



Bayer HealthCare
Consumer Care

Rescheduling Application

for

Naproxen Sodium
275 mg Solid Dose Forms
(Naprogesic®)

From Pharmacy Medicine to
General Sales Medicine

January 2013

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EXECUTIVE SUMMARY

This submission to the New Zealand Medicines Classification Committee seeks rescheduling of naproxen sodium 275 mg oral solid dose forms from the current classification of Pharmacy Medicine to General Sales Medicine. Solid dose forms containing 275 mg of naproxen sodium effectively deliver 250 mg naproxen as the sodium salt.

The indications proposed for naproxen sodium 275 mg solid dose forms as General Sales Medicines are effective in the temporary relief of pain and/or inflammation associated with:

- headache
- migraine headache
- tension headache
- muscular pain
- period pain
- dental pain
- back pain
- arthritic pain
- pain associated with sprains and strains
- aches and pains associated with cold and flu
- joint pain
- tendonitis

Reduces fever.

The proposed dosage is take 2 tablets, followed by one tablet every 6 – 8 hours as required. The total daily dosage should not exceed 5 tablets. Note that further dosing is on an “as required” basis, maintaining the OTC principle of only taking as much medicine as needed. The concept of a loading dose followed by a single tablet treatment is established for NSAID-type analgesics in New Zealand, and this proposal introduces nothing new to the market in this regard.

The classification sought for naproxen is (changes from current are in blue):-

Naproxen, except when specified elsewhere in this schedule	Prescription
Naproxen, in solid dose form containing 250 mg or less per dose form in packs of more than 25 but not more than 30 tablets or capsules, or if the daily dose exceeds 1.25 grams or if not sold in the manufacturer’s original pack	Pharmacy Only

Naproxen, in solid dose form for oral use containing 250 mg or less per dose form with a recommended daily dose of not more than 1.25 grams and when sold in the manufacturer's original pack containing not more than 25 tablets or capsules

General Sale

The intention is to create a general sales category of naproxen solid dose forms up to 250 mg that is equivalent to the current general sales category for ibuprofen tablets or capsules. The Medicines Classification Committee has indicated that a 5 day supply is appropriate for an OTC analgesic and the proposed pack size is consistent with this view.

A similar proposal will be submitted in Australia.

There has been a trend in New Zealand over the last decade or so towards lighter regulation for OTC NSAIDs that has included less restrictive classifications, broadening allowed indications, increasing OTC strengths and increasing allowed pack sizes. This proposal is a natural progression of that trend.

Being mindful of the imminent arrival of ANZTPA and taking into account the warnings required for ibuprofen in New Zealand and the warnings likely to be required in Australia in the near future (RASML 6), the following warnings are proposed for naproxen as a general sales pain medicine in New Zealand (changes from the current ibuprofen requirements are highlighted):-

Do not use in children under 6 years old except on doctor's advice.
Do not use this product if you are aged 65 years or over except on doctor's advice.

Do not use if you have a stomach ulcer.

Do not use if you have heart failure.

Do not use if you have kidney problems or impaired renal function.

Do not use if you have asthma except on doctor's advice.

[Do not use if you are allergic to aspirin or ibuprofen except on doctor's advice]. ~~Warning to be deleted~~

Do not use if you are allergic to naproxen or other anti-inflammatory medicines.

If you get an allergic reaction, stop taking and see your doctor.

Do not use for more than a few days at a time except on doctor's advice.'

Do not exceed the recommended dose. Excessive use can be harmful.

Do not use this product with other medicines containing naproxen, aspirin or other anti-inflammatory medicines or with other

medicines you are taking regularly except on doctor's advice.
Do not use at all during the last 3 months of pregnancy.
Do not use [this product/insert name of the product] during the first 6 months of pregnancy, except on doctor's advice.

The fundamental premise of this proposal to reschedule naproxen is that naproxen sodium 275 mg in a solid dose form is sufficiently similar to ibuprofen 200 mg in terms of efficacy and safety that the same classification should apply to both substances.

Naproxen sodium 220 mg has been available in the United States of America, as a general sales medicine, since 1994 under the trade name Aleve.

Naproxen sodium solid dose forms up to 275 mg would offer the consumer more choice of analgesics at the general sales level. The pain category is hugely diverse, treating many complaints and yet consumers have limited genuine choice of analgesic. Naproxen sodium would offer consumers a new analgesic compound with unique features and benefits:-

- longer-lasting pain relief
- less tablets per day
- fast acting
- toxicity comparable to placebo at OTC doses

Additionally, for current consumers of naproxen sodium 275 mg availability at general sales level is very likely to deliver considerable cost savings.

Naproxen has a longer half-life than ibuprofen and so is expected to offer consumers longer-lasting pain relief. This longer-lasting claim has previously been approved for Aleve. This effect is reflected in the recommended dosing schedules for the compounds – while ibuprofen 200 mg is recommended to be taken every 4 – 6 hours, naproxen sodium is recommended to be taken every 6 – 12 hours. With this longer duration of action, use of naproxen for mild-to-moderate analgesia may lead to the patient requiring fewer tablets per day or per medication episode.

Naproxen sodium is fast-acting, having been shown to start working within 15 minutes.

Occurrences of moderate and severe adverse events with naproxen sodium in an OTC setting were comparable to placebo with no statistically significant differences recorded. The safety profile of the medicine for a ≤ 10 day dosing period was evaluated as “relatively good” is compatible with general sales availability. Low rates of adverse event occurrences (0.003% per patient

exposure) support the Bayer company assessment that “the benefit-risk balance for naproxen sodium remains favourable”.

In November 1999 the Medicines Classification Committee considered that there was no significant difference in safety between naproxen and ibuprofen with OTC use and the classifications of ibuprofen 200 mg and naproxen 250 mg as Pharmacy Medicines were aligned. The classifications have since diverged, with ibuprofen becoming a General Sales Medicine, but this is attributed to the reclassification of ibuprofen having been actively pursued rather than the MCC moving away from its 1999 conclusion.

Studies in many different types of pain have all demonstrated that naproxen sodium is at least as good as, if not more efficacious than, ibuprofen. Ibuprofen is considered the “gold standard” against which other NSAIDs should be judged. There is no detectable difference in the rate of adverse events for OTC dosages of ibuprofen and naproxen, and the risk/benefit profiles of these two medicines in the over-the-counter setting are essentially the same. This being the case, rescheduling of naproxen 250 mg to the same classification as ibuprofen 200 mg is justified.

In terms of efficacy, there are few differences between naproxen and diclofenac, and it is accepted that both are suitable for the treatment of mild-to-moderate pain. However, diclofenac potentially exposes the patient to additional cardiovascular risk at any dosage above the maximum allowed over-the-counter dosage, and may cause more liver-related adverse events. It appears warranted that this medicine would have a more restrictive classification than naproxen sodium, as is proposed by this submission.

Naproxen provides equivalent-to-superior pain relief compared to paracetamol, and the pain relief provided is of longer duration. Adverse events are also relatively similar for naproxen and paracetamol, more particularly for OTC-type complaints requiring lower doses. Conversely, gastrointestinal adverse effects are more commonly reported for naproxen with complaints such as osteoarthritis that often require higher doses.

In summary, naproxen sodium at doses of 220 mg and higher has been demonstrated as efficacious for various pain states, and a number of Health Authorities around the world have concluded that naproxen sodium 220 mg or 275 mg is a safe and effective analgesic/antipyretic for OTC use. The rate and severity of adverse events associated with OTC naproxen are similar to those associated with placebo, and the available data indicates that this medicine compares favourably with other analgesics available over-the-counter. Specifically, the discussion above has demonstrated that naproxen sodium at OTC strengths compares favourably with both ibuprofen and paracetamol.

Reclassification of naproxen sodium 275 mg to General Sales Medicine is justified on the basis that it appears very unlikely to expose the consumer to additional risks compared to the analgesics currently available while offering significant benefits such as extended duration of efficacy, rapid onset of action, less frequent dosing, greater choice, more convenience and possible cost reductions.

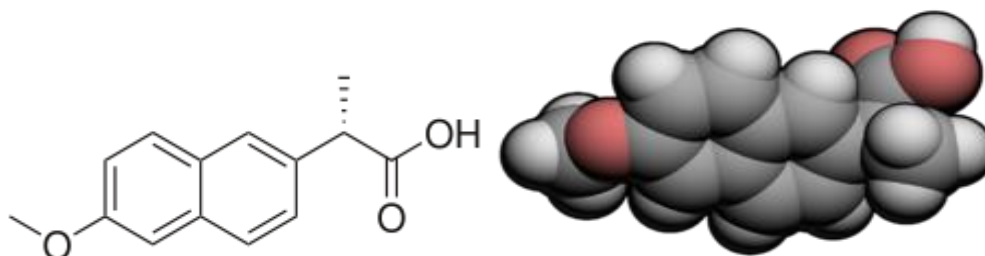
PART A

This submission to the New Zealand Medicines Classification Committee seeks rescheduling of naproxen sodium 275 mg oral solid dose forms from the current classification of Pharmacy Medicine to General Sales Medicine.

Solid dose forms containing 275 mg of naproxen sodium effectively deliver 250 mg naproxen as the sodium salt.

A1. Name of the Medicine

The International Non-Proprietary Name of the active ingredient to be reclassified is naproxen sodium. The systematic (IUPAC) name for naproxen is (+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid.



The proprietary or brand name is Naprogesic®.

A2. Name of the Company

This submission is made by:-

Bayer New Zealand Limited
Consumer Care Business Group
P. O. Box 2825
Auckland

Ph: (09) 443-3093

Contact: Ms. Daniela Westphal
Senior Brand Manager - Naprogesic

A3. Dose Forms, Strengths and Pack Sizes

The following existing registered product is proposed for reclassification:-

Naprogesic, naproxen sodium 275 mg film-coated tablets,
packs of 12 and 24

However, at an international level, Bayer has other brand names, other strengths of naproxen sodium tablets and other pack sizes that may be encompassed by this proposal in future. For example, naproxen sodium 220 mg tablets (Aleve[®]) has previously been registered in New Zealand.

A4. Indications

A4.1 Proposed Indications

Naproxen sodium up to 275 mg is proposed as a general sales medicine for all mild-to-moderate (i.e. OTC) categories of pain management. Aleve tablets

(naproxen sodium 220 mg) were approved by Medsafe on 8 July 1999 as an over-the-counter medicine (ultimately Pharmacy Only Medicine) with the indications “For the short-term management of headache, toothache, muscular ache, backache, minor pain of arthritis, dysmenorrhoea, minor aches and pain associated with the common cold and reduction of fever.”

Other non-steroidal anti-inflammatory agents that have general sales status in New Zealand currently are ibuprofen 200 mg and aspirin. It is appropriate to consider the indications applied to these medicines in the general sales setting – these are (taken from the current labelling for Nurofen caplets purchased 8 January 2013[2]):-

.....effective in the temporary relief of pain and/or inflammation associated with:

- headache
- migraine headache
- tension headache
- muscular pain
- period pain
- dental pain
- sinus pain
- back pain
- arthritic pain
- cold and flu symptoms

Reduces fever.

Aspirin is approved for the additional indications of pain associated with sprains and strains, joint pain and tendonitis also have approval for general sales - refer approved labelling for Aspro tablets [3].

Naproxen sodium is approved as a prescription medicine for the following uses (taken from the Synflex data sheet dated 3 October 2007 [1]):-

.....indicated for the treatment of:

- acute musculoskeletal disorders (such as sprains and strains, direct trauma, lumbo-sacral pain, cervical spondylitis, fibrositis, bursitis and tendonitis);
- dysmenorrhoea, uterine pain following I.U.D. insertion;
- dental pain;
- migraine headaches, prophylaxis and acute treatment;
- rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and acute gout;
- juvenile arthritis

Thus, the potential indications have been developed by combining the approved indications for naproxen sodium and those established for general sales.

The indications proposed for naproxen sodium 275 mg solid dose forms as General Sales Medicines are:-

.....effective in the temporary relief of pain and/or inflammation associated with:

- **headache**
- **migraine headache**
- **tension headache**
- **muscular pain**
- **period pain**
- **dental pain**
- **back pain**
- **arthritic pain**
- **pain associated with sprains and strains**
- **aches and pains associated with cold and flu**
- **joint pain**
- **tendonitis**

Reduces fever.

A4.2 Proposed Dosage

The current Naprogenic dosage recommendation for dysmenorrhoea, as stated on pack, is:-

At the first sign of period pain or menstrual bleeding (whichever occurs first), take 2 tablets with food, followed by one tablet every 6 – 8 hours as required. The total daily dosage should not exceed 5 tablets.

This is essentially the same dosage currently recommended in the Synflex data sheet for all other indications considered appropriate for the proposed general sales medicine [1]:-

Adults

Acute musculoskeletal disorders

The recommended dosage is 550mg at once, then 275mg three or four times daily as needed; most patients will require only seven days treatment but some patients may require up to fourteen days treatment.

Dysmenorrhoea

The recommended dosage is 550mg initially followed by 275mg three or four times daily as needed.

Acute treatment of migraine

The recommended dosage is 825mg (three 275mg tablets) at the first symptom of an impending attack. An additional 275-550mg can be taken throughout the day, if necessary, but not within 30 minutes of administration of the initial dose. The total dose of 1375mg per day should not be exceeded.

Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis

Maintenance dose is usually 550mg per day taken in two doses at 12-hour intervals i.e. 275mg usually given with the morning meal and 275mg about 12 hours later. Dosage adjustment within the range 550-1100mg/day maintaining 12-hourly administration may be employed.

For the patient who requires 825mg per day and whose night-time pain and/or morning stiffness are most troublesome, 550mg should be taken before retiring and 275mg upon awakening. For the patient whose day-time pain and reduced mobility are most troublesome, 550mg should be taken upon awakening and 275mg upon retiring.

While ultimately dosage will have to be evaluated and approved by Medsafe, ***the current dosage recommendations for dysmenorrhoea appear suitable to be applied to most indications proposed for the general sales medicine.***

The key statement within the dosage recommendation is that further dosing is on an “as required” basis, maintaining the OTC principle of only taking as much medicine as needed.

Note that this dosage recommendation includes a loading dose of 2 tablets, followed by a single tablet at 6 – 8 hour intervals up to a maximum of 5 tablets per day. This dosage recommendation is very similar to that currently recommended for ibuprofen 200 mg tablets (2 tablets initially, followed by one tablet every 4 – 6 hours up to a maximum of 6 tablets [2]). There has been discussion within the pharmaceutical/medicinal community in the past that consumers perceive they should always take 2 tablets for OTC analgesics. However, as ibuprofen has been available in New Zealand as a General Sales Medicine since 2004, it is apparent that the concept of a loading dose followed by a single tablet treatment is well established for NSAID-type analgesics in New Zealand at the moment, and this proposal for naproxen sodium introduces nothing new to the market in this regard.

A5. Classification

A5.1 Current Classification

The current classification of naproxen, taken from the Medsafe Web site on 8 January 2013, is:-

Naproxen, except when specified elsewhere in this schedule	Prescription
Naproxen, in solid dose form containing 250 mg or less per dose form in packs of not more than 30 tablets or capsules	Pharmacy Only

This Pharmacy Only Medicine classification was recommended by the Medicines Classification Committee at its November 1999 meeting, and subsequently enacted by Gazette notice. Thus, the medicine has been sold as a Pharmacy Medicine in New Zealand for 13 years without providing cause for concern, suggesting that consumers can use this medicine effectively and safely with minimal supervision from a healthcare professional.

The fundamental premise of this proposal to reschedule naproxen is that naproxen 250 mg is sufficiently similar to ibuprofen 200 mg in terms of efficacy and safety that the same classifications can be applied to both substances. Thus, comparison of the current classifications of ibuprofen and naproxen is instructive:-

The current classification of ibuprofen, taken from the Medsafe Web site on 8 January 2013, is:-

Ibuprofen, except when specified elsewhere in this schedule	Prescription
Ibuprofen, for oral use in tablets or capsules containing up to 400 mg per dose form and in packs containing not more than 50 dose units and that have received the consent of the Minister or the Director-General to their distribution as restricted medicines and that are sold in the manufacturer's original pack labeled for use by adults and children over 12 years of age	Restricted

Ibuprofen, for oral use in liquid form with a recommended daily dose of not more than 1.2 grams for the relief of pain and reduction of fever or inflammation when sold in the manufacturer's original pack containing not more than 8 grams; for oral use in solid dose form containing not more than 200 mg per dose form and with a recommended daily dose of not more than 1.2 grams when sold in the manufacturer's original pack containing not more than 100 dose units, except in divided solid dosage forms for oral use containing 200 mg or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units	Pharmacy Only
Ibuprofen, for external use; in divided solid dosage forms for oral use containing 200 mg or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units	General Sale

Ibuprofen 200 mg oral presentations were considered by the Medicines Classification Committee at its November 2003 meeting. The committee recommended rejection of the proposal, but the Minister's delegate did not accept this recommendation on the basis of an independent review [24], and the change was subsequently enacted by Gazette notice. A challenge to this classification, proposing that the Pharmacy Medicine classification be reinstated, was considered at the June 2006 MCC meeting but not accepted. Thus, ibuprofen 200 mg tablets and capsules have been sold as general sales medicines in New Zealand for 9 years without providing sufficient cause for concern to reconsider this classification. It is apparent that New Zealand consumers can use ibuprofen 200 mg effectively and safely with no supervision from a healthcare professional.

Given that the current classifications specify that ibuprofen must be sold in the manufacturer's original pack, it is clear that the classification is intended to encompass criteria for the medicine as stipulated by Medsafe. The labelling requirements for both naproxen and ibuprofen are relevant.

As of 8 January 2013, there are no requirements on the Medsafe Labelling Statements Database specifically for naproxen or for non-steroidal anti-inflammatory agents. However, Medsafe have the following requirements to be included in data sheets for oral non-steroidal anti-inflammatory agents that have a Prescription or Restricted classification:-

Contraindicated in patients with gastrointestinal ulceration, haemorrhagic diathesis, asthma.
Relatively contraindicated in liver dysfunction.
Dosage should be minimised in the elderly and in patients with renal impairment.

The labelling requirements for solid dose forms of ibuprofen, taken from the Labelling Statements Database on the Medsafe Web site on 8 January 2013, are:

<p>When sold as a General Sale Medicine in a solid oral dose form</p>	<p>Do not use in children under 6 years old except on doctor's advice. Do not use [this product/insert name of product] if you are aged 65 years or over except on doctor's advice. <i>(This statement is not required on products containing ibuprofen indicated exclusively for the treatment of dysmenorrhoea)</i> Do not use if you have a stomach ulcer. Do not use if you have asthma except on doctor's advice. Do not use if you are allergic to aspirin or ibuprofen except on doctor's advice. Do not use if you are allergic to [other] anti-inflammatory medicines. Do not exceed the maximum stated dose. Do not use for more than a few days at a time except on doctor's advice. Do not use with other medicines you are taking regularly except on doctor's advice. Consult a healthcare professional before use if you have kidney problems or impaired renal function. Do not use at all during the last 3 months of pregnancy. Do not use [this product/insert name of the product] during the first 6 months of pregnancy, except on doctor's advice.</p>
<p>When sold as a Pharmacy-only Medicine in a solid oral dose form</p>	<p>Do not use if you have a stomach ulcer. Do not use if you have asthma except on doctor's advice. Do not use if you are allergic to aspirin or ibuprofen except on doctor's advice. Do not use if you are allergic to [other] anti-inflammatory medicines. Do not exceed the maximum stated dose. Do not use for more than a few days at a time except on doctor's advice. Do not use with other medicines you are taking regularly except on doctor's advice. Consult a healthcare professional before use if you have kidney problems or impaired renal function. Do not use at all during the last 3 months of pregnancy. Do not use [this product/insert name of the product] during the first 6 months of pregnancy, except on doctor's advice.</p>

When sold as a Restricted Medicine in a solid oral dose form	<p>Do not use in children under 12 years old.</p> <p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have asthma except on doctor's advice.</p> <p>Do not use if you are allergic to aspirin or ibuprofen except on doctor's advice.</p> <p>Do not use if you are allergic to [other] anti-inflammatory medicines.</p> <p>Do not exceed the maximum stated dose.</p> <p>Do not use for more than a few days at a time except on doctor's advice.</p> <p>Do not use with other medicines you are taking regularly except on doctor's advice.</p> <p>Consult a healthcare professional before use if you have kidney problems or impaired renal function.</p> <p>Do not use at all during the last 3 months of pregnancy.</p> <p>Do not use [this product/insert name of the product] during the first 6 months of pregnancy, except on doctor's advice.</p>
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Essentially, the OTC labelling requirements for ibuprofen encompass all the data sheet warnings required for non-steroidal anti-inflammatory agents and expand upon them, as would be expected for a less stringently classified medicine. Furthermore, additional restrictions on the patient population have been added to allow for the General Sale classification for ibuprofen, in that the very young and the elderly have been excluded. Labelling requirement proposals for naproxen are discussed in Sections A7 and A8.

The current classification for aspirin is:-

Aspirin, for injection; when combined with caffeine, paracetamol or salicylamide	Prescription
Aspirin, in slow release forms; in enteric coated forms containing more than 300 mg per dose form; except when specified elsewhere in this schedule	Pharmacy Only
Aspirin, except when specified in the First Schedule to the Medicines Regulations 1984	General Sales

Aspirin is recognised as a unique non-steroidal anti-inflammatory, and its classification as something of a historical artefact. Nonetheless, the general sales classification of aspirin has been challenged a number of times, and despite these challenges the medicine today has a general sales category that contains neither a daily dose restriction nor a pack size restriction. Despite the lack of restrictions and absence of healthcare professional supervision, consumers appear to use the product safely and effectively – there were 158

reports implicating aspirin, including 5 deaths, to the SMARS database in the last 10 years (1/1/2003 – 31/12/2012).

A5.2 Proposed Classification

The classification sought for naproxen is (changes are in blue):-

Naproxen, except when specified elsewhere in this schedule **Prescription**

Naproxen, in solid dose form containing 250 mg or less per dose form in packs of more than 25 but not more than 30 tablets or capsules, or if the daily dose exceeds 1.25 grams or if not sold in the manufacturer's original pack **Pharmacy Only**

Naproxen, in solid dose form for oral use containing 250 mg or less per dose form with a recommended daily dose of not more than 1.25 grams and when sold in the manufacturer's original pack containing not more than 25 tablets or capsules **General Sale**

The intention of the proposed change is to create a general sales category of naproxen solid dose forms up to 250 mg that is equivalent to the current general sales category for ibuprofen tablets or capsules. At its meeting in April 2010, the Medicines Classification Committee agreed that 5 day's supply is sufficient for short-term use and does not promote chronic usage. As such, 5 day supply is considered appropriate for an OTC analgesic. The proposed pack size is consistent with this view.

A similar proposal will be submitted in Australia.

A5.3 Classification Status in Other Countries

Analgesic preparations, including ibuprofen, naproxen and other non-steroidal anti-inflammatory medicines, are available globally as both prescription and OTC medicines. The classification is usually determined by strength and pack size.

The following table presents the legal classification of naproxen, and in some instances ibuprofen, oral presentations in selected countries.

Status of Naproxen and Ibuprofen Oral Presentations in Selected Countries

Country	Current Classification	Year of Switch from Prescription
Australia	<p>Schedule 2 (Pharmacy Medicine)</p> <p>NAPROXEN in divided preparations containing 250 mg or less of naproxen per dosage unit in packs of 30 or less dosage units.</p> <p>IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:</p> <p>(b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units except when:</p> <ul style="list-style-type: none"> (i) as the only therapeutically active constituent other than an effervescent agent; (ii) packed in blister or strip packaging or in a container with a child-resistant closure; (iii) in a primary pack containing not more than 25 dosage units; (iv) not labelled for the treatment of children 6 years of age or less; and (v) compliant with the requirements of the <i>Required Advisory Statements for Medicine Labels</i>. <p>Schedule 3 (Pharmacist Only Medicine)</p> <p>IBUPROFEN in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units when labelled:</p> <ul style="list-style-type: none"> (a) with a recommended daily dose of 1200 mg or less of ibuprofen; and (b) not for the treatment of children under 12 years of age, <p>except when included in or expressly excluded from Schedule 2.</p> <p>Schedule 4 (Prescription Medicine)</p> <p>NAPROXEN except when included in Schedule 2.</p> <p>IBUPROFEN except:</p> <ul style="list-style-type: none"> b) when included in or expressly excluded from Schedule 2 or 3; or 	1990

USA	OTC - Naproxen as internal analgesic / antipyretic with an adult dosage of 200mg / 8-12 hours (oral).	1994
	OTC - Ibuprofen Adult dosage is 200mg every 4-6 hours. Migraine indication added in 2000.	1984
Canada	OTC - Naproxen sodium 220 mg	1999
	- Ibuprofen	1989
Austria	OTC – Naproxen for internal use up to 200mg per dose and 600mg per day. For children under 12 years on medical prescription only.	1996
Belgium	OTC – Naproxen 220mg is OTC for adults and children over 12 years of age. Maximum daily dose = 660mg.	Unknown
France	Not relevant – no products registered.	
Germany	OTC – naproxen for light to moderate pain and fever. In 2002, single dose increased to 250mg; maximum daily dose to 750mg; maximum pack size to 7500mg.	2001
	OTC – Ibuprofen, from July 1998, the allowed maximum dose was raised to 400mg (instead of 200mg) and the maximum daily dose to 1200mg (instead of 800mg). As from 1 July 2005, ibuprofen became available without a prescription for the treatment of migraine headaches with and without aura	1989
Holland	OTC - 220 mg naproxen-sodium was switched to non-prescription status in 1997. In 2007, the 550 mg version was switched from Rx to OTC. Large packs since 2010 only available in pharmacies.	1997
Ireland	Prescription - naproxen	
Norway	OTC - Naproxen oral 20 tablets x 250mg to be used to treat menstrual pain.	1996
Singapore	OTC - Naproxen sodium tablets 220mg	2003
Spain	OTC - naproxen 200mg (consumer advertising allowed). Maximum daily dose 600mg. For adults and children over 16 only.	1996
Sweden	OTC - naproxen	Unknown
Switzerland	OTC – Naproxen topical and oral forms, tablets 200 mg, daily dose 600 mg	1999
UK	OTC – Naproxen 250mg switched to non-prescription (Pharmacy-only) status for the treatment of primary dysmenorrhoea in women aged between 15 and 50 years. Maximum strength	2007

	<p>250mg, maximum dose 500mg, maximum daily dose 750mg, maximum pack size 9 tablets, maximum duration of treatment 3 days</p> <p>OTC – Ibuprofen, maximum dose 400mg. Prolonged release preparations: maximum dose 600mg. Maximum daily dose 1200mg. In 1995, 200mg ibuprofen became GSL in pack size of 12 or under, in 1999 it was increased to pack size of 16.</p>	1983
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Table adapted from AESGP/WSMI publications <http://www.aesgp.be> status 9 January 2013 and data on file.

These figures demonstrate that during the 1990’s there was a world-wide trend towards reduced restriction of oral naproxen, and that by the year 2000 most large European and Scandinavian countries, Canada, USA, Australia and New Zealand all had naproxen available as an over-the-counter medicine.

In most instances this trend embraced classifications where the customer can self-select and purchase the product without the necessary intervention of a healthcare professional. However, there has been little change in the last 12 years, apart from the United Kingdom and Singapore. With the additional safety information and consumer-led experience gained during this time, Bayer believes it is now appropriate to consider further down-scheduling of the naproxen in New Zealand.

In New Zealand, where there are more classification categories available, there has been a general trend in the last decade towards progressive down-scheduling of NSAID’s, as illustrated by the following table:-

Timeline for Reclassification of NSAID’s in New Zealand

Date of MCC Meeting	Medicine Considered	Recommendation (accepted by the Minister’s delegate unless further commented on)
November 1999	Naproxen 250 mg	From Restricted to Pharmacy Medicine with a pack size restriction of 30 dose units for all OTC indications
November 2002	Diclofenac potassium 12.5 mg	From Restricted to Pharmacy Medicine with a pack size restriction of 20 dose units

May 2003	Ibuprofen topical	Pharmacy to General Sales Medicine
November 2003	Ibuprofen 200 mg	Proposal for Pharmacy to General Sales Medicine with a pack size restriction of 25 dose units – MCC recommended no change, but it was accepted by the Minister’s delegate
June 2006	Ibuprofen 400mg	Prescription to Pharmacist Only Medicine
June 2006	Ibuprofen 200 mg	Proposal for General Sales Medicine to Pharmacy Medicine – MCC recommended no change, which was upheld.
February 2007	Diclofenac potassium	Maximum daily dose for Pharmacy Medicine set at 75 mg
February 2007	Ibuprofen 200mg	Pharmacy Medicine – maximum daily dose set at 120 mg and maximum pack size at 100 dose units
November 2009	Diclofenac potassium 12.5 mg	Proposal to increase Pharmacy Medicine maximum pack size from 20 to 40 dose units – MCC recommended no change, which was upheld
April 2010	Diclofenac potassium 12.5 mg	Increase Pharmacy Medicine maximum pack size from 20 to 30 dose units

Table adapted from <http://www.medsafe.govt.nz> status 9 January 2013

Clearly there has been a trend in New Zealand over the last decade or so towards lighter regulation for OTC NSAID’s that has included less restrictive classifications, broadening allowed indications, increasing OTC strengths and increasing allowed pack sizes. A similar trend has also been observed for Australia [25].

A6. Extent of Usage

A6.1 Usage in New Zealand

Naprogesic, the OTC version of naproxen sodium 275 mg originally registered by Roche Products (New Zealand) Limited, was approved in New Zealand in July 1986 for the treatment of dysmenorrhoea, with final approvals as a Restricted Medicine probably occurring in 1988. Sales of the product in New Zealand for the last four years were:-

Volume – units	2009	2010	2011	2012
12 tabs	13,588	13,225	11,299	8,689
24 tabs	11,067	11,252	10,617	9,743
Total no. tabs (000s)	428.6	428.7	390.4	338.1

No naproxen presentations have been registered as OTC medicines in New Zealand and only three naproxen sodium products have been registered - Aleve 220 mg tablets, Naprogesic 275 mg tablets and Sonaflam 275 mg tablets (reference www.medsafe.govt.nz). Sonaflam sales are presented in Section A9, and the combined sales of these two products represent total usage of naproxen sodium as an OTC medicine.

The SMARS database in New Zealand makes no differentiation between strengths of naproxen, or prescription vs. OTC medication, making an estimate of the number of adverse events attributable to the sales above impossible. However, during this time Bayer New Zealand has not received any notifications of adverse events occurring for the product.

Sales in Australia over this time were:-

Volume – units	2009	2010	2011	2012
12 tabs	160,302	156,144	145,904	126,432
24 tabs	312,750	322,110	319,010	312,130
Total no. tabs (000s)	9,429.6	9,604.3	9,326.0	9,008.3

Over these four years and over 35 million tablets sold, Bayer Australia Limited received a total of 18 reports of adverse events. Even allowing for under-

reporting, this is a very low rate of adverse events and points to the very good safety profile of naproxen at low dosages.

A6.2 Usage World-Wide

Bayer's world-wide sales volumes of naproxen sodium formulations for intervals of the last three years were [4,5]:

Interval	SALES VOLUMES Dose Forms (tablet, capsule, suppository, etc.)
11-Jan-2009 to 10-Jan-2010	2,900,039,247
11-Jan-2010 to 10-Jan-2011	3,578,169,426
2-Aug-2011 to 01-Aug-2012	4,086,166,225

Sales volumes are increasing rapidly, primarily due to the sales growth of Aleve in the United States of America. Over these same periods, 500 medically confirmed ADR reports and 16,554 non-medically confirmed ADR reports were received. ADR reports have increased considerably in the last reporting period due to the company decision to start capturing reports in social media. This represents an ADR reporting rate per dose form of approximately 0.0016%

Although hampered by considerable variations in use, such as duration and/or frequency, total number of treatment courses has been estimated as [4,5]:-

Interval	PATIENT EXPOSURES Dose Forms (tablet, capsule, suppository, etc.)
11-Jan-2009 to 10-Jan-2010	168,772,277
11-Jan-2010 to 10-Jan-2011	177,348,712 (oral dose forms only)
2-Aug-2011 to 01-Aug-2012	203,532,800 (oral dose forms only)

The ADR reporting rate per patient exposure is approximately 0.003%. These low rates of adverse event occurrences support the Bayer company assessment that “the benefit-risk balance for naproxen sodium remains favourable” [5].

A7. Labelling

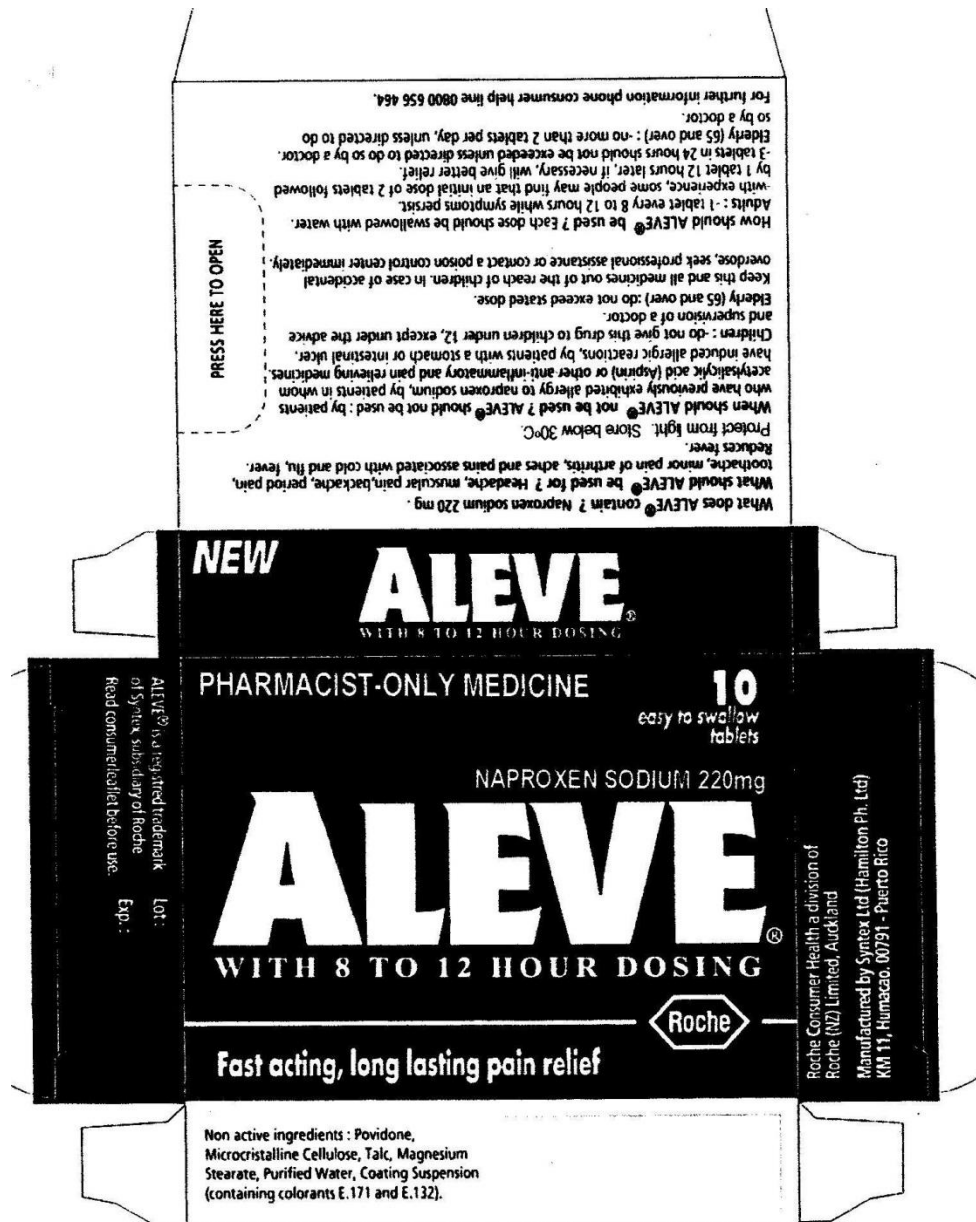
The currently approved label in New Zealand and Australia for Naprogesic is:



While meeting current New Zealand and Australian medicines labelling requirements, this label is not considered adequate for general sales usage. A totally new label, possibly incorporating a new design, is envisaged. The label would incorporate performance-based labelling design and include all the warning statements and other features discussed in Section A8. As with other analgesic medicines currently available for General Sales in New Zealand, a pack insert is not intended to be supplied with the medicine – thus, it is accepted that the label of the product needs to communicate clearly and fully to the consumer. Any label developed would be tested for legibility and comprehension, and adjusted as necessary, before being finalised.

One possible design for the label would be the current Aleve label design, as shown below with firstly the current design from the United States and then the label that was approved in New Zealand:-





Furthermore, Consumer Medicine Information will be developed for the product and posted on the Medsafe Web site, so that full information is available to the public. This Consumer Medicine Information would be based on the current Bayer Company Core Data Sheet [6], and include all warnings discussed in Section A8. A draft of the proposed Consumer Medicine Information is provided in Appendix 1.

A8. Proposed Warnings

As mentioned in Section A5.1 there are currently no required warning statements for naproxen or non-steroidal anti-inflammatory agents in the Medsafe Labelling Statements Database.

When considering appropriate warnings for naproxen as a general sales medicine, two primary sources have been referenced. Firstly, there are the required warnings for ibuprofen in the Medsafe Labelling Statements Database. The required warnings for ibuprofen in New Zealand are:-

Ibuprofen

<p>When sold as a General Sale Medicine in a solid oral dose form</p>	<p>Do not use in children under 6 years old except on doctor's advice. Do not use [this product/insert name of product] if you are aged 65 years or over except on doctor's advice. <i>(This statement is not required on products containing ibuprofen indicated exclusively for the treatment of dysmenorrhoea)</i> Do not use if you have a stomach ulcer. Do not use if you have asthma except on doctor's advice. Do not use if you are allergic to aspirin or ibuprofen except on doctor's advice. Do not use if you are allergic to [other] anti-inflammatory medicines. Do not exceed the maximum stated dose. Do not use for more than a few days at a time except on doctor's advice. Do not use with other medicines you are taking regularly except on doctor's advice. Consult a healthcare professional before use if you have kidney problems or impaired renal function. Do not use at all during the last 3 months of pregnancy. Do not use [this product/insert name of the product] during the first 6 months of pregnancy, except on doctor's advice.</p>
<p>When sold as a Pharmacy-only Medicine in a solid oral dose form</p>	<p>Do not use if you have a stomach ulcer. Do not use if you have asthma except on doctor's advice. Do not use if you are allergic to aspirin or ibuprofen except on doctor's advice. Do not use if you are allergic to [other] anti-inflammatory medicines. Do not exceed the maximum stated dose. Do not use for more than a few days at a time except on doctor's advice. Do not use with other medicines you are taking regularly except on doctor's advice. Consult a healthcare professional before use if you have kidney problems or impaired renal function.</p>

	<p>Do not use at all during the last 3 months of pregnancy. Do not use [this product/insert name of the product] during the first 6 months of pregnancy, except on doctor's advice.</p>
When sold as a Restricted Medicine in a solid oral dose form	<p>Do not use in children under 12 years old. Do not use if you have a stomach ulcer. Do not use if you have asthma except on doctor's advice. Do not use if you are allergic to aspirin or ibuprofen except on doctor's advice. Do not use if you are allergic to [other] anti-inflammatory medicines. Do not exceed the maximum stated dose. Do not use for more than a few days at a time except on doctor's advice. Do not use with other medicines you are taking regularly except on doctor's advice. Consult a healthcare professional before use if you have kidney problems or impaired renal function. Do not use at all during the last 3 months of pregnancy. Do not use [this product/insert name of the product] during the first 6 months of pregnancy, except on doctor's advice.</p>

Secondly, RASML 4 determines the current labelling warning statements for products in Australia. The current requirements are:-

Substance	Conditions	Warnings Required
Naproxen (Entry 1 of 2)	When: a. included in a Schedule to the SUSDP; and b. the preparation is indicated exclusively for the treatment of dysmenorrhoea.	126, 127, 149, 130, 159, 160
Naproxen (Entry 2 of 2)	When: a. included in a Schedule to the SUSDP; and b. the preparation is NOT indicated exclusively for the treatment of dysmenorrhoea.	126, 127, 149, 130, 159, 160, 176

- 126 Do not use [this product/insert name of product] if you have a stomach ulcer.
- 127 Do not use [this product/insert name of product] if you are allergic to [insert name substance] or other anti-inflammatory medicines.
- 130 Unless a doctor has told you to, do not use [this product/insert name of product] if you have asthma.
- 149 Unless a doctor has told you to, do not use [this product/insert name of product] with other medicines containing [insert name of substance] or other anti-inflammatory medicines.

- 159 If you get an allergic reaction stop taking and see your doctor immediately.
- 160 Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.
- 176 Do not use [this product/insert the name of the product] during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.

Compare the RASML 4 requirements for ibuprofen:-

Substance	Conditions	Warnings Required
Ibuprofen (Entry 1 of 4)	For the purpose of exclusion from the Schedules to the SUSDP, when the preparation is for oral use and is indicated exclusively for the treatment of dysmenorrhoea.	126, 127, 151, 130, 131, 132, 159, 160
Ibuprofen (Entry 2 of 4)	For the purpose of exclusion from the Schedules to the SUSDP, when the preparation is for oral use and is NOT indicated exclusively for the treatment of dysmenorrhoea.	126, 127, 151, 130, 131, 132, 159, 160, 176
Ibuprofen (Entry 3 of 4)	When: a. included in a Schedule to the SUSDP; and b. the preparation is NOT indicated exclusively for the treatment of dysmenorrhoea.	126, 127, 149, 130, 159, 160
Ibuprofen (Entry 4 of 4)	When: a. included in a Schedule to the SUSDP; and b. the preparation is indicated exclusively for the treatment of dysmenorrhoea.	126, 127, 149, 130, 159, 160, 176

Essentially the warnings are the same for ibuprofen as they are for naproxen, except that there are two additional warnings for general sales medicines that restrict the very young and the elderly that reflect the warnings for the general sales category in New Zealand.

- 131 Unless a doctor has told you to, do not use [this product/insert name of product] in children 6 years of age or less.
- 132 Unless a doctor has told you to, do not use [this product/insert name of product] if you are aged 65 years or over.

Furthermore, a draft RASML 6 has now been consulted on and is considered likely to come into use in the near future. The draft contained the following requirements for naproxen:-

Substance	Conditions	Warnings Required
Naproxen (Entry 1 of 2)	When: (a) included in a Schedule to the SUSMP; and (b) the preparation is indicated exclusively for the treatment of dysmenorrhoea.	126, 127, 149, 130, 159, 160, 192, 200, 201
Naproxen (Entry 2 of 2)	When: (a) included in a Schedule to the SUSMP; and (b) the preparation is NOT indicated exclusively for the treatment of dysmenorrhoea.	126, 127, 149, 130, 159, 160, 176, 192, 200, 201

Three additional warnings are proposed to be added, and warning 149 has been modified. The proposed warnings are below:-

- 192 Ask your doctor or pharmacist before use if you are dehydrated, or have diarrhoea or vomiting.
- 200 Do not use if you have impaired kidney function.
- 201 Do not use if you have heart failure.
- 149 Unless a doctor has told you to, do not use [this product/insert name of product] with other medicines containing [insert name of substance], aspirin or other anti-inflammatory medicines or other medicines that you are taking regularly.

As part of the consultation, the TGA has agreed that warning 192 only applies in paediatric doses, and that the wording should be changed to align with Medsafe requirements.

The RASML 6 proposed changes for ibuprofen are the same as the changes proposed for naproxen. Inclusion of warning 201 reflects the current ARGOM requirement for ibuprofen.

The TGA started a review of the cardiovascular risks associated with NSAIDs in February 2012 [23] that may result in additional or changed warning recommendations. This review is not yet completed.

Like the TGA, the FDA and EMEA have also conducted reviews of NSAIDs recently and made warning recommendations on the basis of these reviews. Effective from April 2010, the FDA mandated labelling changes for all OTC NSAIDs regarding the addition of stomach bleeding warnings [4]. Requirements included that the word NSAID must appear on the PDP (with a footnote), and that the statements below relating to stomach bleeds must appear on the drug facts label and the immediate container label:-

On products labelled for adult use, under the “Warnings” heading:

“Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding.

This chance is higher if you:

- *are age 60 or older*
- *have had stomach ulcers or bleeding problems*
- *take a blood thinning (anticoagulant) or steroid drug*
- *take other drugs containing prescription or non-prescription NSAIDs (aspirin, ibuprofen, naproxen, or others)*
- *have 3 or more alcoholic drinks every day while using this product*
- *take more or for a longer time than directed*

The addition of these statements in the “Ask a doctor before use:” section:

- the stomach bleeding warning applies to you
- you have a history of stomach problems such as heartburn
- you have high blood pressure, *heart disease*, liver cirrhosis, or *kidney disease*
- *you are taking a diuretic*

The revised statements in the “Stop use and ask a doctor if” section:

- you experience any of the following signs of stomach bleeding: [sub-bullets within this bullet]
 - feel faint
 - vomit blood
 - have bloody or black stools
 - have stomach pain that does not get better

The FDA warnings above that have been italicized are considered to be already included in the currently required Australian or New Zealand warnings.

The EMEA has also undertaken a review of the safety of NSAIDs, and in October 2005 concluded that “No new safety concern has been identified that would

warrant a formal Article 31 referral to the CHMP” for a number of NSAIDs including naproxen, diclofenac and ibuprofen [7], and this view was further upheld in November 2006 [7]. An outcome of this review was an EU-funded independent research project (the SOS project) to further assess and compare the risk of cardiovascular and gastrointestinal events for NSAIDs. In October 2012, the CHMP concluded that evidence from newly available published data sources on the cardiovascular safety of NSAIDs confirmed the findings of previous reviews [8]. For naproxen and ibuprofen the Committee considered that current treatment advice was appropriate, and for diclofenac there appeared a consistent but small increase in the risk of cardiovascular side effects compared with other NSAIDs [8]. This conclusion supports the fundamental hypothesis of this proposal – that naproxen is sufficiently similar to ibuprofen to justify reclassification of naproxen 250 mg to General Sales Medicine.

Like New Zealand at the moment, only ibuprofen is a GSL-classified NSAID in the United Kingdom. The required label statements for ibuprofen in the United Kingdom, last revised in November 2007 (i.e. after the 2006 CHMP review) are [9]:-

Read the enclosed leaflet before taking this product.

Do not take if you:

- *have (or have had two or more episodes of) a stomach ulcer, perforation or bleeding*
- *are allergic to ibuprofen or any other ingredient of the product, aspirin or other related painkillers*
- *are taking other NSAID painkillers, or aspirin with a daily dose above 75 mg*

Speak to a pharmacist or your doctor before taking if you:

- *have or have had asthma, diabetes, high cholesterol, high blood pressure, a stroke, heart, liver, kidney or bowel problems*
- *are a smoker*
- *are pregnant*

If symptoms persist or worsen, consult your doctor.

Package Leaflet wording:

Posology:

Adults, the elderly and children over 12 years: This product is intended for short term use only. You should take the lowest dose for the shortest time necessary to relieve your symptoms. You should not take ‘N’ for longer than 10 days unless your doctor tells you to. If symptoms persist or worsen consult your doctor.

Warnings:

Medicines such as [product] may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.

Any risk is more likely with high doses and prolonged treatment. Do not exceed the recommended dose or duration of treatment [x days OTC products only]. If you have heart problems, previous stroke or think that you might be at risk of these conditions (for example if you have high blood pressure, diabetes or high cholesterol or are a smoker) you should discuss your treatment with your doctor or pharmacist.

X belongs to a group of medicines which may impair fertility in women. This effect is reversible on stopping the medicine. It is unlikely that X, used occasionally, will affect your chances of becoming pregnant, however, tell your doctor before taking this medicine if you have problems becoming pregnant

Side effects:

Medicines such as [product] may be associated with a small increased risk of heart attack ("myocardial infarction") or stroke.

SELECTED SUGGESTED PATIENT INFORMATION LEAFLET (PIL) WORDING REGARDING USE WITH LOW DOSE ASPIRIN, AND GASTROINTESTINAL EFFECTS:

LOW DOSE ASPIRIN:

Do not take this medicine if you are taking aspirin at doses of above 75mg daily. If you are on low-dose aspirin (up to 75mg daily) speak to your doctor or pharmacist before you take [PRODUCT].

GASTROINTESTINAL EFFECTS:

If you suffer from any of the following at any time during your treatment STOP TAKING the medicine and *seek immediate medical help*:

- Pass blood in your faeces (stools/motions)
- Pass black tarry stools
- Vomit any blood or dark particles that look like coffee grounds

STOP TAKING the medicine and *tell your doctor if you experience*:

- Indigestion or heartburn
- Abdominal pain (pains in your stomach) or other abnormal stomach symptoms

The MHRA warnings above in italics are considered to be already included in the currently required Australian or New Zealand warnings.

Comparing the current Australian and New Zealand warnings with those for the United States and the United Kingdom, the primary differences are:-

1. the stomach ulcer warning is stronger in the USA and UK, including other stomach problems such as heartburn
2. Liver disease is included for the USA and UK
3. The heart failure warning is stronger in the USA and UK, including such things as diabetes, high cholesterol, high blood pressure and stroke.

Last, but by no means least, New Zealand currently has ibuprofen included as part of the medicines monitoring programme, due to concerns regarding the potential safety issues of hypokalaemia and renal tubular acidosis.

In summary, a number of NSAID reviews have been or are being conducted throughout the world with variable outcomes. While some jurisdictions consider current warnings sufficient, others are implementing additional warnings but the additional warnings required are not consistent. Furthermore, additional safety data analysis such as the SOS project [14, 15, 16] does not assist in determining if some of these warnings have more merit than others e.g. drinking alcohol vs. smoking. Some of the required warnings seem particularly difficult to justify, such as the USA requirement to put “NSAID” on the front panel (see USA Aleve labelling in Section A7), making large assumptions that this abbreviation means something to American consumers.

Being mindful of the imminent arrival of ANZTPA and taking into account the warnings required for ibuprofen in New Zealand and the warnings likely to be required in Australia in the near future (RASML 6), the following warnings are proposed for naproxen as a general sales pain medicine in New Zealand (changes from the current ibuprofen requirements are highlighted):-

Do not use in children under 6 years old except on doctor's advice.

Do not use this product if you are aged 65 years or over except on doctor's advice.

Do not use if you have a stomach ulcer.

Do not use if you have heart failure.

Do not use if you have kidney problems or impaired renal function.

Do not use if you have asthma except on doctor's advice.

[Do not use if you are allergic to aspirin or ibuprofen except on doctor's advice]. *Warning to be deleted*

Do not use if you are allergic to naproxen or other anti-inflammatory medicines.

If you get an allergic reaction, stop taking and see your doctor.

Do not use for more than a few days at a time except on doctor's advice.'

Do not exceed the recommended dose. Excessive use can be harmful.

Do not use this product with other medicines containing naproxen, aspirin or other anti-inflammatory medicines or with other medicines you are taking regularly except on doctor's advice.

Do not use at all during the last 3 months of pregnancy.

Do not use [this product/insert name of the product] during the first 6 months of pregnancy, except on doctor's advice.

Naturally, should the current TGA review of NSAIDs result in additional required warnings, it is expected that such additional warnings would also be considered in New Zealand.

Taking these proposed warnings into account, a comparison of various OTC analgesics is tabulated on the next page. It is clear from this table that the warnings being proposed for naproxen sodium 275 mg as a general sales medicine are consistent with the required warnings for other general sales analgesics already available in New Zealand. These other medicines are used effectively and safely by New Zealand consumers without healthcare professional supervision. General sales naproxen sodium 275 mg would not present consumers with new challenges, in that precautions currently unfamiliar to analgesics would not be introduced by the reclassification of this medicine as proposed.

Comparison of Regulated Restrictions of Selected Solid Dose Form OTC Analgesic Characteristics
(current proposal in italics)

	Naproxen	Ibuprofen	Diclofenac	Aspirin	Paracetamol
Max strength	PM - 250 mg per tab/cap <i>GSM - 250 mg per tab/cap</i>	RM – 400 mg per tab/cap PM – 200 mg per tab/cap GSM – 200 mg per tab/cap	RM – more than 12.5 mg up to 25 mg PM – 12.5 mg	RM – SR forms, enteric coated forms with more than 300mg	PM – 500 mg per tab/cap GSM – 500 mg per tab/cap
Max. allowed daily dose	PM - No restrictions GSM – 1.25 g (5 tabs/caps)	RM – no restrictions PM – 1.2 g(6 tabs/caps) GSM – 1.2 g(6 tabs/caps)	PM – not more than 75 mg (6 tabs/caps)	No restrictions	
Max. allowed pack size	PM - Not more than 30 <i>GSM – not more than 25 (5 days' supply)</i>	PM – not more than 100 GSM – not more than 25 (4-5 days' supply)	RM – not more than 30 PM - not more than 30 (5 days' supply)		PM – more than 10g GSM – not more than 10g (usually 20)
Age restrictions	No restrictions <i>GSM – not less than 6 yrs, not more than 65 yrs</i>	RM – not less than 12 yrs <i>GSM – not less than 6 yrs, not more than 65 yrs</i>		GSM - Not less than 12 yrs	
Warnings – labelling database	PM – None <i>GSM</i> <i>1. Asthma</i> <i>2. Stomach ulcer</i> <i>3. Allergies</i> <i>4. Other anti- inflammatories</i> <i>5. Pregnancy</i> <i>6. Prolonged use</i> <i>7. Renal function</i> <i>8. Max. daily dose</i>	<i>PM/GSM Classifications</i> <i>1. Asthma</i> <i>2. Stomach ulcer</i> <i>3. Allergies</i> <i>4. Other anti-inflammatories</i> <i>5. Pregnancy</i> <i>6. Prolonged use</i> <i>7. Renal function</i> <i>8. Max. daily dose</i>	None	<i>All Classifications</i> <i>1. Asthma</i> <i>2. Stomach ulcer</i> <i>3. Allergies</i> <i>4. Other anti- inflammatories</i> <i>5. Prolonged use</i> <i>6. Pregnancy</i>	<i>All Classifications</i> <i>1. Overdose warning.</i> <i>2. Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.</i> <i>3. Prolonged use</i>

A9. Other Products

Apart from the possible Bayer naproxen sodium products that have already been mentioned in this submission, there is only one other naproxen product registered as an OTC medicine in New Zealand. It is:-

Brand Name	Active Ingredients	Classification	Pack Size
Sonaflam	Naproxen sodium 275 mg film coated tablets	Pharmacy Only Medicine	12's and 24's

Sonaflam has sales in New Zealand of approximately 224,000 tablets per annum, mostly likely all over-the-counter purchases.

Thus, the proposed reclassification will affect very few products currently available in New Zealand. However, there are more products that could access the reclassification should the sponsors wish to do so. These include Naxen (Douglas) and Noflam (Mylan), current registered presentations of naproxen 250 mg sold only as prescription medicines.

PART B

Over the past several years, consumers have recognised (and become increasingly interested in) the importance of self-care [21]. The availability of OTC medicines plays a vital role in the ability of consumers to take responsibility for minor ailments, and each medicine should be as freely available to consumers (via classification) as is appropriate for the active ingredient.

Pain is one of the most common health conditions for consumers, and untreated can have a considerable impact on the lives of sufferers, often interfering with appetite, sleep and normal activities. Consumers rely on OTC medications when looking for pain relief, and providing consumers with access to safe and effective OTC analgesics is an important and integral part of self-care.

The fundamental premise of this proposal to reschedule naproxen is that naproxen sodium 275 mg in a solid dose form is sufficiently similar to ibuprofen 200 mg in terms of efficacy and safety that the same classification should apply to both substances.

When considering the case for reclassification, the New Zealand Regulatory Guidelines suggest that the following topics should be considered:-

1. A statement of the benefits to both the consumer and to the public expected from the proposed change
2. Ease of self-diagnosis for the condition indicated
3. Relevant comparative data for like compounds
4. Local data or special considerations relating to New Zealand
5. Interactions with other medicines
6. Contraindications
7. Possible resistance
8. Adverse events - nature, frequency etc.
9. Potential for abuse or misuse.

However, as a number of analgesics are already classified as General Sales Medicines, many of these topics are considered already established for a General Sales category and not in need further consideration. In particular, the ease of self-diagnosis does not need further discussion as a range of analgesic indications is already accepted for general sales status and it has been shown in Section A4.1 that naproxen sodium 220 mg or 275 mg tablets have been previously approved in New Zealand for these indications. Likewise, possible resistance and potential for abuse or misuse, if present, would be class effects

for non-steroidal anti-inflammatory medicines, and since there is already an NSAID being sold at general sales level, these issues are considered resolved for naproxen sodium.

1. Benefits from the Proposed Change

In the 9 years since ibuprofen 200 mg was reclassified to a General Sales Medicine, consumers of New Zealand have not had a new analgesic to choose from at the general sales level. Over time the category has continued to develop, with successful introductions of such innovations as ibuprofen/paracetamol combinations, paracetamol/caffeine combinations, and segmented ranges (Nurofen Tension Headache, Nurofen Migraine Pain, Nurofen Period Pain). These successful developments in this category demonstrate that the consumer is receptive to (and by extrapolation, has a need for) products that can offer unique advantages over those currently available. However, despite these developments, choice for the consumer at the general sales level is still restricted to essentially three analgesics – aspirin, paracetamol and ibuprofen.

In comparison, naproxen sodium 220 mg has been available in the United States of America, as a general sales medicine, since 1994 under the trade name Aleve. It is now widely used in the USA, and American consumers report high levels of satisfaction with the OTC options they have available for pain management [21].

Naproxen sodium solid dose forms up to 275 mg would offer the consumer more choice of analgesics at the general sales level. Analgesics are one of the biggest, if not the biggest, medicinal category available for general sales and yet this category is restricted to just three compounds – compare this with the cough/cold category where many compounds are available, and a range of well-differentiated products has developed. In terms of disease, the pain category is hugely diverse, treating many complaints and yet consumers have limited genuine choice of analgesic. Such a large market segment should be able to offer the consumer more options to choose from.

The segmented Nurofen range offers consumers a façade of choice, but in fact offers the same product again and again. How much better for consumers in the general sales arena to be offered a genuinely new product – a new analgesic compound with unique features and benefits?

Naproxen sodium 275 mg offers a number of benefits compared to the currently available products, offering consumers greater opportunity to purchase their painkiller on the basis of features they might desire of a product. Naproxen

sodium 275 mg offers the following unique features for a general sales analgesic:-

- longer-lasting pain relief
- less tablets per day
- fast acting
- toxicity comparable to placebo at OTC doses (lower relative cardiovascular risk than ibuprofen - see Section B2)

Additionally, for current consumers of naproxen sodium 275 mg availability at general sales level is very likely to deliver considerable cost savings, and offers the convenience of purchasing the product through many more outlets. The risk/benefit profile for these consumers (lack of pharmacy environment supervision vs. potential cost savings) is favourable due to the favourable safety profile of naproxen at OTC dosages (see section B1.4).

Naproxen sodium 275 mg represents a worthwhile alternative for consumers, a safe and effective addition to existing general sales analgesics.

1.1 Longer-Lasting Pain Relief

Naproxen has a longer half-life than ibuprofen [10, 11] and so is expected to offer consumers longer-lasting pain relief. This longer-lasting claim has previously been approved for Aleve in New Zealand (see Aleve labels, section A7).

Naproxen sodium's plasma half-life is approximately 13 hours, whereas the half-lives of aspirin, paracetamol and ibuprofen are 3.2 hours or less [21]. This effect is reflected in the recommended dosing schedules for the compounds – while ibuprofen 200 mg is recommended every 4 hours (Signature range) or every 4 – 6 hours (Nurofen caplets) with a maximum of 6 tablets per day, naproxen sodium is recommended to be taken every 6 – 8 hours (Naproxen) or 8 – 12 hours (Aleve) with a maximum of 5 and 3 tablets respectively. These NSAID analgesics both represent a considerable advantage of paracetamol 500 mg in this respect (2 tablets every 4 – 6 hours with a maximum of 8 tablets per day).

At its April 2010 meeting the Medicines Classification Committee considered a proposal to increase the maximum pack size for pharmacy only sale of diclofenac 12.5 mg in solid oral dosage forms. In its submission Novartis presented consumer research that showed consumers use of OTC analgesic medication was the same regardless of the pack size that might be available to them. This implies that consumers use analgesic medication to attend to their pain, and no

more. With its longer-lasting pain relief, consumers are likely to use less naproxen as it will be longer until they re-experience pain (if at all) and take the next dose.

Even in extreme pain medicated with opioid analgesics, it is well known that patients tend to take less medication if they are in control of the medicine administration and can take the next dose when they feel it is needed. Hence, the use of patient-controlled pain pumps for this type of medication generally leads to less, or more appropriate, opioid usage.

1.2 Less Tablets

With its longer duration of action, use of naproxen for mild-to-moderate analgesia may lead to the patient requiring fewer tablets per day or per medication episode.

While for many people the number of tablets required is not an issue, for those who experience difficulty taking tablets or capsules the number and frequency required can cause considerable discomfort.

Ibuprofen 200 mg dosage is recommended as 2 tablets initially followed by 1 – 2 tablets every 4 – 6 hours with a maximum of 6 tablets per day while naproxen sodium is 2 tablets initially followed by 1 tablet to be taken every 6 – 8 hours (Naprogesic) or 1 tablet every 8 – 12 hours (Aleve) with a maximum of 5 and 3 tablets respectively. These NSAID analgesics both represent a considerable advantage of paracetamol 500 mg in this respect (2 tablets every 4 – 6 hours with a maximum of 8 tablets per day). Also, with the lesser amount of active ingredient required, ibuprofen and naproxen tablets tend to be smaller than those containing paracetamol, and this can also be of assistance to people who find taking tablets difficult.

Generally, at over-the-counter doses adverse events are not expected for NSAID analgesics. However, adverse events for this class of medicines are directly related to the intensity of treatment (strength of dose, total dose and duration) [7], and so any potential to lower this intensity of treatment must be viewed positively as having the potential to reduce side effects.

1.3 Fast Acting

As can be seen from the labelling provided in Section A7, Aleve tablets have previously had a claim of fast-acting approved in New Zealand. Naprogesic has

also had the claim approved in New Zealand (CMN approved 16 October 1995), although it is not currently on the label, as it has been shown that naproxen sodium begins to work within 15 minutes [11].

A pharmacokinetic study comparing naproxen 200 mg with naproxen sodium 275 mg showed similar C_{max} concentrations, but the latter peaked on average 50 minutes earlier and had a 40 minute blood level 2.5 times great than that of the former [10].

1.4 Toxicity Comparable to Placebo

Bansal et al. evaluated the safety of OTC naproxen sodium through a meta-analysis of 46 clinical studies [21, 26]. Headache, nausea, somnolence, dizziness, vomiting and dyspepsia were among the most commonly reported adverse events. Rates of headache and vomiting were significantly higher amongst those patients receiving placebo and only the rate of somnolence was significantly higher amongst the naproxen-treated group. There was no statistical difference between placebo and naproxen for gastrointestinal adverse events. Overall occurrences of moderate and severe adverse events with naproxen were comparable to placebo with no statistically significant differences recorded. The safety profile of the medicine for a ≤ 10 day dosing period was evaluated as relatively good. This meta-analysis is considered reflective of the true occurrence of adverse events associated with OTC naproxen sodium when taken as directed, and demonstrates a safety profile for the medicine that is compatible with general sales availability.

When considering reclassification proposals for an NSAID medicine in the past, the Medicines Classification Committee expressed the view that longer term usage may lead to a greater incidence of adverse events. As demonstrated above, OTC dosages of naproxen for up to 10 days incur adverse event rates similar to placebo. The proposed pack size (25 tablets) further limits treatment to 5 days at the maximum recommended dosage, thereby providing additional protection for the consumer against adverse events.

1.5 Interactions with Other Medicines

Naproxen does exhibit some interactions with other medicines. The most serious of these is a potential enhancing effect and anti-coagulants increasing the risk of bleeding, and an increased risk of gastrointestinal bleeding due to interaction with

anti-platelet agents, selective serotonin reuptake inhibitors (SSRIs) and corticosteroids [1, 6]. Naturally, combination use with other NSAIDs or aspirin is not recommended as this increases the possibility of gastrointestinal side effects.

However, all of these interactions are well-known to be NSAID class effects. Naproxen has no unusual medical interactions not shown by other NSAIDs. As such, the classification of ibuprofen 200 mg as General Sales in New Zealand acknowledges that these interactions can be managed by consumers, and the situation remains the same for naproxen 250 mg.

The proposed label warnings advise consumers not to use naproxen sodium 275 mg if they are taking any other medicines, and in particular if they are taking any other NSAIDs or aspirin, unless a doctor tells them to and offer good protection against potential medicine interactions.

2. Relevant Comparative Data for Like Compounds

2.1 Ibuprofen

In November 1999 the Medicines Classification Committee considered a submission for Roche Products (New Zealand) Limited, the sponsor at the time of OTC naproxen sodium registered as Naprogesic (275 mg) or Aleve (220 mg), to reclassify Aleve from Restricted Medicine to Pharmacy Medicine for a range of OTC analgesic indications. It was the fourth submission since 1996, the other three having been unsuccessful. The minutes from this meeting state:

“The Chairman said he thought the company should be commended on producing an interesting and innovative study in order to show that OTC naproxen was not more toxic than ibuprofen.....ibuprofen had been used as a benchmark for OTC safety. Robust data had now been gathered to show that there was no significant difference in safety between naproxen and ibuprofen with OTC use.”

The Committee subsequently recommended that naproxen be classified as a pharmacy-only medicine when in packs containing 250 mg or less per dose form and not more than 30 tablets or capsules. At the time, this change aligned the classifications of ibuprofen 200 mg and naproxen 250 mg as Pharmacy

Medicines, and it is clear that the Committee considered these two compounds at these strengths to be sufficiently equivalent to justify having the same classifications.

Since that time, the classification of ibuprofen 200 mg has been further relaxed to General Sales Medicine for packs of not more than 25 tablets or capsules. However, this subsequent divergence in classifications is attributed to the fact that the further down-scheduling of ibuprofen has been actively and successfully pursued, whereas naproxen has not been further considered by the Medicines Classification Committee since 1999 as it has not received further submissions.

The MCC considered a proposal to reclassify ibuprofen 200 mg to General Sales in November 2003, a change that had recently been accepted in Australia. It recommended against making this change due to concerns about use in the elderly (particularly gastrointestinal effects), renal effects and interactions with other medicines (particularly warfarin). However, the Minister's Delegate did not accept the Committee's recommendation and the medicine was subsequently reclassified as proposed by Gazette notice. The recommendation was not accepted on the basis of a report by Dr. G. R. Boyd to the Deputy Director-General, Public Health [24] which stated "While not without an adverse event profile, [ibuprofen] is generally recognised as the gold-standard against which the safety of other NSAIDs and the newer cox-2 inhibitor medicines are judged".

In June 2006 the Committee considered a serious challenge to this classification of ibuprofen in the form of a submission from the Pharmaceutical Society of New Zealand. However, they agreed there would need to be convincing safety data pertinent to short-term, intermittent, OTC use to justify removal of the general sales status of ibuprofen 200 mg and recommended that the status quo be maintained. Clearly the general sales availability of ibuprofen 200 mg had not provided sufficient cause for concern within the elapsed three years, and appears to have continued to do so until the present day as the general sales classification has not been further challenged.

2.1.1 Efficacy

There is little doubt that naproxen [10] and ibuprofen are both efficacious medicines in the treatment of mild-to-moderate pain and for the reduction of fever, since both have been evaluated and approved by Medsafe for OTC-type indications. There appears to be relatively little difference in efficacy between naproxen and ibuprofen – a 2006 review of effectiveness of analgesics for osteoarthritis (including OTC dosages) found little difference in efficacy for all non-selective NSAIDs [12].

However, naproxen sodium may provide superior efficacy. In a comparison of non-prescription analgesic efficacy in osteoarthritis of the knee [13], naproxen sodium was found to provide superior efficacy to ibuprofen when evaluated for night-time pain. This effect was attributed to naproxen sodium's longer duration of action, and was noted as having important implications for quality of life. The authors noted that naproxen sodium had also been demonstrated as having superior efficacy to ibuprofen for post-operative dental pain and dysmenorrhoea, suggesting these results are applicable generally.

In another study [10] for dental pain there were no significant differences in efficacy between naproxen sodium 220 mg and ibuprofen 200mg, or between naproxen sodium 440 mg and ibuprofen 400mg (although in this case the numerical values were in favour of naproxen sodium and significantly more patients in the ibuprofen group needed rescue medication at the 12 hour time point).

Other studies in headache, musculoskeletal pain, arthritis pain and dysmenorrhoea have all demonstrated that naproxen sodium is at least as good as, if not more efficacious than, ibuprofen [10].

2.1.2 Risks

NSAIDs present a number of potential risks to users – gastrointestinal, cardiovascular, hepatic, renal and allergic reactions. All of these risks are recognised as being NSAID class effects [14,15,16] – the general sales status of ibuprofen 200 mg in New Zealand acknowledges that these risks can be managed at this level of classification, leaving only the question as to whether or not naproxen sodium represents an increased risk to consumers over ibuprofen.

The SOS Project recently undertook a meta-analysis of epidemiological studies for NSAIDs and upper gastrointestinal problems [14], risk of acute myocardial infarction [15] and stroke risk [16, 17]. The studies did not differentiate between prescription and non-prescription dosages. For gastrointestinal risk the authors found that ibuprofen presented a low relative risk to consumers, whereas naproxen presented an intermediate relative risk – however, they also noted that the use of high daily doses of individual NSAIDs doubled or tripled the risk of upper GI complications compared to low or medium doses, bringing into question the relevance of these results for OTC-type dosages. For acute myocardial infarction risk, naproxen presented the lowest pooled relative risk of all NSAIDs studied, while ibuprofen presented the third lowest relative risk. The authors noted that a higher risk was associated with higher doses, except for naproxen and ibuprofen. For stroke, results were mixed and the authors suggested the risk of ischemic stroke across individual NSAIDs was variable.

However, studies that do not differentiate on the basis of dose are recognised as flawed when considering low-dose OTC use. It is recognised that those medicines commonly used at maximum recommended doses, such as diclofenac and naproxen, are more likely to be associated with gastrointestinal adverse events than those predominantly used at low doses such as ibuprofen [7]. Generally no clear differences in the gastrointestinal safety of non-selective NSAIDs are found [12], or if naproxen appears to have a slightly higher risk than ibuprofen, the evidence for drawing such a conclusion is weak [7]. Studies consistently demonstrate that there is a firm association between gastrointestinal side effects and increasing dose and/or the concomitant use of more than one NSAID or aspirin [7]. The proposed label warnings strongly address both of these issues.

Ray et al. [18] studied cardiovascular safety in patients with existing serious coronary heart disease. They found that cardiovascular safety was best for naproxen and that relative to naproxen users, users of ibuprofen had a 25% increased risk of myocardial infarction, stroke or death from any cause. They noted that their findings were consistent with previous studies that were not restricted to people with serious heart disease. This writer acknowledges that these studies involved mostly prescription dosages of NSAIDs, and that overall risks are likely to be much lower for all of the medicines at OTC dosages – nonetheless, the trends are consistently demonstrated and so likely to apply to OTC usage at some (reduced) level. A recent review [8] of available new evidence found that naproxen (compared to ibuprofen and diclofenac) was consistently the only NSAID associated with the lowest thrombotic risk. The proposed warnings for naproxen related to cardiovascular risk (Do not use if you have heart failure, Do not use if you are aged 65 years and over except on doctor's advice) are considered appropriate and sufficient, given naproxen's excellent record on this issue compared to other NSAIDs.

Safety data for naproxen sodium 220 mg from 94 clinical trials has been summarized [10]. The most frequent side effects (headache, gastrointestinal or CNS complaints) occurred to the same degree for placebo, naproxen sodium and ibuprofen. The author concluded that "The risk/benefit assessment of naproxen sodium 200 mg is at least as positive as that for ibuprofen" and the need for re-medication is reduced.

De Armond et al. conducted a meta-analysis on 48 clinical studies [21] to evaluate the safety of OTC naproxen sodium compared to ibuprofen, paracetamol and placebo. They found that 83% naproxen- or placebo-treated patients report no adverse effects, and there were no statistically significant differences in adverse event rates across all three treatments.

Ibuprofen is considered the "gold standard" against which other NSAIDs should be judged. All of the evidence for OTC dosages of ibuprofen and naproxen is

that there is no detectable difference in the rate of adverse events, and the risk/benefit profiles of these two medicines are essentially the same. This being the case, rescheduling of naproxen 250 mg to the same classification as ibuprofen 200 mg is justified.

2.2 Diclofenac

Diclofenac has been included in this discussion because, outside general sales medicines, it is probably the most used and well known OTC analgesic in New Zealand, although the topical presentation under the brand name Voltaren would be the best known of these. Furthermore, relaxation of the classification of diclofenac potassium has been actively pursued in New Zealand over the last decade, during which the 12.5 mg oral dose presentation has been reclassified to Pharmacy Medicine, and the pack size for this classification increased to 30 dose units.

2.2.1 Efficacy

There is less comparative evidence between the efficacy of naproxen sodium and diclofenac available than between naproxen and ibuprofen. However, there seems to be general agreement that there are few differences between the two medicines [11, 12], and it is accepted that both are suitable for the treatment of mild-to-moderate pain.

2.2.2 Risks

Recent developments in the study of NSAID risks have uncovered significant differences between naproxen and diclofenac. The SOS Project studies [14, 15, 16, 17] classed diclofenac as equivalent to naproxen for relative risk from upper gastrointestinal complications, but of a much higher relative risk for acute myocardial infarction (although this is acknowledged as being dose-related). They also found that diclofenac is the only non-selective NSAID that could be associated with an increased risk of ischemic stroke.

Ray et al. [18] found that for patients recently hospitalised for serious coronary heart disease, relative to nonusers of NSAIDs, short-term use of diclofenac (< 90 days) increased the risk of further heart disease (RR = 1.86) whereas short-term use of naproxen did not (RR = 0.88). Relative to naproxen, current users of

diclofenac had an increased risk of serious coronary heart disease (1.44, $P = 0.076$) and serious cardiovascular disease/death (1.52, $P = 0.0002$). While this study was conducted on a vulnerable population, the results strongly suggest that overall the cardiovascular safety profile of diclofenac is not as favourable as that of naproxen.

Likewise, Olsen et al. [19] studied the cardiovascular risk of NSAIDs according to time passed after a first-time myocardial infarction. They found that naproxen was the NSAID with the lowest relative risk (compared with ibuprofen, diclofenac, and a grouping of “other NSAIDs”), and noted that their results were consistent with the view the naproxen has the safest cardiovascular risk profile. A recent review of available new information [8] concluded that the results for diclofenac indicated an increased cardiovascular risk which was generally higher than that for other non-selective NSAIDs, and similar to those reported for some of the coxibs. Furthermore, doses above 75 mg diclofenac per day are associated with progressively higher thrombotic risks [8]. The current Pharmacy Medicine classification for diclofenac allows dosages up to 75 mg/day, while the current Pharmacist Only Medicine classification does not specify a maximum daily dosage.

When comparing a range of analgesics for symptom relief from osteoarthritis, and while acknowledging that clinically significant hepatotoxicity was rare, the AHRQ found that only diclofenac was associated with a significantly higher rate of liver-related treatment discontinuation compared to placebo [12].

Diclofenac potentially exposes the patient to additional cardiovascular risk at any dosage above the maximum allowed over-the-counter dosage, and may cause more liver-related adverse events. It appears warranted that this medicine would have a more restrictive classification than naproxen sodium, as is proposed by this submission.

2.3 Paracetamol

2.3.1 Efficacy

Kiersch et al. [22] studied the analgesic efficacy of naproxen sodium, paracetamol and placebo for pain associated with dental extraction. Dental extraction is a suitable model for examining duration of pain relief as it provides a predictable and persistent level of pain. They found that time to re-medication was significantly longer with naproxen sodium (median 9.9 hours) than with either

paracetamol (median 3.3 hours) or placebo (median 2.0 hours). Naproxen sodium was also superior to paracetamol for peak pain intensity difference, summed pain intensity differences, total pain relief, peak pain relief and time to reduction of pain by 50%. Other studies [10] have found similar results.

In a headache study [10] naproxen sodium and paracetamol were both found to be superior to placebo for all endpoints and did not differ significantly from each other. For arthritic pain, naproxen sodium was found to be significantly better than paracetamol with respect to resting pain symptom improvement [10].

For osteoarthritis, paracetamol was found slightly inferior to NSAIDs for pain and function across four systematic reviews [12].

2.3.2 Risks

De Armond et al. conducted a meta-analysis of 48 clinical studies [21] to evaluate the safety of OTC naproxen sodium compared to ibuprofen, paracetamol and placebo. In the 9 studies that directly compared placebo, naproxen or naproxen sodium and paracetamol, the only statistically significant difference observed for adverse events was for vomiting, occurring more frequently in the paracetamol group (4.5%) than for naproxen (2.2%) or placebo (2.5%).

Bayer has summarized safety data from 94 clinical trials performed up to 2010 [10], and found that the most frequent side effects (headache, gastrointestinal or CNS complaint) occurred to the same degree for naproxen sodium and paracetamol.

A comparative review of treatments for osteoarthritis [12] found that paracetamol has fewer gastrointestinal side effects or serious complications than NSAIDs, but cardiovascular risk was increased with heavy use of paracetamol, similar to that with heavy use of NSAIDs. Lastly, like NSAIDs, paracetamol may be associated with increases in blood pressure and renal dysfunction.

Between 1995 and 2000 no fatal overdoses involving naproxen/naproxen sodium were reported by the American Association of Poison Control Centers – the greatest number of fatal OTC analgesic overdoses (672) during this period occurred with paracetamol [21]. Given the relatively recent availability of naproxen as an OTC medication at that time, it is acknowledged that these numbers may to some extent be reflective of absolute usage – however, consumers of the time were well-experienced with paracetamol and relatively naïve of naproxen, suggesting that consumers do not necessarily have more problems with a medicine new to the OTC market.

In summary, naproxen provides equivalent-to-superior pain relief compared to paracetamol, and the pain relief provided is of longer duration. Adverse events are also relatively similar for naproxen and paracetamol, more particularly for OTC-type complaints requiring lower doses. Conversely, gastrointestinal adverse effects are more commonly reported for naproxen with complaints such as osteoarthritis that often require higher doses.

2.4 Summary

The safety and efficacy of naproxen sodium in an OTC setting has been evaluated in over 100 studies [21]. Doses of 220 mg and higher have been demonstrated to be efficacious for various pain states, and a number of Health Authorities around the world have concluded that naproxen sodium 220 mg or 275 mg is a safe and effective analgesic/antipyretic for OTC use. The rate and severity of adverse events associated with OTC naproxen are similar to those associated with placebo, and the available data indicates that this medicine compares favourably with other analgesics available over-the-counter. Specifically, the discussion above has demonstrated that naproxen sodium at OTC strengths compares favourably with both ibuprofen and paracetamol. Reclassification of naproxen sodium 275 mg to General Sales Medicine is justified on the basis that it appears very unlikely to expose the consumer to additional risks compared to the analgesics currently available while offering significant benefits such as extended duration of efficacy, rapid onset of action, less frequent dosing, more convenience and possible cost reductions.

APPENDICES

Appendix 1

Proposed Consumer Medicine Information for naproxen sodium 275 mg as a general sales medicine.

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