APPLICATION TO THE MEDICINES CLASSIFICATION COMMITTEE, MEDSAFE, NEW ZEALAND FOR RECLASSIFICATION OF A MEDICINE

PROPOSAL FOR RECLASSIFICATION

OF

IBUPROFEN 400 MG IN DIVIDED PREPARATIONS WITH A RECOMMENDED DOSE OF 400 MG AND A MAXIMUM TOTAL DAILY DOSE OF 1200 MG

FROM PRESCRIPTION MEDICINE TO PHARMACY ONLY MEDICINE

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Submitted by:

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EXECUTIVE SUMMARY

Purpose of the application

The purpose of this application is to seek reclassification of divided doses of ibuprofen 400 mg from Prescription to Pharmacy Only Medicine in preparations for oral use when labelled with a recommended dose of 400 mg and a daily dose not exceeding 1200 mg of ibuprofen in packs of 50 or less dosage units. This is conservative because, in theory, a 12 pack of the 400 mg contains the same quantity of ibuprofen as an unscheduled 24 pack of the 200 mg.

The intention is to provide the consumer with a convenient, single dosage unit format such that there is the option to take the recommended non-prescription dose of 400 mg ibuprofen as a single dosage unit rather than the usual two x 200 mg dosage units.

In summary, the application to reschedule 400 mg ibuprofen is:

- not proposing any classification as a Restricted Medicine
- not proposing any change to the conditions for General Sale classification of 200 mg ibuprofen in packs of 25 of less

but rather is solely:

- proposing change to allow 400 mg tablets in packs of 50 or less to become Pharmacy Only Medicine. The maximum amount of ibuprofen per pack would be the same amount as the Pharmacy Only Medicine maximum pack size of the 200 mg.

Justification for reclassification to Pharmacy Medicine

Ibuprofen 400 mg (in divided preparations) has been available in New Zealand on prescription since 1975 with a dosage regime of 1200-1600 mg daily in three to four divided doses. For acute exacerbations of arthritic conditions in patients already on treatment, a maximum daily dosage of 2400 mg may be prescribed.

Ibuprofen 200 mg (in divided preparations) is available without prescription in New Zealand. Packs of 25 or less dosage units are exempt from classification and packs of more than 25 dosage units are Pharmacy Only Medicine. The current dosage regime for ibuprofen 200 mg products is 400 mg then 200-400 mg every four hours as necessary to a maximum of 6 tablets in 24 hours i.e. 1200 mg.

In the UK and other parts of Europe, ibuprofen 200 mg and 400 mg in various pack sizes have been available without prescription as Pharmacy products since 1984 with a maximum daily dose of 1200 mg.

Worldwide non-prescription availability of either 200 mg or 400 mg strengths and consumption of ibuprofen (in divided preparations) suggests that consumers, health care professionals and regulators regard ibuprofen as an effective and useful pain reliever with a safety profile suitable for general sale use at a maximum daily dose of 1200 mg.

Whether the dosage is 2 x 200 mg tablets or capsules or 1 x 400 mg tablet (or capsule) as is proposed in this application, a maximum daily dose of 1200 mg is already considered to be a dose suitable to be accessed without a prescription. The essence of this proposal is to allow the sale without prescription of a single tablet dose of 400 mg of ibuprofen with a total daily dose of 1200 mg. This brings the single tablet dose in line with the scheduling of the current two-tablet dose. The Pharmacy Only Medicine classification for ibuprofen 400 mg will provide an

adequate and arguably conservative restriction on supply which is consistent with larger packs of ibuprofen 200 mg.

Reckitt Benckiser intends to clearly differentiate the 400 mg tablet from the currently available 200 mg tablets. The request for a Pharmacy Only Medicine classification could be considered conservative because, in theory, a 12 pack of the 400 mg contains the same quantity of ibuprofen as an unscheduled 24 pack of the 200 mg, however Reckitt Benckiser considers it is appropriate to ensure there is an opportunity for pharmacy advice and consumer education as to the availability of a single tablet dose.

Overall summary of supporting information

- The MCC has considered the scheduling of ibuprofen substances several times over the past number of years and has approved the rescheduling of solid dose oral ibuprofen 200 mg tablets from Prescription, to Pharmacy Only Medicine and subsequently to unscheduled status where the maximum daily dose is 1200 mg.

- This application requests the MCC to consider the rescheduling of solid dose ibuprofen 400 mg tablets to Pharmacy Only Medicine status, with a recommended dose of 400 mg and maximum daily dose of 1200 mg with a pack size of 50 tablets or less. This equates to the current Pharmacy Only Medicine availability for ibuprofen 200 mg that has the same unit dose and maximum daily dose and a pack size of 100 tablets or less.

- Ibuprofen has been available internationally for more than 40 years, firstly as a prescription product then as a non-prescription product.

- Ibuprofen 400 mg tablets have been available without prescription in the UK since 1984. Evidence has shown that the broader availability has not

resulted in an increase in the incidence of adverse effects and in particular gastrointestinal adverse effects.

- Ibuprofen's safety record is significantly better than other non-steroidal antiinflammatory agents (NSAIDs). In particular, the comparison with naproxen, aspirin and diclofenac (other NSAIDs available as non-prescription medicines) shows a much lower risk of GI toxicity with ibuprofen, particularly at non-prescription doses (i.e. up to 1200 mg/day). Several publications support this view. The GI ranking by relative risk of commonly used non-prescription NSAIDs shows ibuprofen < diclofenac < aspirin < naproxen.

- The wide margin of safety and mild toxic effects, particularly in overdose situations, which is reflected in the low number of adverse reactions and fatalities reported internationally over the past 20 years makes 400 mg ibuprofen tablets suitable for availability as a Pharmacy Only Medicine when the total daily dose is limited to 1200 mg.

- Ibuprofen has a half-life of 2-2.2 hours and given its pharmacokinetic profile, the risk of accumulation or potential for toxicity is limited. The half-life is not prolonged in overdose.

- A published report of an adolescent who overdosed with ibuprofen suggests that even though a massive overdose as high as 100 gram (i.e. equivalent to 250 x 400 mg ibuprofen tablets) resulted in some elements of significant toxicity (coma, metabolic acidosis mild thrombocytopenia), the renal function remained normal and no gastrointestinal bleeding occurred. The patient improved rapidly within 3 days with supportive care and recovered with no medical sequelae.

- The study pivotal to the decision to exempt ibuprofen 200 mg from scheduling in packs of 25 or less tablets was a large-scale randomised clinical trial which compared the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia (The PAIN study). More than 8,600 patients were randomised to either aspirin, paracetamol (both up to 3 gram per day) or ibuprofen (up to 1.2 gram per day) for common pain conditions such as back pain, sore throat, common colds and flu. The duration of the study was up to 7 days, which is ideal for assessing short-term treatment. The results of the study showed rates of significant adverse events as: aspirin 18.7%, ibuprofen 13.7% and paracetamol 14.5%. Ibuprofen was shown to be statistically equivalent to paracetamol and both were significantly better tolerated than aspirin. Total gastrointestinal events were less frequent with ibuprofen than with paracetamol. Six cases of gastrointestinal bleeding were reported – four with paracetamol and two with aspirin, and one case of peptic ulcer with aspirin was also reported. The authors concluded the "findings could lead to a reassessment of the use of first-line analgesics for short term management of painful conditions, recommending ibuprofen first, because of the poor tolerability of aspirin and the potential risks of paracetamol overdose.

- A further study in patients with osteoarthritis or rheumatoid arthritis considered the prevalence of serious GI events in patients taking aspirin, paracetamol or ibuprofen, with particular focus on low or intermittent use. Some 5692 patients with RA and 3124 patients with OA with more than 36,000 patient-years of observation who had taken one of the three study analgesics were studied from 12 databank centres to examine the frequency of serious GI events requiring hospitalisation. The results from this prospective observational study showed that much of the associated toxicity of the three analgesics was related to use of the particular analgesic with other concurrent drug use, and when concurrent

drug use was excluded, rates of serious GI events were low and statistically indistinguishable, particularly in low risk patients. It was noted that when taken concurrently with corticosteroids or other NSAIDs, risks for paracetamol were the highest for all three study drugs in both RA and OA although numbers were relatively small. Conclusions from this study supported the PAIN study in that non-prescription use of aspirin, ibuprofen or paracetamol carries little risk of serious GI toxicity for most patients.

- Ibuprofen 400 mg, with a dose of 400 mg and a maximum daily dose of 1200 mg in packs of 50 dosage units or less is suitable for classification as a Pharmacy Only Medicine given the following:

    - It is suitable to be taken for self-treatment of mild to moderate self-limiting ailments such as headache, backache, dental pain, period pain etc which are capable of being monitored by consumers
    - There is no evidence of abuse potential or diversion for illicit use
    - There is a low potential for harm from inappropriate use
    - The few adverse effects and contraindications are well characterised and the labelling directs consumers to seek medical advice in these circumstances
    - The few interactions with commonly used substances are well characterised and the substances in question are available only with a prescription. The labelling for ibuprofen directs consumers to seek medical advice where there is the potential for drug-drug interaction
    - Ibuprofen has a wide margin of safety. A fatal dose has not been defined.
    - There is a low risk of masking serious disease, largely due to the easily recognised conditions for which non-prescription ibuprofen is indicated and to the short-term duration of use. The labelling directs consumers to seek medical advice is symptoms continue.

- There is a low risk of compromising the medical management of a disease because of the excellent safety profile, rare and well-defined drug interactions and short-term usage pattern.

- The labelling for 400 mg ibuprofen will be designed to clearly differentiate it from the 200 mg product. A free call number will be included on labels to allow consumers access to information about the product. A qualified pharmacist manages this free call line.

- Ibuprofen does not cause major complications in overdose situations nor does it cause other untoward problems when taken according to the directions on the label.

- The efficacy of ibuprofen in headache, period pain, dental pain, muscular aches and pains, and fever have been extensively proven in clinical trials which have been reviewed by regulatory authorities.

- Ibuprofen has been proven more effective than paracetamol and aspirin in moderate to severe tension type headache, sore throats and muscle pain and has the added benefit of an anti-inflammatory action. It has a longer duration of action in fever than paracetamol.

- It is not expected that availability of 400 mg strength of ibuprofen will increase the size of the analgesic market. Rather, it is expected that those people who desire the convenience of taking one tablet instead of two and who wish to purchase their product from a pharmacy outlet where advice and assistance is readily available will switch from products with a two unit dose to a the single unit dose product because of the convenience and because ibuprofen is potentially safer than many of the other currently available non-prescription analgesics available through pharmacy.

- The single unit dose is preferred by healthcare professionals needing to manage medication compliance in patients on multiple medications and wider availability of a 400 mg single unit dose of ibuprofen will be of substantial benefit for this group.

- Advertising and promotion will be aimed at educating the consumer as to the availability of the single tablet dose product and to use medicines strictly according to the labelling and recognise the value of consulting a health care professional for advice where there may be some lingering doubt over the correctness of their choice.

PART A

1. International Non-proprietary Name

Ibuprofen 400 mg

2. Proprietary Name

To be advised

3. Name of Company requesting reclassification

Reckitt Benckiser New Zealand
289 Lincoln Rd
Henderson, Auckland

Note: in February 2006, Boots Healthcare and its various brands was acquired by Reckitt Benckiser. Boots will be referred to frequently during this application to place into context the historical background of ibuprofen.

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4. Dose form(s) and strength(s) for which change is sought

Ibuprofen 400mg single oral tablet

5. Pack size and other qualifications

This reclassification request is to permit 400 mg ibuprofen tablets in packs of 50 or less to become a Pharmacy Only Medicine when labelled with a recommended daily dose of not more than 1200 mg of ibuprofen.

6. Indications for which change is sought

The indications for use and dosage regimen proposed in this reclassification application for 400 mg ibuprofen are essentially identical to those for 200 mg non-prescription ibuprofen, with the only differentiating feature being that it provides for a single tablet dose rather than a two-tablet dose.

The indications for non-prescription ibuprofen are for the temporary relief of pain and/or inflammation associated with headache, migraine headache, back pain, period pain, tension headache, muscular pain, dental pain, cold and flu symptoms, arthritic pain and reduction of fever.

7. Present classification of medicine

Ibuprofen 400 mg is currently classified as a prescription medicine in New Zealand.

8. Classification sought

This application requests reclassification to Pharmacy Medicine status

9. Classification status in other countries

A similar reclassification application for 400 mg ibuprofen has been filed in Australia and will be considered by the Australian NDPSC at its February 2006 meeting.

The following table shows those countries where ibuprofen 400 mg preparations are already available without a prescription

Table 1

Territory	Status	Switch Date	Registration date
Belgium	OTC Pharmacy Behind Counter		5/11/1998
Czech Republic	OTC Pharmacy Behind Counter		19/5/1999
Estonia	OTC Pharmacy Behind Counter		13/8/2004
Germany	OTC Pharmacy Behind Counter	1989	16/6/1998
Hungary	OTC Pharmacy Behind Counter		12/3/1999
Israel	OTC Pharmacy in Front of Counter	1999	13/6/1997
Latvia	OTC Pharmacy in Front of Counter		24/10/2003
Luxembourg	OTC Pharmacy Behind Counter		30/9/1998
Netherlands	OTC Pharmacy Behind Counter		30/9/1998
Poland	OTC Pharmacy in Front of Counter		14/4/2000
Romania	OTC Pharmacy in Front of Counter		11/08/1998
Russian Federation	OTC Pharmacy in Front of Counter		25/11/2004
Slovakia	OTC Pharmacy in Front of Counter		1/11/1992
South Africa	OTC Pharmacy Behind Counter		27/9/1998
Spain	OTC Pharmacy Behind Counter	1986	23/10/1989
Thailand	OTC Pharmacy Behind Counter		15/12/1997
Ukraine	OTC Pharmacy Behind Counter		23/3/2004
United Kingdom	OTC Pharmacy in Front of Counter	1983	25/3/1985

The following European countries also have non-prescription status for the 400 mg product but Reckitt Benckiser (formerly Boots Healthcare

International) do not have a registered product in that country: Denmark (1989), Finland (1986), Italy (1984), Sweden (1988), Norway (1989), Switzerland (2003).

In May 2001, ibuprofen dosage forms of up to 400 mg when labelled with a maximum daily dose of 1200 mg were also re-classified to non-prescription status. Ibuprofen 400 mg products remain as prescription only in the United States of America. There is no “Pharmacy Only” or “Pharmacist Only” equivalent in the USA.

10. Extent of usage in NZ and elsewhere

Boots first introduced ibuprofen into New Zealand in 1975, and in Australia in 1979 under the brand name BRUFEN. It was available only on prescription and marketed in 400 mg and 200 mg strengths. Both 600 mg and 800 mg sustained release preparations were also subsequently marketed in New Zealand under the BRUFEN brand name.

In 1985, Boots switched the 200 mg strength to Pharmacy Only Medicine status and introduced this non-prescription version as NUROFEN. Progressive reclassification of ibuprofen has occurred after extensive experience and detailed and thorough regulatory review at each stage.

In 2004, following the 30th meeting, the NZ Medicines Classification Committee also approved the reclassification of ibuprofen 200 mg to be available for general sale when sold in packs of 25 tablets or less.

Throughout this 30-year period, BRUFEN has remained the brand name of the prescription product whilst NUROFEN has been the market-leading non-prescription brand.

In 1997, the ownership of the NUROFEN and BRUFEN brand names was transferred worldwide such that The Boots Company (and its subsidiary Boots Healthcare) has exclusive use of the Nurofen brand name and Knoll (now Abbott Australasia) has exclusive use of the Brufen brand name.

A search of the NZ Medsafe database suggests that the only ibuprofen 400 mg product currently available on the New Zealand market is the BRUFEN 400 mg product marketed by Abbott Laboratories (NZ) Ltd. This proposal is not expected to alter the classification of the BRUFEN product as it would require the relabelling of the product to provide for a maximum daily dose of 1200 mg.

In summary, ibuprofen has long history of use in New Zealand both as a prescription product and, since 1985, as a non-prescription product. Given the extensive experience of the non-prescription product as an analgesic for short term self-limiting conditions which are easily recognised by the consumer, and the excellent safety profile in doses of 1200 mg/day or less, ibuprofen 400 mg tablets with a daily dose limit of 1200 mg or less will provide the same safety and efficacy profile of other non-prescription ibuprofen products with the convenience of a single tablet dose.

There is substantial local experience with ibuprofen both in the prescription and non-prescription settings that can be relied upon in lieu of the specific experience. There is also international experience with ibuprofen in the prescription and non-prescription setting as well as experience specifically with the single unit dose of ibuprofen 400 mg.

All of the experience with ibuprofen renders it a safe and effective analgesic. It is ranked as the safest of the NSAIDs and is considered to have at least equivalent gastrointestinal tolerability as paracetamol and

better gastrointestinal tolerability than aspirin and other NSAIDs at non-prescription doses and usage patterns.

United Kingdom

Ibuprofen, originally synthesised and developed by The Boots Company nearly 50 years ago, was launched in the UK as a prescription medicine in 1969. Some 15 years later, in 1983, NUROFEN 200 mg and 400 mg tablets were both approved for non-prescription Pharmacy use with a maximum daily dose not exceeding 1200 mg. It should be noted there is no 'Pharmacist Only Medicine' equivalent in the UK. Reckitt Benckiser (formerly Boots) and numerous other ibuprofen manufacturers, continue to market 200 mg pack sizes up to and including 96 tablets.

In January 1996, ibuprofen 200 mg was further reclassified in the UK to general sale (GSL) status in packs of 12 tablets or less however this was subsequently increased to 16 tablets in line with other changes for paracetamol and aspirin.

Canada

In 1985 ibuprofen 200 mg per dosage unit was approved as a non-prescription medicine and since 1989 has been marketed by Wyeth as ADVIL. It is restricted to drug store outlets only. In May 2001, ibuprofen dosage forms of up to 400 mg when labelled with a maximum daily dose of 1200 mg were also re-classified to non-prescription.

United States of America

Ibuprofen was launched as a prescription product in the USA in 1974, and the FDA approved the switch to general sale in 1984. There is no

'Pharmacy' or 'Pharmacist Only Medicine' equivalent in the USA. Marketed as ADVIL by Wyeth Consumer Health, there is no pack size restriction on the 200 mg strength of ibuprofen when sold through general sale outlets in child resistant packaging.

Several prescription brands of ibuprofen continue to be marketed in the USA in higher strengths along with sustained release and combination products.

Ibuprofen 400 mg strength products remain as prescription only in the USA.

11. Labelling for the proposed new presentation

Label copy is to be finalised and is currently under regulatory review.

It should be noted that Reckitt Benckiser has undertaken market research on proposed labelling for 400 mg ibuprofen products. This market research has shown that consumers can clearly differentiate this product from existing 200 mg ibuprofen and understand that only one dosage unit (in comparison with up to 2 tablets for 200mg ibuprofen) should be taken each time.

12. Proposed warning statements

The warning statements required are:

Do not take
- if you have a stomach ulcer
- during the last 3 months of pregnancy
- if you are allergic to ibuprofen or other anti-inflammatory medicines

Unless a doctor has told you to, do not use:

- for more than a few days at a time, except with your doctor's advice
- if you are taking other medicines containing ibuprofen or other anti-inflammatory medicines
- if you suffer asthma
- if you are pregnant

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change

As the proposed change will only apply to 400 mg ibuprofen tablets in packs of 50 tablets when labelled with a maximum daily dose of 1200 mg it is not expected that this will affect any other product on the New Zealand market. Prescription ibuprofen products are indicated for more severe pain states. As mentioned previously the only other 400 mg ibuprofen product is marketed under the BRUFEN brandname which would require labelling changes and review of approved indications to permit OTC availability.

The approved indications for ibuprofen preparations that are available on prescription are rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, primary dysmenorrhoea, pyrexia and also for the relief of acute and/or chronic pain states in which there is an inflammatory component.

The recommended initial daily dose of prescription ibuprofen is 1200-1600 mg in three to four divided doses, with food or fluids. For acute exacerbations of rheumatoid arthritis and osteoarthritis in patients already on treatment with ibuprofen, a maximum daily dosage of 2400 mg may be prescribed, reverting to a maximum of 1600 mg daily once the patient is stabilised. In primary dysmenorrhoea, the initial dose is 400-800 mg at the first sign of pain or menstrual bleeding, then 400 mg 4-6 hourly with a maximum total daily dose of 1600 mg.

The proposal to reclassify ibuprofen 400 mg tablets to Pharmacy Only Medicine when labelled with a dose of 400 mg or less and a maximum daily dose of 1200 mg for non-prescription–type indications will not affect the current scheduling or availability of the prescription ibuprofen which is indicated for more severe pain states.

The non-prescription indications are for the temporary relief of pain and/or inflammation associated with headache, migraine headache, back pain, period pain, tension headache, muscular pain, dental pain, cold and flu symptoms, arthritic pain and reduction of fever. These indications will be the same for the 400 mg single dosage unit product.

PART B

The purpose of this application is to seek reclassification of divided doses of ibuprofen 400 mg from a Prescription Medicine to a Pharmacy Only Medicine classification, in preparations for oral use when labelled with a recommended single dose of 400 mg and a daily dose not exceeding 1200 mg of ibuprofen in packs of 50 or less dosage units.

The intention is to provide the consumer with a convenient, single dosage unit format such that there is the option to take the recommended non-prescription dose of 400 mg ibuprofen as a single dosage unit rather than the usual two x 200 mg dosage units.

Ibuprofen oral preparations are currently exempt from classification (unclassified), Pharmacy Only Medicine or Prescription Medicine classification, depending on the strength of the individual dosage unit, the total daily dose, and the pack size. This is because at lower daily doses (up to 1200 mg per day) ibuprofen is an established analgesic suitable for non-prescription use in mild to moderate pain and fever, whereas at higher doses (typically up to 1600-2400 mg per day) it is used as an anti-inflammatory for chronic arthropathies and other conditions under the care of a medical practitioner. The currently available non-prescription ibuprofen products are presented as oral solid dosage forms of 200 mg (with or without additional active ingredients) as well as oral liquid preparations and topical formulations.

This application is for the reclassification from Prescription to Pharmacy Only Medicine of ibuprofen 400 mg in divided preparations with a dose of 400 mg and a maximum daily dose of 1200 mg in packs of less than 50 dosage units. There are no changes proposed to the non-prescription indications, warning statements, or method of administration apart from a restriction on the age range for use in children due to the inflexibility of dosing children with a 400 mg dose unit. The oral liquid preparations and 200 mg solid preparations remain available

for children. The dosage instructions for 400 mg ibuprofen will be to take 1 tablet per dose with no more than 3 tablets to be taken in any 24-hour period.

The pharmacology of ibuprofen, including efficacy, pharmacokinetics etc is well established and summarised as Supporting Data.

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

The non-prescription availability of a 400 mg strength tablet through pharmacy outlets is expected to provide those consumers who prefer to only take one tablet with a convenient, easy to use single dose format.

Since 1996 more than 1 billion NUROFEN-branded 200 mg tablets per annum have been manufactured and delivered to the Reckitt Benckiser (formerly Boots Healthcare) market worldwide (excludes USA and Canada as Reckitt Benckiser does not market ibuprofen in these territories).

Over the annual period from October 2003 to September 2004, 139 million 400 mg ibuprofen tablets have been manufactured and delivered to the Reckitt Benckiser market worldwide. Over the same period 932 million NUROFEN-branded 200 mg tablets have been manufactured and delivered to the Reckitt Benckiser market worldwide.

Reckitt Benckiser will clearly differentiate the 400 mg ibuprofen tablet from the currently available 200 mg ibuprofen tablets. The request for a Pharmacy Medicine classification could be considered conservative given the GSL availability of 200 mg ibuprofen because, in theory, a 12 pack of the 400 mg contains the same quantity of ibuprofen as an uncalssified 24 pack of the 200 mg; however Reckitt Benckiser considers it is appropriate to ensure there is an opportunity for pharmacy advice and consumer education as to the availability of a single tablet dose.

With ibuprofen 200 mg products readily available through general sale outlets in packs of 25 or less, it is not expected that making 400 mg ibuprofen available through pharmacy outlets will cause any concern from a public health and safety perspective.

Equally there is no public health imperative for maintaining the current restriction on a 400 mg single dose unit.

A Pharmacy Only Medicine classification offers a conservative level of access to consumers such that the benefits are likely to outweigh any risks.

As has been highlighted previously, having 400 mg tablets available as a non-prescription medicine will not cause any increased risk factors nor will cause major complications in either intentional or unintentional overdose situations because the daily dose remains unchanged in the non-prescription setting and the maximum quantity of ibuprofen permitted per pack remains unchanged in the non-prescription setting.

Of note is that in overdose there are inevitable negative ramifications for all compounds. The successful treatment for ibuprofen overdose is primarily through supportive measures rather than the necessary administration of an antidote. Ibuprofen does not carry the same concerns as paracetamol of delayed hepatotoxicity that can be fatal.

The total amount of ibuprofen in a commercial pack of 400 mg x 50 tablets is 20 g, which is the same amount of active ingredient as is permissible in a pack of 100 tablets of 200 mg. This is the maximum pack size limit being requested.

Reckitt Benckiser is an ethical pharmaceutical company dedicated to responsible marketing under the highest code of ethics and standards. In every respect the Company adheres to and acts within the legislation for therapeutic goods, and the all relevant codes including those relating to advertising.

All advertising and promotion for non-prescription 400 mg ibuprofen will be conducted in accordance with the Advertising Standards Authority Codes, the Medicines Act 1981 and the Medicines Regulations 1984 and their respective amendments. A vital part of the marketing strategy for the proposed product is the education of consumers regarding the responsible use of analgesics and to motivate them to recognise the value of consulting a health care professional for advice where there was any doubt or concern regarding the correctness of their choice.

Reckitt Benckiser will continue its responsible education programme for healthcare professionals as well as its education programme for pharmacy assistants. In addition, the availability of a freephone telephone number on all 400 mg ibuprofen non-prescription packs will provide consumers and healthcare professionals with ready access to information. An in-house qualified pharmacist manages the freephone number.

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

The indications for use and dosage regimen proposed in this reclassification application for 400 mg ibuprofen are essentially identical to those for 200 mg non-prescription ibuprofen, with the only differentiating feature being that it provides for a single tablet dose rather than a two-tablet dose.

Non-prescription 400 mg ibuprofen 400 mg is indicated for temporary relief of pain and/or inflammation associated with headache, period pain, dental pain, migraine headache, tension headache, cold & flu symptoms, muscular pain, back pain, arthritic pain and for the reduction of fever. All of these pain symptoms are well characterised, usually of limited duration, and easily identified by a consumer who currently self-medicates with non-prescription analgesics.

The easily recognisable and short-term nature of the indications for use ensures that neither medical diagnosis nor ongoing medical management are required. The proposal for a Pharmacy Only Medicine classification for the ibuprofen 400 mg single tablet dose ensures that professional advice is available at the point of purchase.

There is a low risk of masking serious disease, largely due to the easily recognised conditions for which non-prescription ibuprofen is indicated and to the short-term duration of use. The labelling directs consumers to seek medical advice is symptoms continue.

Simple analgesics have a long history of non-prescription use without medical supervision. Labelling and advertising clearly indicates that simple analgesic products are for short-term use unless recommended by their doctor. As such we believe that consumers understand that prolonged pain is a sign of something more serious and are able to adequately judge this and therefore seek appropriate medical treatment.

The proposed pack sizes of 50 tablets or less and the controlled availability through pharmacies, provide for a maximum of 16 days treatment however the labelling clearly states that the product should not be taken for more than 3 days at a time except with a doctor’s advice. The packaging clearly indicates that the product is indicated for the

temporary relief of pain and/or inflammatory associated a number of easily recognised conditions such as headache, back pain, period pain, dental pain etc.

There is a low risk of compromising the medical management of a disease because of the excellent safety profile, rare and well-defined drug interactions and short-term usage pattern.

3. Relevant comparative data for like compounds (Refer also to point 8, this section)

A range of paracetamol 500 mg products as well as aspirin containing products are readily available through general retail and pharmacy outlets. These 'simple' analgesics are available for the same range of non-prescription indications, including pain, fever, migraine headache, period pain etc as approved for ibuprofen.

Paracetamol and aspirin in packs larger than 20 tablets are available as Pharmacy Only products. In addition to aspirin and paracetamol, naproxen sodium, diclofenac and mefenamic acid are also available for non-prescription use through pharmacy outlets.

Naproxen sodium is primarily used for the treatment of dysmenorrhoea, or other non-prescription conditions such as headache, backache, etc. and is permitted as Pharmacy Only in solid dose forms containing 250 mg or less in packs up to 30 tablets or capsules.

Diclofenac preparations are also used for the same indications as ibuprofen, with 12.5 mg dose units in packs of 20 tablets being Pharmacy Only and diclofenac 25 mg dose units in packs of 30 tablets Pharmacist Only.

Mefenamic acid in packs of 30 tablets is available as Pharmacy Only medicines primarily for the treatment of dysmenorrhoea.

Ibuprofen is a substance that has been approved for broader distribution through general sale outlets as it is potentially preferred over other available substances, its clinically proven effectiveness as an anti-inflammatory, analgesic, antipyretic agent for self-limiting conditions and its high margin of safety in overdose situations. The availability of a 400 mg tablet will provide consumers with a convenient single dosing format, with the recommended dose being one 400 mg dosage unit rather than up to two 200 mg dosage units, as per current non-prescription solid dose preparations containing 200 mg ibuprofen.

The presentation of 400 mg ibuprofen will be clearly differentiated from current 200 mg ibuprofen solid dose preparations, having noticeably distinctive product name and pack graphics. All required Pharmacy only warnings and cautionary statements for ibuprofen will be included on the back of pack copy, and the consumer's attention will be drawn to the fact that only 1 tablet or capsule is taken at a time. The added advantage of having ibuprofen 400 mg available as a Pharmacy Only Medicine preparation will provide an additional buffer and access to pharmacy advice regarding dosage.

4. Local data or special considerations relating to NZ

It is not expected there would be any special considerations relating to NZ for this change.

5. Interactions with other medicines

Most clinically significant NSAID drug interactions result from the ability of NSAIDs to inhibit cyclooxygenase, thereby reducing prostaglandin biosynthesis. Some NSAID drug interactions result from the fact NSAIDs are highly bound to plasma proteins and therefore may compete with other drugs for binding sites.

The combined use of ACE inhibitors, diuretics and NSAIDs, termed the "triple whammy" effect, is implicated in a significant number of reports to regulatory authorities of drug-induced renal failure. Following the exemption from scheduling of ibuprofen 200 mg in small pack sizes in Australia and New Zealand, there was much sensationalist media coverage about risks of the “triple whammy” in patients purchasing ibuprofen without healthcare professional advice.

The ADRAC (Adverse Drug Reactions Advisory Committee, Australia) Bulletin of August 2003 reminded prescribers that the combination of ACE-inhibitors, diuretics and NSAIDs (including COX-2 inhibitors) should be avoided if possible and care should be taken with the combination of ACE inhibitors and NSAIDs in patients with renal impairment. Non-prescription ibuprofen used in doses up to 1200 mg per day for the short-term relief of mild to moderate pain and fever has an extremely low risk of causing serious renal adverse effects. When these adverse effects do occur, they are almost exclusively in patients with pre-disposing risk factors, such as existing renal disease, moderate to severe volume depletion, diuretic therapy or heart failure.[1] [2] [3]

[1] Mann et al, Clin Neph 1993; 39(1):1-6
[2] Whelton A. J Clin Pharmacol 1995: 35: 454-463
[3] Derby et al. Pharmacotherapy 1991: 11(6): 467-471

In 1992, a study was carried out in elderly patients with mild thiazide-treated hypertension and renal impairment. These patients were treated with ibuprofen 400 mg three times a day for seven days and there was no evidence of worsened renal function or blood pressure control [4].

No unexpected drug interactions have been reported to the company for the Nurofen range to date. Interactions are unlikely to occur with short-term use of ibuprofen at a dose of 1200 mg/day and other commonly used non-prescription medicines, although interactions can be seen with chronic use of ibuprofen at higher dosages, particularly with prescribed medicines such as lithium, methotrexate, anticoagulants and a combination of ACE inhibitors and diuretics. However these are prescribed medicines and, as such, would have healthcare professional management and intervention. In such circumstances, the prescribing doctor would be in a position to assess the risk benefit to the patient of combining ibuprofen and other medications.

In addition, the labelling for non-prescription 400 mg ibuprofen clearly indicates that a consumer should check with their doctor or pharmacist before use if they are receiving regular treatment with other medications and should not take if they have a stomach ulcer, other stomach disorders, kidney, or heart problems.

6. Contraindications

There are few contraindications to the use of ibuprofen and the labelling clearly provides cautionary advice. Consumers are advised to seek medical advice before use if they are asthmatic or taking other preparations containing ibuprofen, aspirin or other anti-inflammatory medicines. In addition, medical advice is also recommended if the consumer consumes other medication regularly or if they are aged over 65 years.

[4] Henry D et al, BMJ 1996; 312 (7046) 1563-6

Consumers are advised not to take non-prescription 400 mg ibuprofen if they have a stomach ulcer or other stomach disorders, kidney or heart problems; suffer allergic reactions to aspirin, ibuprofen or other anti-inflammatory medicines or during pregnancy. Further information is provided below :

6.1 Use in Pregnancy and Lactation

Along with other NSAID preparations, ibuprofen is classified as a Category C drug with regard to use in pregnancy. This category relates to drugs, which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible.

Nonsteroidal anti-inflammatory drugs inhibit prostaglandin synthesis as a class. As the influence of prostaglandin synthesis inhibition is unclear specifically for ibuprofen, it is recommended not to use ibuprofen during the first six months of pregnancy unless under strict medical supervision.

Ibuprofen is contraindicated in the last three months of pregnancy due to the mechanism of action inhibition of uterine contractions, premature closure of ductus arteriosus and pulmonary hypertension of the neonate, an increased bleeding tendency in the mother and child and increased formation of oedema in the mother could occur.

In limited studies, ibuprofen appears in breast milk in very low (0.0008%) concentrations and is unlikely to affect the breast fed infant adversely. It is unnecessary to interrupt breast-feeding for short-term treatment with the recommended maternal dose for mild to moderate pain and fever. Ibuprofen suspension is used widely

in children down to 6 months of age without adverse consequences; therefore the minute amount present in breast milk during short-term use by the mother should not cause any problems.

6.2 Respiratory effects, including use in asthmatic patients

There is a widespread misconception amongst many healthcare professionals which suggests that all asthmatics should avoid NSAIDs. Bodies such as the National Asthma Council of Australia accept that aspirin sensitivity only affects approximately 10-12% of all asthmatics[5].

Aspirin-induced asthma is a distinct clinical entity and appears to be a specific subtype of asthma. It is characterised by asthma a triggered within 1-3 hours of ingestion of aspirin or other NSAIDs. The asthma attack is often accompanied by symptoms of rhinitis and facial flushing.

It is a published fact that between 8% and 25% of aspirin sensitive people can also exhibit cross-sensitivity to paracetamol at doses of more than 1000 mg. While the effects appear to be dose dependent, the reactions also occur later than those due to aspirin or NSAIDs and are of less intensity. A 2000 survey in the UK suggested that frequent paracetamol use may also contribute to asthma morbidity in adults [6] although the study wasn't specifically designed to establish a causal relationship.

A review article published in 2001[7] entitled *"The Use of Analgesics in Patients with Asthma"* recommends that asthmatics who are

[5] Vally H et al, Thorax 2002; 57: 569-574
[6] Shaheen SO et al, Thorax 2000; 55: 266-70
[7] Levy S at Volans G: Drug Safety 2001: 24(11): 829-841

known to be intolerant of NSAIDs or who exhibit any of the high risk clinical features for intolerance to such drugs (severe asthma, nasal polyps or chronic rhinosinusitis) should use NSAIDs under close medical supervision. The article suggests that while routine warnings about paracetamol use in asthma are not warranted, healthcare professionals should be aware of the potential for worsening of asthma symptoms in some individuals when using paracetamol.

The results of a further systematic review on the prevalence of aspirin induced asthma and its implications for clinical practice were published in the BMJ in 2004[8]. In this review the incidence of aspirin-induced asthma on oral provocation testing was determined at 21% and not the 10% as previously thought, however the clinical relevance of this was not explained in the paper. Following publication of the article, considerable comment appeared in the BMJ with one[9] pointing out the many methodological flaws and errors that questioned the validity of the research. In particular it was pointed out that the prevalence of 21% was derived from only 5 studies, 2 of which related to the same patients and one that was an abstract. The authors of the critique provided comment on three other population based studies that showed a prevalence of 'doctor-diagnosed' aspirin-induced asthma to be between 4.3% and 10.9% depending on the methodology and the reference and not as high as the 21% quoted in the Jenkins paper. It was also noted that the studies included in the review were skewed towards the subjects recruited from hospital allergy clinics who are likely to not have been representative of the general community asthmatic population.

[8] Jenkins C et al. BMJ 2004; 328, 434-40
[9] Thien F et al, BMJ 2004 March

Bronchospasm in children with asthma has been associated with paracetamol doses greater than 1500 mg per day and the cross-reactivity of aspirin induced asthma in children can be as much as 30%.

As a general rule, ibuprofen should be avoided in all asthmatics that are sensitive to aspirin or other NSAIDs but need not be withheld from those asthmatics who have previously been shown to tolerate aspirin or other NSAIDs. Proposed labelling for non-prescription 400 mg ibuprofen contains a cautionary statement directing the patient to check with their healthcare professional if they are asthmatic.

6.3 Cardiovascular issues

In early 2005, following the withdrawal of Vioxx and Bextra, the US FDA reviewed all COX-2 selective and other NSAID medications to determine with there was any increased cardiovascular risk and whether the labelling for these medicines required further advice and strengthening.

In June 2005, the FDA advised that patient information distributed with non-prescription NSAIDs should state that taking an NSAID for longer than 10 days or at more than the recommended dose may increase the risk of heart attack or stroke.

However the FDA also confirmed that official advice acknowledged that –

- There was no evidence that NSAIDs taken at non-prescription doses and durations increase the risk of heart attack or stroke

- It was unclear how evidence from long-term clinical trials of high doses of prescribed NSAIDs could be applied to the short-term low-dose use typical of non-prescription NSAIDs to treat acute pain; and
- The cardiovascular risk associated with short-term intermittent use of low doses of NSAIDs is very small, if any, in the absence of a predisposing condition (e.g. coronary heart disease).

Similarly, following the market withdrawal of the COX-2 products and potential concerns that the increased risk of myocardial infarction (MI) and stroke identified with selective COX-2 inhibitors may also apply to non-selective nonsteroidal anti-inflammatory drugs (NSAIDs), the UK Committee on Safety of Medicines (CSM) reviewed all the available safety data relating to non-selective NSAIDs, including ibuprofen, diclofenac and naproxen. The CSM concluded that the evidence reviewed was insufficient to change the balance of risks and benefits of NSAIDs, and no changes to current prescribing practice was recommended on the basis of current evidence on thrombotic risk.

In relation to non-prescription ibuprofen (i.e. 1200 mg/day) the CSM specifically concluded that at the doses in OTC medicines, ibuprofen has an excellent safety record, particularly in respect of gastrointestinal adverse effects. Whilst evidence relating to any cardiovascular risk associated with prolonged treatment and high doses of ibuprofen is not entirely clear, short-term use at the doses that can be bought over the counter is unlikely to be associated with any measurable increased risk.

The European Medicines Agency (EMEA) reached a similar conclusion and recommended no change to advice already

provided to patients and prescribers and reinforced that prescribing should be based on overall safety profiles of non-selective NSAIDs (i.e. gastrointestinal concerns) and individual risk factors.

The Australian TGA is also carrying out its own review of information on non-selective NSAIDs and at the time of submitting this application, is still reviewing the data. It is anticipated that the outcome of their review will be considered by the ADEC and the MEC during 2006. It is the understanding of Reckitt Benckiser that, at this stage, Medsafe has no immediate plans to conduct a similar review, but will carefully consider the outcome of the TGA review. Given the outcomes from the US FDA, the UK and the European authorities relating to non-prescription ibuprofen it is not expected that the TGA's review will reach a different conclusion viz: that intermittent short-term use of non-prescription ibuprofen is unlikely to be associated with any increased cardiovascular risk.

Reckitt Benckiser (formerly Boots Healthcare Australia) has undertaken a full review of the literature in preparing its submission to the TGA review of the safety of NSAIDs and has drawn the same conclusions as the UK CSM.

A number of research papers have been published regarding the effects on patients with heart disease when taking ibuprofen at the same time as daily aspirin to avoid a second heart attack. A 2003 paper published in the Lancet[10] reported that patients under medical treatment with aspirin following a heart attack should avoid taking ibuprofen at the same time. The authors suggest that, "although our findings are not conclusive, they lend support to the hypothesis that treatment with a combination of ibuprofen and

[10] Macdonald TM &Wei L, Lancet 2003; 361: 563-4

aspirin given for secondary prevention may be deleterious, possibly by antagonising the cardioprotective effects of aspirin in patients with established cardiovascular disease".

This study evaluated the relationship between low dose aspirin and ibuprofen taken on prescription for long periods of time at higher doses than are recommended for over-the-counter use. All the patients studied had been admitted to hospital as a result of serious cardiovascular disease. The study shows no evidence that occasionally taking ibuprofen, as directed for 'over the counter' use, has any effect on the cardioprotective effects of aspirin.

Previous studies have reached different conclusions. In fact, they have shown either a beneficial effect[11] [12]or no effect[13] on heart disease when taking ibuprofen at the same time as daily aspirin to avoid a second heart attack.

The effect on platelets is the property used when aspirin is administered after a heart attack or stroke. Ibuprofen has been used for over forty years and is relied on by millions of people worldwide every day as a highly effective pain reliever. Both ibuprofen and aspirin are classified as non-steroidal anti-inflammatory drugs (NSAIDs) and patients should seek advice from their doctor before taking more than one NSAID at a time.

The proposed labelling for non-prescription 400 mg ibuprofen clearly states, "**Before use – if you are receiving regular treatment with other medications, check with your pharmacist or doctor."** The labelling further advises that non-prescription

[11] Garcia Rodriguez LA et al, Epidemiology 2000;11(4) 382-387
[12] Hudson M et al, Am J College of Rheumat Ann Scientific Meeting 2002
[13] Patel K & Goldberg K, Am Heart Assoc Scientific Meeting, 2002

ibuprofen should not be taken for more than 3 days at a time except on doctor's advice.

6.4 Impaired renal function

Ibuprofen has not been shown to have any significant effects on the renal system at the low doses (up to 1200 mg/day) used for short-term treatment. Renal impairment has been reported at doses greater than 1600 mg/day, generally in the presence of other factors that increase the risk such as heart failure, kidney disease, dehydration or advanced age.

Epidemiological studies suggest that the incidence of renal failure occurring in people taking low-dose ibuprofen (up to 1200 mg/day) is 0.007%. This favourable safety profile can be explained by several factors - ibuprofen is quickly metabolised, so it does not build up in the body; and otherwise healthy people use over-the-counter ibuprofen products in low doses for short-term treatment.

Murray et al [14] investigated the incidence of ibuprofen-associated renal impairment and risk factors for its development in a large number of patients prescribed NSAIDs. Predictors of risk were believed to be age, prior renal insufficiency, coronary artery disease, male gender, elevated systolic blood pressure and diuretic use. While the results suggested that ibuprofen was not among the independent predictors of risk, two subsets of 'at risk' patients were identified. The results suggest that elderly patients and patients with coronary artery disease are potentially at risk for ibuprofen-associated renal impairment and these patients should

[14] Murray MD & Brater DC, IN: Rainsford KD ed. Ibuprofen: A critical bibliographic review 1999,459

have regular renal function monitoring carried out when NSAIDs are prescribed.

However, it is not expected that intermittent short-term use of low dose ibuprofen would cause problems in these patients and in any event, the labelling warning statements advise that if patients are receiving regular treatment with other medications they should check with their doctor or pharmacist.

6.5 Use in Children

It should be emphasised that this application does not seek to change the classification of ibuprofen for use in children under 7 years nor for any liquid preparation, however, in view of the higher unit dose, it is proposed that labelling for non-prescription 400 mg ibuprofen will contain a warning statement not to give the tablets to children under 12 years.

There is no indication that children are more at risk from ibuprofen products than adults as ibuprofen is absorbed and metabolised in a similar manner by subjects from 3 months or older[15].

Some studies in the literature have suggested an association might exist between NSAIDs and serious bacterial infections such as necrotising fasciitis. Systematic searches of the worldwide literature have been carried out which identified several case control studies [16] [17] [18] and a retrospective study [19]. The results of the search identified there is no clinical evidence of a causal link

[15] Brown RD et al, 1992 J Clin Pharmacol 32: 231-41
[16] Brogan TV et al. Pediatr Infect Dis J 1995; 588-594.
[17] Choo-P-W et al Ann Epidemiol 1997; 7(7): 440-445.
[18] Kahn L.H, Styrt B A. The Annals of Pharmacotherapy 1997; 31:1034-1039.
[19] Marie-Cardine A et al. Arch Pediatr 2001;8: 1325-1332

between ibuprofen and necrotizing fasciitis. The usage of ibuprofen is common, whilst necrotising fasciitis is very rare, thus any association is likely to be chance rather than causal effect. In fact one of the responses to the symptoms is to give an effective analgesic/anti-inflammatory/antipyretic drug.

The Food and Drug Administration (FDA), the Regulatory Authority in the United States have also discussed this issue previously. The FDA tracks the safety of all drugs on an ongoing basis. In 1995, the FDA issued a clear statement, after considering all the available data, concluding that no association has been demonstrated between the use of ibuprofen and necrotising fasciitis.

6.6 Use in the Elderly

The labeling for all non-prescription ibuprofen preparations advise that patients aged 65 years or over should check with their doctor before using such products.

A number of pharmacokinetic studies have been conducted with ibuprofen in the elderly. The majority have been published in the literature during the period 1984 to 1995. A thorough review of the data has been performed by Davies (1998)[20] and his conclusions are also supported by Brocks *et al* (1999).[21] The studies were mainly conducted in healthy volunteers or rheumatoid arthritis patients investigating racemic ibuprofen. However, the conclusions drawn are that age has little or minimal influence on the pharmacokinetics of ibuprofen and that repeated administration of ibuprofen does not result in drug accumulation.

[20] Davies NM.. The first thirty years. Clin Pharmacokinet 1998; 34(2): 101-154
[21] Brocks DR, Jamali F.n: Rainsford KD ed. Ibuprofen A Critical Bibliographic Review. Taylor and Francis Ltd 1999; 124

Although caution should be exercised with the use of all NSAIDs in the elderly because of the potential for increased adverse reactions, it can be concluded that ibuprofen is absorbed and metabolised in a similar manner by subjects of all ages, and no dose reduction is required in the elderly. However where the elderly patients are also suffering from renal, hepatic or cardiac impairment ibuprofen should be taken with caution, and only under medical supervision.

Ibuprofen is equally well tolerated in old and young patients alike. The reason for the reported increased morbidity in elderly patients is that elderly patients tend to have other illnesses such as cardiac and renal impairment. They also tend to take regular prescribed medication. It is the concurrent illnesses and medication that increase their risk of AEs. As stated previously, there are already adequate warnings on the labeling relative to patients aged 65 or over and to remind consumers not to take the product if they have renal, cardiac, hepatic impairment or bronchospasm, if they are taking other medications including NSAIDs, as well as patients with stomach ulcers.

The labeling for 400 mg non-prescription ibuprofen , as for all non-prescription ibuprofen preparations states that the consumer should seek medical advice if they are taking regular medication or are aged 65 or over.

6.7 Use in other patient groups

Caution is required in patients with existing autoimmune disorders (such as systemic lupus erythematosus, mixed connective tissue disease) as during treatment with ibuprofen single cases of

symptoms of aseptic meningitis such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed.

7. Possible resistance

It is not expected that short term use of ibuprofen will cause any resistance to develop.

8. Adverse events – nature frequency etc.

Substantial evidence exists from very large case controlled studies to demonstrate the low risk in the more widespread use of ibuprofen for self-medication in approved indications.[22] [23] [24] [25] [26] Much of this data has previously been reviewed by the MCC and demonstrates that at doses used for self-medication (i.e. 1200 mg/day), ibuprofen should not be considered as just another NSAID but rather a safe, proven analgesic which is internationally acknowledged for self-medication.

Notwithstanding the above, a common concern with NSAIDs is gastro-toxicity which has been shown substance, dose and duration of use dependent. Case-control studies have shown an increased risk of GI bleeding even with low dose aspirin, whereas all doses ibuprofen seem to have a lower risk of gastro-toxicity than other NSAIDs at equivalent therapeutic doses.[27] In some studies low doses of ibuprofen have been shown to have a GI toxicity risk that is similar to or less than placebo or paracetamol.

[22] Moore N et al, Clin Drug Invest 1999: 18(2): 89-98
[23] Fries JF & Bruce B. J Rheumatol 2003; 30:2226-33
[24] Rainsford KD et al, J Pharm Pharmacol 1997; 49(4):345-76
[25] Lesko et al, JAMA 1995; 272(12): 929-33
[26] Cooper SA, Am J Med 1984; 77(1A): 70-77
[27] Furey SA, Pharmacotherapy 1992; 12(5): 403-7

In terms of the important safety issue of the potential for gastrointestinal (GI) toxicity (including bleeding and perforation) with prescription NSAIDs, differences appear to exist between individual agents. It is possible to rank the relative risks of GI toxicity among NSAIDs.[4]

Compound	Rank by relative risk
Ibuprofen	1
Diclofenac	2
Diflunisal	3
Fenoprofen	4
Aspirin	5
Sulindac	6
Naproxen	7
Indomethacin	8
Piroxicam	9
Ketoprofen	10
Tolmetin	11
Azapropazone	12

Although this data cannot be directly correlated with non-prescription use (i.e. <7 days) and adherence to maximum non-prescription dosage guidelines, ibuprofen demonstrates the lowest relative risk of GI toxicity with aspirin and naproxen having intermediate positions.

A large multicentre tolerability study [23] in more than 8,600 adults compared aspirin (up to 3 g per day) with paracetamol (up to 3 g per day) and ibuprofen (up to 1200 mg per day) in common painful conditions such as musculoskeletal and back pain, and symptoms associated with sore throat, the common cold and flu. The results showed that the overall tolerability of ibuprofen was equivalent to paracetamol and better than that of aspirin. Rates of significant adverse events were: aspirin 18.7%,

ibuprofen 13.7% and paracetamol 14.5%. Total gastrointestinal effects (including dyspepsia), which might be expected to be greater for the two NSAIDs, were less frequent for ibuprofen (4%) than for paracetamol (5.3%) or aspirin (7.1%). In this study there were six cases of non-serious gastrointestinal bleeding, four with paracetamol and two with aspirin, and one case of peptic ulcer with aspirin.

A further study[24] in patients with osteoarthritis or rheumatoid arthritis considered the prevalence of serious GI events in patients taking aspirin, paracetamol or ibuprofen, with particular focus on low or intermittent use. Some 5692 patients with RA and 3124 patients with OA with more than 36,000 patient-years of observation who had taken one of the three study analgesics were studied from 12 databank centres to examine the frequency of serious GI events requiring hospitalisation. The results from this prospective observational study showed that much of the associated toxicity of the three analgesics was related to use of the particular analgesic with other concurrent drug use, and when concurrent drug use was excluded, rates of serious GI events were low and statistically indistinguishable, particularly in low risk patients. It was noted that when taken concurrently with corticosteroids or other NSAIDs, risks for paracetamol were the highest for all three study drugs in both RA and OA although numbers were relatively small. Conclusions from this study supported the PAIN study in that non-prescription use of aspirin, ibuprofen or paracetamol carries little risk of serious GI toxicity for most patients.

These data support the view that the incidence of adverse effects, and in particular gastrointestinal adverse effects, is not expected to be any worse than that of paracetamol and considerably better than aspirin. Therefore, at low doses used for short periods of time for self-limiting common conditions, unexpected or serious side effects would be extremely unlikely.

A study published in 2000[28] acknowledged that the relative risk of non-prescription doses of NSAIDs (i.e. not non-prescription usage) is less than the published risk of prescription doses, yet there is still a clinical concern due to the widespread use of such medications when self-selected. The database from which the information was gathered was a prospective observational non-interventional cohort study. The study is considered to be a biased study of poor design based on information from predominantly older, mostly female, patients who were being treated for rheumatoid arthritis. Many of the patients were taking non-prescription NSAID products for long periods of time for their rheumatoid arthritis. The study was a non-randomised study and patients were allocated to one of five treatments on the basis of their condition. The authors concluded that their work warranted further investigation to determine the level of risk.

Data are presented on the Adverse Drug Reaction (ADR) reports for all strengths of ibuprofen available from the Reckitt Benckiser parent company as well as those on ibuprofen available from the ADRAC database is provided as Supporting Data. For comparison, the Australian Adverse Drug Reactions Advisory Committee (ADRAC) reports for aspirin, paracetamol, naproxen and diclofenac products have also been included. Information from the CARM database will be requested.

9. Potential for abuse or misuse

There is no evidence of abuse potential with ibuprofen and the compound is not a candidate for diversion for illicit or recreational use.

As has been highlighted previously, having 400 mg tablets available as a non-prescription medicine will not cause any increased risk factors nor will

[28] Singh G, Am J Therapeutics 2000, 7; 115-121

cause major complications in either intentional or unintentional overdose situations because the daily dose remains unchanged in the non-prescription setting and the maximum quantity of ibuprofen permitted per pack remains unchanged in the non-prescription setting.

Of note is that in overdose there are inevitable negative ramifications for all compounds. The successful treatment for ibuprofen overdose is primarily through supportive measures rather than the necessary administration of an antidote. Ibuprofen does not carry the same concerns as paracetamol of delayed hepatotoxicity that can be fatal.

Extensive use of ibuprofen internationally from 1969 has shown that it possesses a wide margin of safety and low toxicity following overdose. There is no defined toxic dose of ibuprofen on a mg/kg basis and there have been well documented reports of overdose in children and adults with survival after supportive measures with no lasting negative effects.

One such publication reports a dose in excess of 100 g of ibuprofen being ingested by a teenage girl attempting suicide.[29] The patient developed coma, metabolic acidosis and mild thrombocytopenia but improved rapidly with supportive care. Renal function remained normal and no gastrointestinal bleeding occurred.

In contrast, a comparison of the potentially lethal doses of aspirin, paracetamol and ibuprofen shows that even relatively small numbers of doses can result in serious problems, particularly delayed hepatotoxicity in the case of paracetamol where prompt medical intervention does not occur. Ibuprofen arguably offers the best combination of safety and efficacy among the analgesics that are available both with and without a prescription.

[29] Seifert SA et al, Toxicol Clin Toixicol 2000; 38(1): 55-7

Table 2 - Comparison of potentially lethal doses of paracetamol, aspirin and ibuprofen

COMPOUND	RECOMMENDED SINGLE DOSE	ESTIMATED LETHAL DOSE	NUMBER TABLETS LETHAL DOSE
Paracetamol	2 x 500 mg	13 g	26
Aspirin	2 x 300 mg	30 g	100
Ibuprofen	1 x 400 mg or 2 x 200 mg	> 40 g	> 100

It can be concluded therefore that massive ingestion of ibuprofen may result in some elements of toxicity but supportive care usually results in survival without sequelae. Management of aspirin overdose usually requires measures that prevent the absorption of salicylate from the GI tract. Paracetamol overdose rarely results in fatality as management with an effective antidote (*N-acetylcysteine)* often takes place. However, because of the potential for delayed fatal hepatic necrosis, intentional or unintentional overdose can create a major medical emergency.

The presentation of non-prescription 400 mg ibuprofen tablets will be clearly differentiated from current non-prescription ibuprofen 200 mg solid dose preparations, having noticeably distinctive product name and pack graphics as well as distinct and relevant markings on the unit dose. All required warnings and cautionary statements for ibuprofen will be included on the back label of the packaging, and the consumer's attention will be drawn to the fact that only 1 tablet or capsule is to be taken at a time.

In the event that consumers inadvertently take 2 x 400 mg tablets instead of 1 tablet and take these for a day or more, this only equates to 2.4 g per day which is the maximum prescription dose recommended for acute exacerbations of arthritic conditions. In the USA the maximum

prescription dose is 3.6 g/day. Therefore an inadvertent dose of 2.4g/day is not considered to produce clinically harmful effects, particularly since the usage pattern is likely to remain short term as instructed on the labelling.

It is in Reckitt Benckiser's interest to clearly differentiate the proposed non-prescription 400 mg ibuprofen product from existing 200 mg products for both commercial and safety reasons.

10. CONCLUSIONS

The objective of this application is to provide the consumer with the convenience of a single tablet dose of a well-known safe and effective non-prescription medicine with both analgesic and antiinflammatory properties.

- Ibuprofen 400 mg presented as described in this application meets the profile of a medicine suitable for self-selection. It will not cause untoward problems when taken according to the labelling and nor will it cause major complications in overdose situations.

- The presentation of ibuprofen 400 mg as described in this application is the same as for ibuprofen 200 mg except that it is a single tablet dose and the use in children less than 12 years of age is not provided for.

- It is not expected that broader distribution of non-prescription 400 mg ibuprofen tablets will increase the size of the analgesic market. Rather, it is expected people will switch from other products to one which provides convenience.

- Advertising and promotion will be aimed at educating the consumer to use medicines strictly according to the labelling instructions and to recognise the value of consulting a health care professional for advice where there may be some lingering doubt over the correctness of their choice.

- Consumers are entitled optimal medication at appropriate levels of access for the treatment of self-limiting conditions. There is no public health reason why ibuprofen 400 mg in packs of 50 tablets or less should not be available without a prescription through pharmacy.

BIBLIOGRAPHY

1. Mann et al, Clin Neph 1993; 39(1):1-6
2. Whelton A. J Clin Pharmacol 1995: 35: 454-463
3. Derby et al. Pharmacotherapy 1991: 11(6): 467-47
4. Henry D et al. BMJ 1996; 312(7046): 1563-6
5. Vally H et al, Thorax 2002; 57: 569-574
6. Shaheen SO et al, Thorax 2000; 55: 266-70
7. Levy S at Volans G: Drug Safety 2001: 24(11): 829-841
8. Jenkins C et al. BMJ 2004; 328, 434-40
9. Thien F et al, BMJ 2004 March
10. Macdonald TM & Wei L, Lancet 2003; 361: 563-4
11. Garcia Rodriguez LA et al, Epidemiology 2000;11(4) 382-387
12. Hudson M et al, Abstract Am J College of Rheumat Ann Scientific Meeting 2002
13. Patel K & Goldberg K, Abstract, Amer Heart Assoc Scientific Meeting, 2002
14. Murray MD & Brater DC, IN: Rainsford KD ed. A critical Bibliographic Review. Taylor and Francis Ltd, 1999, 460
15. Brown RD et al, J Clin Pharmacol 1992; 32: 231-41
16. Brogan TV et al. Pediatr Infect Dis J 1995; 588-594.
17. Choo P-W et al Ann-Epidemiol 1997; 7(7): 440-445.
18. Kahn H, Styrt B A. , Annals of Pharmacotherapy 1997; 31:1034-1039.
19. Marie-Cardine A et al. Arch Pediatr 2001;8: 1325-1332
20. Davies NM.. Clin Pharmacokinet 1998; 34(2): 101-154
21. Brocks DR, Jamali F. IN Rainsford KD ed. Ibuprofen A Critical Bibliographic Review. Taylor and Francis Ltd 1999; 124
22. Moore N et al; Clin Drug Invest 1999: 18(2): 89-98
23. Fries JF and Bruce B. J Rheumatol 2003; 30: 2226-33
24. Rainsford KD et al, J Pharm Pharmacol 1997; 49(4): 345-76
25. Lesko S et al, JAMA 1995; 272(12): 929-33
26. Cooper SA, Am J Med 1984; 77(1A): 70-77
27. Furey SA, Pharmacotherapy 1992 12(5): 403-407
28. Singh G, Am J Therapeutics 2000, 7; 115-121
29. Seifert SA et al, J Toxicol Clin Toxicol 2000; 38(1): 55-7
30. Nebe J et al Cephalagia 1995; 15:531-535,

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31. Broome et al, Aviat Space Environ Med 1994; 65: 19-20
32. Schachtel BP et al, J Clin Pharmacol, 1996; 36(12): 1120-5,
33. Morrison JC e et al Southern Med J 1980; 73(8): 999-1002
34. Zhang WY & Li Wan Po A, Br J Obstetrics & Gynaecol 1998; 105: 780-789
35. Rondeau PL et al J Canad Dent Assn; 1980; 7: 433-439
36. Planas et al Eur J Clin Pharmacol 1998; 53(6) 405-409
37. Cooper SA et al J Oral Surg 1977; 35: 898-903
38. Muckle DS, Rheumatol and Rehabil, 1974; 13 (141): 229-235
39. Welker Y et al, Med Mal Infect 1998; 28:1-6
40. Kelley MT et al, Clin. Pharmacol. Ther. 1992; 52: 181-189