APPLICATION TO THE MEDICINES CLASSIFICATION COMMITTEE FOR RECLASSIFICATION OF A MEDICINE

PROPOSAL FOR RECLASSIFICATION OF IBUPROFEN 200 MG IN LIMITED PACK SIZES TO AN UNSCHEDULED MEDICINE

30 July 2003

Submitted by:

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Commercial-in-Confidence

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BOOTS HEALTHCARE NEW ZEALAND LTD

JULY 2003

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DETAILS OF COMPANY MAKING APPLICATION

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SPONSOR DECLARATION

I, Sanyogita (Sanya) Ram, declare that to the best of my knowledge, all information relevant to this application is included and is true and accurate.

…….
Sanyogita (Sanya) Ram 30 July 2003

1. EXECUTIVE SUMMARY

1.1 Purpose of the Application

The purpose of this application is to seek approval for the exemption from scheduling of ibuprofen 200 mg (single active, divided preparations) in preparations for oral use when labelled with a recommended daily dose of not more than 1200 mg of ibuprofen in packs of 25 or less dosage units.

It is proposed that divided preparations containing up to 200 mg of ibuprofen and no other active ingredient in pack sizes of up to 25 dosage units, and labelled with a maximum daily dose of 1200 mg and appropriate warnings, be exempt from scheduling.

1.2 Justification for the exemption from scheduling

In New Zealand, ibuprofen has been available without prescription as a Pharmacy medicine since, 1985. Ibuprofen (in divided preparations) has been available without prescription in Australia as either Schedule 3 or Schedule 2 preparations since 1989, ten years after it was first launched as a prescription product.

The NDPSC in Australia recently considered and recommended approval for the exemption in line with this proposal.

In the UK and other parts of Europe, ibuprofen has been available without prescription for general sale in any outlet since 1996 and in the USA it has been available from general outlets since 1984.

Worldwide OTC availability 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 OTC (general sale) use.

The objective of this submission is to ultimately provide the consumer with the choice of a safe and effective product with both analgesic and antiinflammatory properties where their current choices are limited to products

with either analgesic only effects (paracetamol) or aspirin which has a significantly worse GI side effect profile than ibuprofen.

1.3 Overall summary of supporting information

- The Medicines Classification Committee (MCC) and in Australia the National Drugs and Poisons Schedule Committee have considered the scheduling of ibuprofen substances over the past years and has approved the switching of solid dose oral ibuprofen tablets from Prescription, to Schedule 3, and subsequently to Schedule 2 status.

- This application requests the MCC to consider the further rescheduling to unscheduled status for small packs of solid dose ibuprofen 200 mg tablets.

- Headache is the most common indication for which consumers purchase analgesics with most purchases in the 25-44 year age group i.e. generally well, healthy individuals[1].

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

- Prescription formats of ibuprofen intended for chronic use in doses up to 2.4 g per day have different indications than those formats intended for self-selection, short term use and mild-to moderate common pain states

- Ibuprofen 200 mg tablets have been available in small packs without healthcare professional supervision in the USA and the UK since 1984 and 1996 respectively. 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.

- Since 1996 more than 1 billion NUROFEN 200 mg tablets per annum have been manufactured and delivered to Boots Healthcare companies worldwide, with no significant increase in adverse events

being reported to the global database as a result of the broader availability in the United Kingdom.

- 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 OTC doses. Several publications support this view. The GI ranking by relative risk of commonly used OTC NSAIDs shows ibuprofen < diclofenac < aspirin < naproxen[2] [3].

- 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 including the Centre for Adverse Reactions and the Australian Drug Reactions Advisory Committee over the past 20 years makes it suitable for broader distribution in New Zealand.

- At the present time, the New Zealand consumer is limited in the free choice of analgesics in comparison to other countries with similar economic stature.

- Only aspirin and paracetamol products are available in New Zealand via general sale outlets in packs of 20 tablets or less.

- Paracetamol, taken according to directions is a useful analgesic for the treatment of mild-to-moderate pain. However, when taken in either intentional or unintentional overdose situations, the potential for delayed hepatotoxicity is high.

- Recent TGA reviews have considered whether stronger warning statements are necessary on paracetamol packs and have urged increased educational programmes about potential dangers of paracetamol.

[1] The National Health Survey, Use of Medicines in Australia (1999)
[2] Lesko et al, JAMA 1995; 272(12): 929-33

- Case controlled studies have shown an increased risk of gastrointestinal bleeding even with low dose aspirin as used in cardiovascular prevention. Aspirin exhibits dose dependent pharmacokinetics with a prolonged half-life in overdose situations, which can complicate management.

- 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. 500 x 200 mg Nurofen Tablets) resulted in some elements of significant toxicity i.e. coma, metabolic acidosis mild thrombocytopenia, in this particular case, 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.

- A large scale randomised clinical trial compared the tolerability of aspirin, ibuprofen and paracetamol for short term analgesia (The PAIN study)[4]. 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,

[3] Henry D et al, BMJ 1996; 312 (7046); 1563-6
[4] Moore et al, Clin Drug Invest 1999: 18(2): 89-98

because of the poor tolerability of aspirin and the potential risks of paracetamol overdose.

- A recently published report based on data from the 1999 Paracetamol, Aspirin and Ibuprofen New (P.A.I.N) tolerability study, has shown that the risk of AEs for patients taking multiple medications may be greater when taking paracetamol or aspirin compared to those taking ibuprofen[5]. From the results of this study, there is no demonstrable advantage or protection against any of the common risk factors for common AE by using paracetamol instead of ibuprofen for short-term treatment of common pain, when the labelling is respected. Even when it was not, for example in the case of the forbidden drugs, there was no difference in tolerability between the drugs.

  The main risk factors for adverse events were indication for use and increasing number of other concomitant medications. Approximately 45% of subjects in the study took concomitant medications ranging from 1 (21%), 2-3 (18.5%) or more than 3 (5.4%). Although not permitted by the labelling, some of the patients in the study also took prohibited medications (2.5%). The most common concomitant medications were, by decreasing order of frequency antibiotics (11.4% of the patients), oral contraceptives (6%), cough preparations (5.3%), lipid lowering agents (5.1%), psycholeptics (5%), ACE inhibitors or angiotensin II antagonists (4.2%), beta-blockers (3.7%), venotonic agents (3.2%), cold preparations (3.1%), calcium antagonists (2.8%), antidepressants and psychoanaleptics (2.7%) etc. The top individual subclasses were oral penicillins (5.2%), betablockers (3.7%), macrolide antibiotics (3.2%), benzodiazepines (3.1%), fibrates (2.9%), venotonics (2.9%), expectorants (2.7%), antidepressants (2.6%), single component calcium antagonists (2.6%), cephalosporins (2.2%).

- Ibuprofen 200 mg in small packs no longer satisfies the criteria for Schedule 2 classification and should be considered for broader distribution viz:

[5] Moore N et al. Pharacoepidemiology and Drug Safety 2003; 12:1-10 (published on-line 22nd April 2003)

- Suitable for self treatment of a mild to moderate self-limiting ailment such as headache, backache, dental pain, period pain etc
- No evidence of abuse potential or diversion for illicit use
- Low potential for harm from overdose – not possible to define a potentially fatal dose[6]
- Well characterised incidence of adverse effects
- Lowest risk of GI toxicity of all commonly used NSAIDs[7] [8]
  - Better tolerated than aspirin and as well tolerated as paracetamol[9]
- Well characterised interactions with commonly used substances
- May be used by breastfeeding mothers
- Suitable for most asthmatics – should be avoided by aspirin-sensitive asthmatics (about 10% of asthmatic population)[10]
- No evidence of effect on cardiovascular parameters when taken according to directions for OTC use[11] [12] [13]
- Suitable for use in children from 7 years
- No dose reductions required in elderly populations[14] [15]

- Efficacy in headache[16], period pain[17] [18], dental pain[19], muscular aches and pains[20], and fever extensively proven in clinical trials which have been reviewed by regulatory authorities. Ibuprofen has been proven more effective than paracetamol and aspirin in headache[21], sore throats and fever[22]. With the added benefit of an anti-inflammatory action, ibuprofen is also very effective for muscular aches and pains.

[6] Seifert SA et al, J Toxicol Clin Toxicol 2000; 38(1): 55-7
[7] Lesko et al, JAMA 1995; 272(12): 929-33
[8] Henry D et al, BMJ 1996; 312 (7046): 1563-6
[9] Moore et al, Clin Drug Invest 1999: 18(2): 89-98
[10] Vally H et al, Thorax 2002; 57: 569-574
[11] Patel K & Goldberg K, Am Heart Assoc Scientific Meeting, 2002
[12] Gaziano M, Inflammopharmacology Meeting (Abstract) Edinburgh, April 2002
[13] Hudson M, Inflammopharmacology Meeting (Abstract) Edinburgh, April 2002
[14] Davies N M., The first thirty years, Clin Pharmacokinetics 1998; 34(2): 101-154
[15] Brocks D R, Jamali F N, Rainsford K D et al, Ibuprofen: A Critical Bibliographic Review, Taylor and Francis Ltd 1999; 124
[16] Nebe J et al, Cephalgia 1995; 15:531-535
[17] Zhang W Y & Li Wan Po, Br J Obstet & Gynaecol 1998; 105:780-789
[18] Morrison J C et al, Southern Med J 1980; 73(8): 999-1002
[19] Rondeau PL et al, J Canad Dent Assn; 1980; 7: 433-439
[20] Muckle DS, Rhematol and Rehab., 1974; 13 (141): 229-235
[21] Schachtel BP et al, J Clin Pharmacol, 1996; 36(12); 1120-5
[22] Kelley MT et al, Clin Pharmacol. Ther. 1992; 52: 181-189

- Revised labelling has been prepared and approved by the Medsafe for NUROFEN to ensure the consumer clearly understands what the product is for, how to use it, when not to use it and any risks associated with the product. In addition a 1800 number will be placed on packs to encourage consumers to call a 'hot line' for information. This number will be managed by a qualified pharmacist

- Consumer research on the proposed new label has been conducted in specific groups of consumers (pregnant women, asthmatics, consumers with stomach ulcers and consumers on long term prescription medications) to assess their use and understanding of the pack information and their behaviour with regard to seeking advice from healthcare professionals on the suitability of a particular analgesic for their situation[23]

- The research indicates consumers actively seek out information prior to purchasing analgesics for the first time from a new outlet, and the preferred source of information is their general practitioner. In addition it was shown that consumers draw on prior experience with both the product and prior professional recommendation before choosing to take analgesics.

- Ibuprofen best fits the profile of a product for self medication which will not cause major complications in overdose situations nor will it cause other untoward problems when taken according to the labelling.

- It is not expected that broader distribution of small packs of NUROFEN will increase the size of the analgesic market. Rather, it is expected people will switch from other brands to a brand which is considered to be more effective than many of the currently available brands available through broader distribution.

- Advertising and promotion will be aimed at educating the consumer to use medicines strictly according to the labelling and to recognise the

[23] Boots Healthcare Australia, Research Report on effectiveness of proposed packaging, February 2002

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 to access the most appropriate OTC medications from appropriate outlets to relieve symptoms of their self-limiting conditions and there is no scientific reason why ibuprofen 200 mg in small packs should not be available outside pharmacy channels.

2. CURRENT SCHEDULING DETAILS

SCHEDULE 4

IBUPROFEN **except** when specified elsewhere in this Schedule.

SCHEDULE 2

IBUPROFEN

For external use; in solid dose form containing 200 milligrams or less per dose form and in packs containing not more than 100 tablets or capsules; in liquid form for oral use in medicines which have received the Minister's consent to their distribution as pharmacy-only medicines and sold in the manufacturer's original pack containing not more than 200mL and in strengths 100mg or less per 5mLs.

As a result of the current Scheduling entry, sales packs of NUROFEN 200 mg tablets in 12's, 24s, 48s and 96s are available from Pharmacies as Pharmacy (S2) medicines. These products are currently sold in blister packs or bottles with a child-resistant closure, even though ibuprofen is not included in the relevant Medicines Regulations for Child-Resistant Containers.

The purpose of this rescheduling application is to seek an unscheduled status for pack sizes of up to 25 dosage units of ibuprofen 200 mg divided preparations, when packaged in child-resistant packaging. Suggested wording for the new Scheduling entry required to effect this change is provided overleaf.

3. PROPOSED NEW SCHEDULE 2 ENTRY

IBUPROFEN

(a) in preparations for oral use when labelled with a recommended daily dose of not more than 1200 mg of ibuprofen:

(i) in divided preparations in packs of 100 or less dosage units each containing 200 mg or less of ibuprofen,

EXCEPT

in divided preparations containing 200 mg or less of ibuprofen and no other therapeutically active constituent when packed in blister or strip packaging or child resistant containers of not more than 25 dosage units

(ii) in liquid preparations when sold in the manufacturer's original pack each containing 4 grams or less of ibuprofen;

Note: Medsafe has approved the use of solid dose forms of ibuprofen for children seven years and over.

Warning Statements

The following Warning Statements will be included on all packs.

For the relief of minor and temporary ailments. Use strictly as directed. ***Incorrect use or prolonged use*** *without medical supervision could be harmful.*