial of antacids and this trial did not show any statistically significant benefit compared to placebo (total 109 patients; Relative Risk Reduction [RRR] = -2%; 95% CI = -36% to 24%). In contrast, 11 eligible trials with H_2 antagonists were reviewed and these results were statistically significant compared to placebo (total 2,164 patients; RRR = 22%; 95% CI = 7% to 35%).

Based on its own review of the literature, the New Zealand Guidelines Group has concluded that antacids appear to provide little benefit in the management of non-ulcer dyspepsia.[33] This is further supported in Australia by the National Prescribing Service[15] and by the Australian Medicines Handbook, which states that antacids may be used 'when required' in some patients with dyspepsia, but that these drugs appear to be no better than placebo in functional dyspepsia (where placebo response is 20–60%).[16]

Importantly, antacids at best provide only short term relief from symptoms which lasts up to 3 hours, while ranitidine provides long lasting relief up to 24 hours with two tablets of 150mg dose of ranitidine.[10]

Table 3. Major drug interactions with antacids.[32]

Drug	Effects
Chlorpromazine	Reduced absorption
Ciprofloxacin, norfloxacin	Reduced absorption
Digoxin	Reduced absorption
Enteric-coated tablets of any medicine	Coating disrupted in stomach (as a consequence the release of the drug may be unpredictable and adverse events may occur if the drug is in contact with the stomach)
Iron	Reduced absorption
Lithium	Serum levels reduced by sodium (bicarbonate)
Penicillamine	Reduced absorption
Rifampicin	Reduced absorption
Sucralfate	Efficacy reduced as pH increases
Tetracyclines	Reduced absorption
Warfarin and phenindione	Reduced absorption

3.6 Local data or special considerations relating to NZ

3.6.1 Local data regarding the burden of dyspepsia (heartburn and indigestion)

Even though a fairly high proportion of patients with dyspepsia do not seek medical advice, it still represents a costly and important health problem in New Zealand. Haque and colleagues have reported that in 1993, prescribed pharmaceuticals used in the treatment of dyspepsia cost the New Zealand health system $42.8 million (excluding the cost of over-the-counter medicines).[1] More recently, the New Zealand Guidelines committee has reported that this cost has risen annually, with a figure of $44 million for 2002 (equating to nearly 700,000 prescriptions).[33] This group suggests that: ***" … great care is required to ensure careful and rational choice of medication to derive most benefit from the health dollar. In many cases, there are treatment***

alternatives and the cheaper option can often be chosen if there is reasonable evidence for equal outcome."[33]

3.7 Interactions with other medicines

Since cimetidine — the predecessor drug of ranitidine — interacts with a variety of other agents and ranitidine is often administered in combination with other drugs the interaction potential of ranitidine has been subject to extensive investigations. In 1991, Klotz reviewed the available data and reported that pharmacokinetic interactions of ranitidine with other drugs may occur at the site of absorption, metabolism and renal excretion.[41] This author stressed that most of the interactions reported at each of the three levels are minor and of low clinical significance, concluding that "***numerous controlled studies have proven that ranitidine can be safely coadministered with other drugs***."[41]

3.7.1 Interactions with warfarin

Ranitidine has been implicated in both increasing and decreasing warfarin's hypoprothrombinemic-effect (noted in the warfarin package insert), despite the majority of investigations demonstrating no warfarin clearance changes. Having evaluated the literature on this topic, Hussey and Dukes conclude that: "***careful examination of the implicating data indicates that the majority of the warfarin pharmacodynamic and pharmacokinetic variance that occurs with combined ranitidine-warfarin therapy cannot be attributed to a drug-drug interaction.***"[42]

3.7.2 Interactions with alcohol

There are conflicting data on the existence of significant first-pass metabolism of alcohol (ethanol) in the human stomach and its inhibition by histamine H2-receptor antagonists.[43] Pipkin and colleagues have reported that no interaction occurs between ranitidine and alcohol when alcohol 0.3 g/kg or more is taken by either fed or fasted subjects.[44] These authors comment that while ranitidine is associated with small increases (2-4 mg/dl) in blood alcohol concentrations in subjects given alcohol 0.15 g/kg under specific experimental conditions, mean peak blood alcohol concentrations nevertheless remain low (< 20 mg/dl) after the amount, which is equivalent to about 3 oz of wine or 1 oz of 80-proof liquor. Such changes also occur when alcohol is ingested after different types of foods, and are smaller than the increases when it is drunk on an empty compared with a full stomach. These authors conclude that: "***any pharmacokinetic effect seen with ranitidine is without apparent clinical or social significance***."[44]

Toon and colleagues investigated the effects of multiple dosing with ranitidine (300 mg four times a day) on the absorption of a moderate dose of alcohol (0.5 gm/kg),

consumed post-prandially or on an empty stomach at different times of day, and to investigate if co-administration of ranitidine affects psychomotor function. Two double-blind, randomized, two-way crossover, and placebo-controlled studies were performed in a university research establishment. The study subjects were 36 (18 in each study) normal, healthy, nonalcoholic men aged from 25 to 48 years. They received either 300 mg ranitidine four times a day or placebo for 8 days with oral alcohol (0.5 gm/kg) in the morning on day 4, at midday on day 6, and in the evening on day 8. Alcohol was consumed 45 minutes after standard meals and 30 minutes after ranitidine in the first study; it was consumed on an empty stomach 30 minutes after ranitidine in the second study. Maximum blood alcohol concentrations, area under the blood alcohol concentration--time curve, and time to maximum concentration were not significantly different during ranitidine co-administration compared with co-administration of placebo. This result held true for each time of day and for fed and fasting states. Similarly, ranitidine had no detectable effect on any of the results from tests of psychomotor function. These authors concluded that "***irrespective of the time of day, ranitidine has no statistically or clinically significant effects on blood alcohol profiles***."[45]

3.7.3 Interactions with sucralfate

The hypothesis that the cytoprotective agent sucralfate interacts with the H2-antagonist ranitidine by decreasing ranitidine absorption has been tested in vitro and in vivo. [46] The in vitro results showed that ranitidine may bind to a small extent (approximately 10%) to sucralfate paste in the gastrointestinal fluids. The in vivo interaction of 150 mg of ranitidine and 1 g of sucralfate was evaluated in a crossover study in six healthy volunteers. The results indicated no significant difference in pharmacokinetic parameters when ranitidine was given alone and in combination with sucralfate. Thus, Mullersman concluded that: ***"Ranitidine bioavailability is not diminished by sucralfate and the two drugs can be given concomitantly."*** [46]

3.8 Contraindications

The proposed Data Sheet and CMI will include a comprehensive list of contraindications.*[Refer to Attachment 2]*

3.9 Possible resistance

Not applicable.

3.10 Adverse events

Worldwide, the clinical experience with H_2 antagonists spans almost 30 years and includes a number of careful post-marketing surveillance studies. Since its launch, ranitidine has been used to treat millions of patients and is considered to be extremely well tolerated with a low incidence of adverse reactions.

A review of data from 189 controlled clinical trials (in which more than 26,000 patients received daily doses of ranitidine for 4 weeks or more; note that more than 80% of patients were treated with up to 300 mg ranitidine daily whilst the remaining patients received doses of up to 1200 mg daily) as well as analyses of postmarketing surveillance studies and spontaneously reported adverse events has confirmed the excellent safety profile of ranitidine.[8] The net result of the available information is that ranitidine is amongst the safest drugs known.[9]

A small proportion of patients have developed a reaction to the drug shortly after the start of treatment, usually as a result of 'individual idiosyncrasy'. Reactions during continuous, long term treatment with ranitidine are uncommon, such that maintenance treatment of the chronic peptic diseases with ranitidine for more than 10 years has not been associated with significant iatrogenic disease.[47]

3.10.1 Safety data from clinical studies and post-marketing pharmacovigilance studies

Ranitidine hydrochloride is one of the most extensively studied and widely used drugs of all time. This has provided an excellent opportunity to define its safety profile. Adverse events reported in clinical trials of ranitidine in daily doses of up to 1200 mg (i.e. three times the maximum OTC dose) include headache, tiredness and mild gastrointestinal disturbances. The incidence of these adverse events is similar to or less than that for placebo.[48]

Mills and colleagues reviewed data from 189 controlled clinical trials in which more than 26,000 patients received daily doses of ranitidine for 4 weeks or more.[8] More than 80% of patients were treated with up to 300 mg ranitidine daily; the remaining patients received doses of up to 1200 mg daily. Eighty-seven trials were placebo controlled. Analyses of post-marketing surveillance and a database of all spontaneously reported adverse events were also evaluated.

Overall in the clinical trial programme adverse events were reported by 20% of those receiving ranitidine compared with 27% of those receiving placebo. The pattern of events was similar in all treatment groups with no evidence of dose-related toxicity in regimens encompassing an eightfold range of therapeutic doses. This review of data from a large population of controlled clinical trials with analyses of postmarketing surveillance studies and spontaneously reported adverse events has confirmed the excellent safety profile of ranitidine.[8]

3.10.2 Data from safety databases

Government initiated safety databases serve as an important tool in monitoring the safety of medicines. They hold reports of suspected reactions to drugs, the majority of which have been submitted voluntarily by healthcare professionals. It is important to note that just because a report has been submitted it does not necessarily mean that the medicine has proven to cause such a reaction.

New Zealand: CARM

- The total number of reports in the CARM database for ranitidine (up to and including 31 December 2006) is 258.[49] These represent these causal reactions – those where the reaction has been assessed as having a certain, probable or possible association with ranitidine. As with the Australian data, below, it should be noted that this data relates to all reportings for ranitidine, whether at prescription or OTC doses and does not provide details of the indication for use or the denominator in terms of the number of doses of ranitidine consumed during the observation time-period.

Australia: ADRAC Data

- Australia's Adverse Drug Reaction Advisory Committee (ADRAC) pharmacovigilance database holds details of Australian reports of suspected reactions to drugs received since November 1972.[50] The ADRAC database contains 1,757 cases (representing 3,469 reactions) in which ranitidine has been suspected as being a possible, probable or certain cause of an adverse drug reaction in the 24 years that it has been available on the market. Ranitidine was the sole suspected drug in 827 of these 1,757 cases. ADRAC lists only 47 deaths in which ranitidine has been suspected, this represents less than 2 deaths per year as a possible result of ranitidine use from any source. It should be noted that this data relates to all reportings for ranitidine, whether at prescription or OTC doses and does not provide details of the indication for use or the denominator in terms of the number of doses of ranitidine consumed during the observation time-period.

- A further review of the data from the ADRAC database pertaining to adverse event reports in Australia since January 2001 for OTC Zantac has revealed the following:

    - Zantac 150mg: There have been only 15 reports (which includes 1 serious adverse event) recorded. During the same time frame, 2,350,936 packs (14's and 28's) were; which corresponds to 0.64 reports per 100,000 packs sold.

- Zantac 300mg: There have been only 2 reports recorded. During the same time frame, 606,774 packs (14's) were; which corresponds to 0.33 reports per 100,000 packs sold.

UK: MHRA Data

- The UK Medicines and Healthcare Products Regulatory Agency (MHRA) keeps a database of suspected adverse drug reactions reported through the Yellow Card scheme by healthcare professionals and patients. In the 25 years between the launch of ranitidine s a prescription product in the UK until June 2005 a total of 5,561 suspected adverse reactions in persons taking ranitidine have been entered into the database, and only 27 are listed as having a fatal outcome.[51] As with the ADRAC data, above, it should again be noted that this data relates to all reportings for ranitidine, whether at prescription or OTC doses.

GlaxoSmithkline Global Clinical Safety and Pharmacovigilance

- The GlaxoSmithkline Global Clinical Safety and Pharmacovigilance team have collected safety data on Zantac since it was launched.

- During the period July 2005 to May 2006 it is estimated that patient exposure to ranitidine tablets (all OTC and prescription use of 150mg and 300mg but excluding 75mg OTC formulations) was 1.1 billion treatment days. In addition, 78 million ampoules of injectable ranitidine, 224 million milliliters of ranitidine syrup, and 100 million ranitidine 75mg OTC tablets were sold during the time period. During this time, 218 serious and non-serious reports have been received worldwide.[52] A detailed listing of each of these reports can be found in Appendix 3 of the Ranitidine Safety Update Report.[52]

Based on the review of this data it has been concluded that the safety profile of ranitidine is adequately reflected in the Global Datasheet.

3.10.3 Safety of ranitidine in OTC use

The available data indicate that in the decade that ranitidine has been available as a non-prescription product there is limited if any evidence of abuse or misuse. Moreover, there are some published studies demonstrating that consumers understand and comply with the labeled instructions for non-prescription ranitidine, supporting the argument that ranitidine can be used safely without medical supervision.

Prior to the non-prescription switch of ranitidine in the USA, a study was undertaken to explore how the non-prescription availability of these agents would alter the patterns, effectiveness, and risks of self-treatment for acid-peptic disorders.[53] At the time of the study, it was estimated that about 5.7 million people experienced an episode of dyspepsia during any given quarter and that 60% (3.5 million) of these people were self-medicating with antacids. The study results indicated that the non-prescription availability of H2-antagonists would increase the proportion of people with dyspepsia

who self-medicate from 61.8% to 64.1%. However, due to the superior efficacy of H_2 antagonists, it would also increase the proportion of people who experience complete relief of their symptoms while self-medicating from 37.9% to 43.2%.

Ranitidine 75mg was switched to non-prescription status in the USA (equivalent to unscheduled status in Australia) in 1995, and then later as a 150mg dose tablet in 2005. A study was conducted to determine how well unsupervised consumers understand and comply with the labeling of a non-prescription ranitidine preparation (Zantac 75).[22] Adult male and female consumers (n = 1405) in a shopping mall environment who were attracted to a poster asking, "Do you have stomach problems?" were recruited for the label comprehension phase (two different label formats) and the 3-week usage phase if after reading the Zantac 75 package label they decided the product was appropriate for them. No instructions regarding the use of Zantac 75 were provided beyond what was printed on the package label. Subjects recorded use in a diary and tablet counts were performed at the end of the study period. A medical history was also taken at this time and an assessment of product use was performed by a physician. The direction to take one tablet per dose was adhered to by 90% of consumers, and 90% of consumers followed the instructions to take no more than two tablets in 24 hours. Ninety-six percent of consumers complied with the direction not to take the maximum daily dose for more than 14 consecutive days. Notably, the maximum daily dose was taken for 3 or less consecutive days by the vast majority (79%) of consumers. The authors concluded that: "***The study demonstrated that the vast majority of a large sample of unsupervised consumers understood the package label and fully complied with the package directions by not exceeding the maximum daily dosage and length of use. Nonprescription consumers safely used Zantac 75 without medical supervision.***"[22]

In order to examine the presentation frequency for dyspeptic complaints before and after the OTC release of the H_2 antagonists in the USA and the self-reported effectiveness of these products, two cross-sectional surveys were used in a community sample.[23] The patients comprised a random age- and sex-stratified sample of 1600 ambulatory adults in 1993 and 1800 in 1997. Self-report, valid mail surveys gathered information on healthcare seeking and gastrointestinal symptoms in 1993 and 1997 and anti-secretory use in 1997. Presentation frequency for dyspepsia was 22% in 1993 versus 23.5% in 1997, demonstrating that dyspeptic patients will visit a physician when, despite self directed treatment, symptomatic relief is not achieved.

3.11 Specific safety issues of relevance to the rescheduling of Ranitidine

3.11.1 Ranitidine use during pregnancy

Heartburn is very a common and uncomfortable problem during pregnancy, and can affect up to half of all pregnant women to some degree. Pregnant women are often advised that they can relieve heartburn with an antacid solution or tablets, after having

first checked with their pharmacist, doctor or midwife that such medicines are suitable to use in pregnancy.

The proposed wider availability of ranitidine hydrochloride from general sales outlets must therefore account for the potential for use of this product by pregnant women. Zantac is not recommended for use in pregnancy unless advised by a healthcare professional, this precaution will continue to be in place for the proposed unscheduled product. The Zantac pack insert clearly alerts women who are pregnant or trying to become pregnant or breast feeding not to use the product unless directed to do so by their doctor.

This more cautious approach to the use of ranitidine in pregnancy is based on the fact that published data on pregnancy outcome after exposure to H_2 antagonists is scarce. However, it should be noted that these data that are available are comprehensive and do not suggest any increase in risk of teratogenicity or malformations even after use in the first trimester.

Garbis and colleagues have recently evaluated the data collected by the memberships of the European Network of Teratology Information Services (ENTIS).[54] The patients were pregnant women who or whose doctor or midwife did contact a Teratology Information Service for risk assessment after the use of a H2-blocker in pregnancy. The data were prospectively collected (i.e. before the outcome of pregnancy was known). Data on the outcome of 553 pregnancies with exposure to an H2-blocker were evaluated (ranitidine n=335; cimetidine n=113, famotidine n=75; nizatidine n=15, roxatidine n=15) and compared to those of a control group exposed to non-teratogenic substances. Most of the women had been exposed at least in the first trimester. Although the incidence of premature deliveries was higher in the exposed group compared to the control group, there was no increase in the incidence of major malformations. Two pregnancies with maternal use of famotidine in early pregnancy were terminated after the prenatal diagnosis of a neural tube defect. On the basis of their research, the authors concluded that "***there is no indication for an increased risk of major malformations after the use of H2-blockers during pregnancy.***"[54]

The results of Garbis et al[54] correlate with those from an earlier study conducted on databases from the UK and Italy.[55] The authors assessed the prevalence of congenital malformations in first trimester-exposed pregnancies to cimetidine, omeprazole, and ranitidine and compared it with nonexposed pregnancies between 1991 and 1996. Two different sources were used, the United Kingdom General Practice Research Database and the Italian Friuli-Venezia Giulia Health Database. The final study cohort included 1,179 pregnancies from the United Kingdom and 1,057 from Italy. Abortions or ectopic pregnancies were not included. There were 20 stillbirths and 2,261 live-born babies in both cohorts combined, with 100 offspring identified with a malformation. The overall malformation rate was 4.4%. The relative risks for nongenetic congenital malformations associated with the use of cimetidine, omeprazole, and ranitidine were 1.2 (95% confidence interval (CI): 0.6, 2.3), 0.9 (95% CI: 0.3, 2.2), and 1.4 (95% CI: 0.8, 2.4), respectively, compared with the nonexposed. No specific grouping in the distribution of malformations was observed in any of the three exposed groups. Moreover, no relation was found between drug exposure and preterm delivery or

growth retardation. These findings suggest that the use of acid-suppressing drugs during the first trimester of pregnancy is not associated with a major teratogenic risk.[55]

Despite the lack of identified teratogenic effect, ranitidine is a B1 category medicine and as such its safety in pregnancy has not been established.

3.11.2 Ranitidine use in the elderly

The efficacy and safety of H_2 antagonists is of considerable importance in the management of peptic ulcer disease in elderly people. The increasing mortality and morbidity associated with peptic ulcer disease in elderly people may be due partly to differences in presentation of peptic ulcer disease in elderly compared with younger patients, with the first manifestation often relating to a complication of the disease. In addition, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is widespread in the elderly population leading to an increased incidence of ulceration, haemorrhage and perforation. Elderly NSAID users may be four times more likely to develop peptic ulcer disease than non-users,[56] but the analgesic effects of NSAIDs may modify pain symptoms hence delaying treatment and increasing the risk of complication.[57]

Polypharmacy among elderly people increases the chances of clinically relevant drug interactions occurring. In addition, the pharmacokinetics of some drugs may be altered in elderly people, particularly the rate of elimination. These factors, in combination with multiple illnesses require that greater care is taken in the selection of medication for the treatment of peptic ulcer disease in elderly people.

Dixon et al conducted a multinational double-blind trial to compare the efficacy and safety of ranitidine 300 mg nocte, 300 mg post-evening meal (pem) and cimetidine 800 mg nocte in patients with endoscopically verified duodenal ulcer disease aged less than 60 years (n = 1318) and 60 years or over (n = 354).[58] They demonstrated that age does not affect the absolute or relative efficacy of the treatments given. In this study, ranitidine was well tolerated and the incidence of adverse events was slightly lower in the older patients (The proportion of patients reporting adverse events in the elderly group for ranitidine 300 mg pem and 300 mg nocte was 3.7% and 3.3%, respectively, which was slightly less than for the younger group of 8.7% and 5.9%, respectively).[58]

In addition, Sirgo et al conducted a retrospective review of 21 United States trials of ranitidine in acid peptic diseases and compared the adverse events in elderly (65 years or over) and nonelderly (less than 65 years) patients.[59] Ranitidine dosages ranged from 150 mg/day to 300 mg twice daily for treatment periods of 4 to 52 weeks. Of the 4041 patients included in this review, 402 elderly and 2188 nonelderly patients received ranitidine and 245 elderly and 1206 nonelderly patients received placebo; 29%, 29%, 32%, and 26% of these patients, respectively, reported some type of adverse event. When only drug-related adverse events (as judged by the investigators under blinded conditions) were evaluated, these percentages dropped to 2%, 2%, and 1% and 2%, respectively. The authors concluded that ranitidine is as

safe in elderly patients as it is in nonelderly patients. No difference in the incidence of adverse events was found between older and younger patients who received ranitidine or placebo.

When viewed in the context of the above discussion, it can be seen that ranitidine in particular provides a safe and effective therapy for use in the management of elderly patients.

3.11.3 Ranitidine use in children and adolescents

Experience with ranitidine in children is limited and such use has not been fully evaluated in clinical studies. The product has, however, been used successfully in children aged 8 to 18 years in doses of up to 150mg twice daily (i.e. the proposed unscheduled dose).[10] Importantly, despite the apparent safety and efficacy associated with ranitidine use by children, Zantac 150mg tablets are not indicated for use in children under 12 years of age. The packaging clearly stipulates this, as does the pack insert, both of which direct consumers not to use the product in children under 12 without consulting a doctor.

Data in the literature suggests that the use of non-prescription antacids has increased in children under the age of 12 years, and that this has been followed by an apparent increase in the use of non-prescription H_2 antagonists. Orenstein and colleagues conducted a study to evaluate the pharmacokinetics and pharmacodynamics of a single dose of the ranitidine 75mg in children with symptoms of gastro-oesophageal reflux disease. Children aged between 4 and 11 years with symptoms of heartburn suspected to be due to gastro-oesophageal reflux disease were recruited at six clinical centres. Following a single dose of either oral ranitidine, 75 mg (n=19) or placebo (n=10), recording of intragastric pH and serial blood sampling were carried out for 6 hours. Ranitidine 75 mg significantly increased the intragastric pH in children aged 4-11 years; however these pharmacokinetic and pharmacodynamic profiles were similar to those in adults. The authors concluded that: "***Ranitidine 75 mg, appears to be effective for the control of intragastric acidity for 5-6 h in children aged 4-11 years***."[60] In this paediatric population ranitidine 75mg was generally well tolerated although adverse events were reported. The most frequent events were those induced mainly by fasting and occurred 4 hours or more after study drug administration when subjects had be subjected to a prolonged fast. Extensive literature reports attest to the relative safety of ranitidine in adults and children, and support the conclusion that the adverse event findings are likely to be unrelated to ranitidine use. Additionally, the majority of paediatric clinical trials with ranitidine have reported few side-effects or abnormal laboratory values.

The pharmacokinetics and pharmacodynamics of ranitidine were evaluated during three methods of administration in 12 children ranging in age from 3.5 to 16 years with documented gastric or duodenal ulcer disease.[61] First, a continuous intravenous infusion of ranitidine was administered to determine the serum concentration necessary to suppress gastric acid secretion by at least 90%. From these data a therapeutic dose of ranitidine was calculated and administered on separate days via the intravenous bolus and oral routes. Half-life, volume of distribution, and clearance

values for ranitidine were the same after intravenous bolus and oral doses (1.8 vs 2.0 hours, 2.3 vs 2.5 L/kg, and 794.7 vs 788.0 ml/min/1.73 m2, respectively). The bioavailability of ranitidine given orally averaged 48%. Serum ranitidine concentrations necessary to inhibit gastric acid secretion by at least 90% ranged between 40 and 60 ng/ml for all children studied. No adverse clinical or biochemical effects were observed in any child during the 6 weeks of orally administered treatment. Endoscopic reevaluation after 6 weeks indicated complete healing of initial ulcers.

The US FDA has approved prescription ranitidine for the treatment of gastroesophageal reflux disease and healing of erosive esophagitis in children >or=1 month of age. A low-dose strength of ranitidine is now available in a citrus-flavored 25 mg effervescent tablet (dissolved in 5 mL of water); this formulation was developed to facilitate use in infants and smaller children. In a recently conducted randomized, single-blind, crossover, taste test trial in 102 children and 102 parents/legal guardians, all subjects received a single 45 mg dose of each formulation.[62] This study found that adverse events consistent with product labeling were mild and were reported in four children and three adults: headache (n = 3), drowsiness (n = 1), abdominal pain/cramps (n = 2), and bloating/gas (n = 1).

As already mentioned, Zantac 150mg tablet is not indicated for use in children under 12 years of age. The packaging and pack insert clearly stipulates that this product is not for use in children under 12 without consulting a doctor

3.12 Potential for abuse or misuse

The available data indicates that in the decade that ranitidine has been available as a non-prescription product there is limited if any evidence of abuse of this product. Moreover there is no evidence that ranitidine has any euphoric effect or any potential for abuse.

A recent actual use study has demonstrated that ***'the vast majority of a large sample of unsupervised consumers understood the package label and fully complied with the package directions by not exceeding the maximum daily dosage and length of use. Nonprescription consumers safely used Zantac 75 without medical supervision.***"[22]

3.13 Overdose

Adverse events reported in clinical trials of ranitidine in daily doses of up to 1200 mg (i.e. three times the maximum OTC dose) include headache, tiredness and mild gastrointestinal disturbances. The incidence of these adverse events is similar to or less than that for placebo.[48] Reported acute oral ingestions of up to 18g have been associated only with transient adverse effects which are similar to those observed in normal clinical use.[10]

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5. APPENDICES

Appendix.1 Proposed Prescribing Information

Appendix.2 Proposed Consumer Medicine Information