APPLICATION TO THE MEDICINES CLASSIFICATION COMMITTEE FOR RECLASSIFICATION OF A MEDICINE

PROPOSAL TO EXEMPT FROM SCHEDULING IBUPROFEN IN PREPARATIONS FOR EXTERNAL USE

29 January 2003

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Commercial-in-Confidence

PROPOSAL TO EXEMPT FROM SCHEDULING IBUPROFEN PREPARATIONS FOR EXTERNAL USE

BOOTS HEALTHCARE NEW ZEALAND PTY LTD

JANUARY 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 Ram 29 January 2002

1. EXECUTIVE SUMMARY

1.1 Purpose of the Application

The purpose of this application is to seek a revision of the scheduling of ibuprofen preparations for external use from Pharmacy Medicine to being exempted from scheduling.

This will bring ibuprofen for external use in line with the schedules for other products within the class of topical NSAID agents (i.e. diclofenac and piroxicam) and in line with Australia.

The Australian National Drugs and Poisons Schedule Committee considered the proposal to exempt ibuprofen in preparations for topical use on 17 October 2002. The committee agreed to exempt ibuprofen for external use from the requirements of scheduling on the basis of available safety data. Noting that ibuprofen for external use was for minor ailments, that were easily diagnosed and treated by consumers, without the need for pharmacist advice. A copy of section 18.8 of the NDPSC Record of the Reasons for Meeting 36 held on 17 October is attached.

1.2 Current Scheduling details

The current classification of ibuprofen is as follows:

Pharmacy Only Medicine

IBUPROFEN

For external use; for oral use in either liquid form in packs containing not more than 4 grams or in solid dose form containing not more than 200 milligrams per dose form and when in medicines which have received the consent of the Minister or the Director-General to their sale as pharmacy-only medicines and which are sold in the manufacturer's original pack.

Prescription Medicine

IBUPROFEN:

Except when specified else where in this schedule

As a result of this scheduling, NUROFEN GEL (50mg/g) in 50g tubes is currently available from Pharmacies as a Pharmacy Only Medicine.

1.3 Proposed amendment to schedule entries

The suggested wording for the new entry required to effect this change is shown below with amendments shown in bold type.

Presciption Medicine (S4)

IBUPROFEN except

(a) when classified as a Pharmacy Only Medicine (S2).

(b) In preparations for external use

Pharmacy Only Medicine (S2)

IBUPROFEN;

(a) for oral use in either liquid form in packs containing not more than 4 grams or in solid dose form containing not more than 200 milligrams per dose form and when in medicines which have received the consent of the Minister or the Director-General to their sale as pharmacy-only medicines and which are sold in the manufacturer's original pack.

(b) **except** in preparations for external use.

1.4 Arguments for the exemption from scheduling

- Other NSAIDs with similar profiles are already exempt from scheduling (i.e. diclofenac and piroxicam)
- External preparations of ibuprofen have a comparable risk/benefit ratio to diclofenac and piroxicam
- Internal preparations of ibuprofen have a comparable or better risk/benefit ratio to other internal NSAID formats.
- There is no evidence of increased risk to consumers in the availability of external preparations of ibuprofen as unscheduled medicines
- NUROFEN Gel has been approved by the TGA and Medsafe as a safe and effective external preparation
- This will bring ibuprofen for external use in line with the recent decision of the NDPSC to exempt ibuprofen for external use from scheduling.

1.5 Overall summary of supporting information

- Ibuprofen has been available orally in Australia and New Zealand for more than 20 years and has been available OTC for more than 12 years.
- OTC doses of ibuprofen (i.e. 1200mg/day) have a favourable risk/benefit ratio compared to other OTC simple analgesics and NSAIDs
- Topical preparations of ibuprofen have a comparable side effect profile to other exempt NSAID preparations
- Topical ibuprofen preparations have been available as unscheduled medicines in overseas markets for some considerable time
- Approximately 95% of topical ibuprofen has a localised action with a relative systemic bioavailability of around 5%
- Topical ibuprofen has been proven to have a statistically significant benefit over placebo
- The overall incidence of adverse events is low and associated mainly with local skin reactions which are minor and transient

1.6 Proposed labelling

A copy of the current tube and carton labels is shown below. .

2. BACKGROUND INFORMATION ON IBUPROFEN

2.1 Indications and presentations for non-prescription use

Ibuprofen preparations currently fall within either Non-prescription (S2) or Prescription (S4) classifications, depending on the format or the strength of the individual dosage unit or the total daily dose. 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 2400 mg per day) it is used as an anti-inflammatory for chronic arthropathies and other conditions under the care of a medical practitioner.

In the currently available non-prescription products, ibuprofen is typically presented in solid oral dosage forms of 200mg (with or without additional active ingredients) as well as oral liquid preparations and external formulations.

It is proposed that all external formulations of ibuprofen should be exempt from scheduling, and hence classified as General Sale Medicine.

External ibuprofen products are indicated for the temporary relief of pain and inflammation associated with acute soft tissue injuries including sprains, strains and sports injuries, for backache and for rheumatic and arthritic pains.

2.2 Chemical and pharmacological properties of Ibuprofen

Ibuprofen is a white powder or crystalline solid with a slight odour and taste being also non-hygroscopic. It has a low water solubility but is soluble in aqueous solutions of alkali hydroxides (especially sodium hydroxide) and carbonates. It has a melting point of 75ºC and is physically and chemically stable in the dry state. It is supplied as a racemic mixture of its two enantiomers.

Ibuprofen has anti-inflammatory effects in addition to having analgesic and antipyretic actions. The analgesic effects are due to both a peripheral and a central effect and are distinct from its property as an anti-inflammatory drug. At oral doses of up to 1200mg daily, ibuprofen has predominantly analgesic properties and is also effective in reducing temperature in febrile patients.

The concept of treating conditions such as strains, sprains, rheumatic and muscular pain by applying an external preparation to, or close to, the affected area offers the patient a less invasive approach with potentially fewer side effects. Several NSAIDs are now available in topical/external presentations in New Zealand, Australia and world-wide (e.g. diclofenac, piroxicam, indomethacin, benzydamine). Efficacy of such products has been established with significantly lower plasma levels than would be expected if a systemic preparation had been used.

Ibuprofen is absorbed through the skin and has a relative bioavailability of around 5% following topical administration. Around the world, external ibuprofen preparations are available as gel preparations or oil-in-water creams, although gel formats are more common.

2.3 Clinical overview of ibuprofen external preparations

In an attempt to quantify the benefit of externally applied NSAIDs, Moore et al,[1] (1998) reviewed 86 clinical trials involving 10,160 patients. The objective of the review was to assess the effectiveness and safety of external non-steroidal anti-inflammatory drugs in acute and chronic conditions. Main compounds included in the analysis included, ibuprofen, piroxicam, naproxen, ketoprofen, indomethacin, flurbiprofen, benzydamine (other compounds not marketed in Australia were also included). The main outcome measures in the review were at least a 50% reduction in pain, and an assessment of the local and systemic adverse effects.

The review showed that in acute pain conditions such as soft tissue injuries, strains and sprains, the placebo-controlled trials provided evidence that externally-applied nonsteroidal anti-inflammatory agents were significantly better than placebo over 1 week, with the number needed to treat (NNT) for all NSAIDs in these conditions of 3.9 (range 3.4 – 4.4). Ibuprofen, ketoprofen and piroxicam were shown to have significant efficacy over placebo and the number needed to treat for ibuprofen was 3.5. This means that 3.5 patients treated with external ibuprofen achieve at least a 50% reduction in pain compared with only one who would have done so on placebo. The NNT for external piroxicam was 4.2, and for benzydamine the figure was 6.7, indicating that more patients need to be treated in order to achieve a 50% benefit. For chronic conditions (osteoarthritis, tendonitis, rheumatism) externally-applied nonsteroidals were significantly better than placebo over 2 weeks with a NNT for all NSAIDs was 3.1 (2.7 to 3.8). The individual NNT for ibuprofen in chronic conditions was not identified.

In both acute and chronic pain, local and systemic adverse events and withdrawal from the study for reasons related to drug treatment showed a very low incidence and the adverse events and withdrawal reasons were no different to those in the placebo group.

Details of the review are shown below on Table 1 (adapted from Moore et al). For further details refer to actual paper,(Reference 1).

Table 1 Relative benefit and number needed to treat in randomised studies of external non-steroidal anti-inflammatory drugs in acute and chronic painful conditions

Condition/drug	Total trials	Total patients	Average No of treated patients	Response* with placebo (%)	Response* with active treatment (%)	Relative benefit (95% CI)	No needed to treat (95% CI)
Acute painful conditions							
Combined efficacy data	37	3239	47	39	71	1.7 (1.5 to 1.9)	3.9 (3.4 to 4.4)
Local adverse effects				3.0	2.6	1.2 (0.8 to 1.7)	
Systemic adverse effects				0.7	0.8	1.0 (0.6 to 1.8)	
Withdrawal due to adverse effects				0.4	0.6	0.8 (0.4 to 1.4)	
Ketoprofen	9	724	43	36	74	2.0 (1.5 to 2.6)	2.6 (2.3 to 3.2)
Felbinac #	3	413	70	32	66	2.0 (1.5 to 2.7)	3.0 (2.4 to 4.1)
Ibuprofen	4	284	36	34	70	1.9 (1.2 to 3.0)	3.5 (2.5 to 5.6)
Piroxicam	4	589	74	39	69	1.6 (1.2 to 2.2)	4.2 (3.1 to 6.1)

Benzydamine	4	245	31	62	84	1.4 (0.9 to 2.0)	6.7 (3.8 to 23)
Indomethacin	3	394	66	32	47	1.3 (0.9 to 1.8)	10 (5 to ∞ †)
Chronic painful conditions							
Combined efficacy data	12	1097		30	65	2.0 (1.5 to 2.7)	3.1 (2.7 to 3.8)
Local adverse effects				5.3	5.9	0.9 (0.4 to 1.7)	
Systemic adverse effects				1.3	1.1	1.1 (0.5 to 2.3)	
Withdrawal due to adverse effects				0.7	0.7	1.0 (0.4 to 2.4)	

*Response is either proportion of patients with successful outcome or of patients with adverse effect.
This product not available in Australia
†Indicates that there may be no benefit with treatment over placebo.

In a further study which was a multi-centre, double-blind, parallel group study conducted in France (Lopez, 1994[2]) the efficacy and tolerance of ibuprofen gel 5% was compared with placebo gel over a 1 week study.

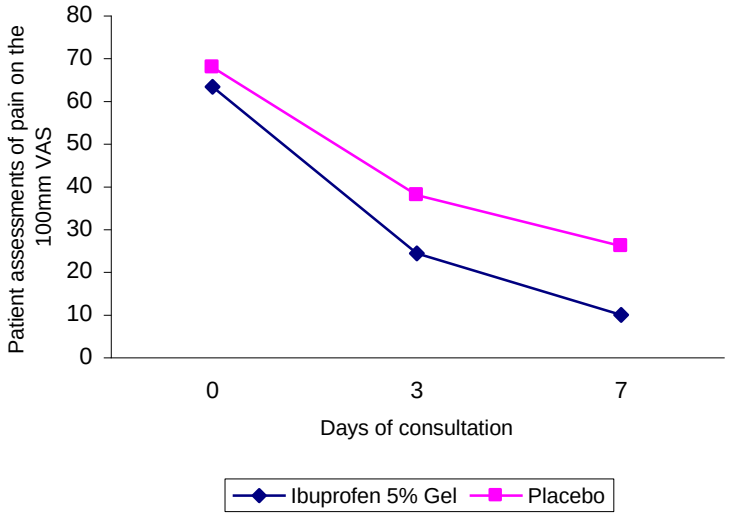
Sixty patients (31 males and 29 females) with acute uncomplicated ankle sprains were enrolled in the trial after giving written informed consent. 70% of the patients were injured in sporting activities and 30% in other ways. The patients applied the gel (active or placebo)), three times a day, at a measured dose 10 cm of gel. Only oral paracetamol (500 mg) was allowed, if required, for supplementary pain relief.

The patients were reviewed in the clinic on Day 0, 3 and 7 where both patient self-assessments and investigator assessments were made. At home, the patients made a self-assessment of pain on a Visual Analogue Scale (VAS) in mm at 8 am , 12 pm and 8 pm from Day 0 to Day 3, and recorded the scores in a self-assessment book. These scores were reviewed by the investigators when the patients were examined.

The principal measure of efficacy was the patient's self-rating of pain on a 100 mm (VAS) conducted on Day 0 before treatment , Day 3 and Day 7. Patients also stated whether they could stand alone on the affected leg. The investigator carried out assessments of pain at rest, pain on passive movement, pain on active movement, pain on palpation and loss of function of the affected ankle.

The group of patients treated with ibuprofen 5% gel had a statistically significant lower mean pain score (p=0.002) at Day 3 than the placebo group. This effect of treatment on pain, the pre-declared principal measure assessed by the patients, is shown in the following figure for Days 0, 3 and 7.

Figure 1: Patient's evaluation of pain Days 0-7



A number of secondary variables relating to the pain and function of the injured ankle were also assessed by the patient or the investigator at baseline and on Days 3 and 7.

The requirement for rescue medication of paracetamol was very low with only 7% (2/30) of patients from the ibuprofen 5% gel group and 17% (5/30) from the placebo group having consumed any up to Day 3. No patient took paracetamol between Day 3 and Day 7. The findings of the study are therefore unlikely to have been influenced by the provision of paracetamol.

Only one patient experienced local irritation caused by rubber from ankle socks and therefore unlikely to be due to treatment. This patient was receiving the active ibuprofen 5% gel, and the irritation was moderate when assessed on Day 7. Overall tolerability was good or very good and no patient withdrew from the study.

Based on the mean values for the principal measure of ankle pain the ibuprofen 5% gel group showed an additional 17% improvement over placebo on Day 3 and a 23% extra reduction in the mean pain score compared with placebo on Day 7. This is a clinically significant additional benefit. As many of the study assessments shows statistically significant benefits for active treatment over placebo it may be concluded that this study fully validates the clinical efficacy of ibuprofen 5% gel.

Clinical conclusions: The data supports the view that ibuprofen 5% gel as marketed in Australia and New Zealand is a safe and effective topical treatment.

2.4 Indications and Dosage

NUROFEN GEL is currently registered in Australia and New Zealand as a topically applied external analgesic and anti-inflammatory. In New Zealand it is indicated for the temporary relief of pain and inflammation associated with acute soft tissue injuries including sprains, strains and sports injuries, backache, muscular pains, rheumatic and arthritic pains.

The dosage instructions for adults (including elderly) and children over 12 years is as follows:

Squeeze 4 to 10cm of the gel onto the affected area and replace the cap. (This represents a dose of 50 to 125mg of ibuprofen). Gently rub the gel in until it is absorbed – then wash your hands.

Do not apply more than 4 times in 24 hours.

Do not use it on broken skin, on the lips or near the eyes.

Talk to your doctor if your symptoms worsen, if there is no improvement after 7 days use or if new symptoms develop.

2.5 Warnings, Precautions and Contraindications (as per pack instructions)

The current pack instructions for Australia and New Zealand carry the following warnings and precautions

Do not use if you are allergic to aspirin, ibuprofen or other anti-inflammmatory medicines

If you have asthma which you know is aggravated by the use of analgesics (pain relievers) check with your pharmacist or doctor before using Nurofen Gel.

Seek medical advice before using on children under 12 years of age

Discontinue use if a rash or irritation occurs. It is recommended that Nurofen Gel should not be used during pregnancy except under medical supervision. Do not use during the last three months of pregnancy.

It is believed these warnings and precautions are adequate for ibuprofen external preparations available as general sale medicines for self-selection.

Note – the following section (Marketing and Post-marketing Experience) contains Commercially sensitive information and is confidential.

3. MARKETING AND POST-MARKETING EXPERIENCE

3.1 International Experience

Ibuprofen gels with an identical formulation to the proposed NUROFEN Gel have been approved in the UK, New Zealand, Ireland, Spain, Belgium and France. The formulation, originally developed in Switzerland, has been marketed there since 1991, under various tradenames (Antalgit, Ibugel, Optifen). In addition, several cream based products have also been available for some time. Thus, the post-marketing experience on ibuprofen external preparations is considerable.

Other formulations of ibuprofen gels and creams at varying strengths (some also containing menthol) are also marketed worldwide.

It should be noted that Boots Healthcare currently markets a 10% ibuprofen gel product in the UK and Ireland under the brand name of NUROFEN Gel Extra Strength. This product is a menthol containing formulation and is marketed as an OTC general sale product in these markets.

The NUROFEN Gel formulation marketed in Australia and New Zealand (ibuprofen 5% gel) is also marketed in many European countries under a variety of trade names, including the following:

COUNTRY	BRAND	OWNER	APPROVAL DATE	STATUS
United Kingdom	Fenbid	Goldshield	Approved 1996	GSL
Ireland	Fenbid Nurofen Gel	Goldshield Boots Healthcare	Approved 1997 Approved 2002	GSL
France	Intralgis	Urgo	Approved 1995	GSL
France	Tiburon	Pharminter	Approved 1995	OTC
Belgium	Dolofin	Farmabel	Approved 1996	GSL
Switzerland	Optifen	Spirig	Approved 1992	OTC
Switzerland	Ibugel	Medinova	Approved 1992	OTC
Switzerland	Antalgit	Klinge	Approved 1991	OTC
Spain	Nurofen	Boots Healthcare	Approved 2002	OTC Pharmacy

Further registration application for this formulation is also currently pending in Norway.

3.2 New Zealand

Nurofen Gel 5% ibuprofen was approved and launched in New Zealand in early 2001 as a pharmacy only medicine. Since launch approximately 35**,**000 packs have been sold and to date no reports of adverse events have been reported to the company or to CARM. Other NSAID external preparations are available in New Zealand containing benzydamine, indomethacin, salicylic acid, ketoprofen, etofenamate and diclofenac. From data available it appears that piroxicam gel preparations were discontinued from the market in early 2001.

3.3 Australian marketing history

Boots Healthcare first introduced oral ibuprofen in Australia in 1979 as BRUFEN. It was available only on prescription and marketed as 400mg and 200mg strengths. Ten years later, in 1989, the same company introduced the non-prescription version, NUROFEN, as an Pharmacist Only Medicines (S3) product after which other generic brands also became available. In 1995, ibuprofen 200mg preparations including liquids, were reclassified to Pharmacy Medicines (Schedule 2).

Following evaluation by the TGA, 5% ibuprofen topical gel (50mg/g) was approved by the Medicines Evaluation Committee in mid-2001 registered and launched in January 2002 as a Schedule 2 medicine. In the 6 month period since launch approximately 97,000 packs have been marketed. Since launch no adverse events have been reported to the company however two individual reports appear on the ADRAC database which could potentially relate to an external preparation. Unfortunately these two reports do not identify the drug form or route, and a 'possible' or 'probable' causality has been applied. One report relates to a 69 year old male who reported thrombocytopenia, and purpura and who was also taking aspirin daily and ophthalmic eye drop preparations for conjunctival reasons. The second report was a 26 year old female with rigors, fever, malaise, abdominal pain, and increased ESR and creatinine. The patient was also taking Ventolin, and Pulmicort for asthma and an oral contraceptive. Causality was marked as probable. Although the dose form and route

was not identified in either of these two cases, it is more likely these were oral doses rather than related to external use. In view of the potential for a relationship to external presentations, they have been reported here for completeness.

Nurofen Gel has been available for more than 24 months in New Zealand and 12 months in Australia. Although there has only been a short period of marketing in Australia, this formulation (Ibugel 5% ibuprofen gel) has been available in overseas markets for more than 11 years.

Note - Many years ago, an external ibuprofen preparation was available as a prescription product, marketed by Drug Houses of Australia, although a recent search of the ARTG indicates only Nurofen Gel is currently registered.

3.4 Adverse drug reaction reports

Since launch of the external ibuprofen preparation , there have been only two possible (although unlikely) adverse drug reaction reports in Australia and none in New Zealand (see above).

Given the number of different brands of this formulation available overseas, specific pharmacovigilance data from countries other than the UK are not available to us. However from published data available (see Moore et al, reference 1) and other sources, the most probable adverse events are likely to be local reactions which are reversed on cessation of use.

Data from the UK ADROIT system[3] (Adverse Drug Reactions Online Information Tracking) for all external ibuprofen products available in UK between 1989 and 2000, is available and this shows a total of 46 adverse event reports during the 11 year period. UK sales of external ibuprofen products for the 5 year period 1995 - 1999 exceeded 13 million tubes.

The ADROIT system was instigated in the United Kingdom by the licensing authority (MCA) and enables a list of pharmacological monitoring reports to be obtained for a given active principle.

The report supplied by the UK licensing authority on externally applied ibuprofen showed 46 pharmaco-monitoring reports for the period 1989 -2000 (ADROIT 2000). The 46 reports combine to give a total of 60 adverse events which are cited, without any statement as to causality, from July 1989 to June 2000 (Table 2). However, the MCA has confirmed that none of the reports on reactions on the ADROIT database are specifically associated with Fenbid 5% brand gel. This is important since this gel is an identical formulation to the Boots Healthcare Nurofen gel marketed in Australia and New Zealand.

The external ibuprofen 5% medications on the market for a part of the period covered by the ADROIT report were:-

Brand	**Company**	**Date product launched**
Proflex 5% cream	(Zyma)	Launched in May 1989
Ibuleve 5% gel	(DDD)	Launched in March 1992
Ibugel 5% gel	(Dermal)	Launched in September 1992
Ibuspray 5% spray	(Dermal)	Launched early 1996

Fenbid 5% (Goldshield) Launched end 1996

It is not possible to provide sales data for the full 11 year period covered by the ADROIT report (July 1989 to June 2000). However, for five of the years covered, (between 1995 and 1999) sales of these external products reached over 13 million individual sales packs in the United Kingdom (source IMS).

Table 2: Reactions reported for external ibuprofen in the context of pharmacological monitoring in the United Kingdom (1989-2000)

System Organ Class	Number of adverse events
Disorders of metabolism & nutrition	2
Disorders of the ear	2
Disorders of the eye	1
Disorders of the immune system	1
Gastrointestinal disorders	6
General disorders	5
Haemopoietic disorders	1
Musculoskeletal, connective tissue & bone disorders	2
Neurological disorders	2
Renal & urinary disorders	7
Respiratory disorders	7
Skin & subcutaneous tissue disorders	24

It is clear that local reactions were the most frequent by far (24/60). There were no unexpected or fatal reactions reported. All adverse reactions settled on withdrawal of the product as would be expected for a product with limited systemic absorption.

Although ibuprofen was applied externally, it is noted that the typical NSAID class effects such as gastrointestinal, renal and respiratory disorders were still observed but to a much lesser degree.

Figueras et al[4] (1994) in a review of the adverse event database from the Spanish System of Pharmacovigilance also reviewed side effects of external NSAID products. Although the report was mainly focussed on oral preparations, it showed there were 98 reports describing ADRs attributed to external NSAIDs (69 to ketoprofen, 14 to piroxicam, 8 to diclofenac, 5 to naproxen and 2 to indomethacin). The reports involve 5 patients who were taking two NSAIDs concomitantly, one orally and the other by external application. 58.8% of the ADRs reported were dermatological and 35.6% were local lesions at the application site. The remaining ADRs were systemic reactions which occurred in 5 patients. These reactions related to either piroxicam or ketoprofen and the patients reported duodenal ulcer, gastrointestinal bleeding, diarrhoea, dyspnoea, facial oedema, and aggravated bronchospasm.

I It may be concluded that the overall incidence of adverse events with external ibuprofen is very low. Most of these adverse events are non-serious and are associated primarily with local reactions. Given the favourable side effect profile of ibuprofen when given orally, (i.e. comparable to paracetamol[5],at OTC doses) the risks to consumers of an adverse event with ibuprofen external preparation are extremely low.

4. LABELLING AND PACKAGING

4.1 Proposed label for exempt product

A copy of the current label and carton is shown on page 6. The only change to this label for the exempt product will be removal of the signal heading.

For completeness, a further copy of the carton and label is shown at attachment 1.

There is an increasing body of evidence, including the work undertaken by the TGA (Labelling Project – Effective by Design), about the principles to be applied to develop more effective labels for non-prescription medicines, including those for analgesics. As the consumer is increasingly reliant on labels when deciding to purchase medicines and electing to use them without professional help, performance-based labelling is of paramount importance.

It is believed that the current Nurofen Gel Pharmacy Medicine (Schedule 2) pack clearly identifies what a consumer needs to know to appropriately self-select an external pain reliever. It is proposed to only remove the signal heading from the unscheduled pack. The layout of the label is structured in such a way that consumers can readily identify how to use the product, the situations when it should not be used, and what to do if skin reactions occur.

This will enable this product to compete alongside other similar NSAID pain relievers on shelf in pharmacy or in grocery. .

5 CURRENT AVAILABILITY OF OTHER SUBSTANCES WITH SIMILAR PRESENTATIONS

5.1 Piroxicam

Piroxicam was scheduled as a Pharmacy Only Medicine until 2000 when it was reclassified to General Sale medicine. The recommendation that piroxicam for topical use be reclassified to general sale medicine was made at the 23rd meeting of the Medicines Classification Committee in May 2000.

In Australia, Piroxicam (Feldene Gel) had Schedule 4 status until 1998 when it was reclassified to Schedule 2 status in external preparations containing 0.5% or less of piroxicam. In March 2000, the permissible non-prescription concentration was increased to 1%.

At its 27th meeting in May 2000, NDPSC supported a proposal to exempt from scheduling external preparations of piroxicam on the basis the safety profile justifies exemption of the external preparation and the indication is appropriate for self-selection without access to professional advice.

Since 1997, twelve reports of adverse reactions have been reported to ADRAC in Australia. These are predominantly rash, bruising, and skin discolouration with one report of indigestion and one of gastric bleeding also occurring.

5.2 Diclofenac

In New Zealand Diclofenac (Voltaren Emulgel) is exempt from scheduling hence classified as a General Sale medicine for external use.

In Australia, Diclofenac (Voltaren Emulgel,) was switched in 1997 from Schedule 4 to Schedule 2 status in preparations for external use containing 1% or less of diclofenac.

At its 26th meeting in February 2000, NDPSC supported the proposal to exempt from scheduling external preparations of diclofenac on safety grounds.

Since 1997, twenty-one reports of adverse events have been reported to ADRAC. These are mainly skin rash, oedema, swelling, with two reports of an increase in INR levels on patients taking warfarin and two reports of abdominal pain and nausea. It is possible these reactions relate to oral forms of diclofenac, however the ADRAC report is unclear in this respect.

5.3 Benzydamine

Benzydamine for external use is currently classified as a Pharmacy Only Medicine in New Zealand.

In Australia, benzydamine external preparations were rescheduled in 1987 from S4 to S2 for preparations containing 3% or less benzydamine. The upper limit of 3% concentration was removed in 1999 for external preparations, so that all strengths of external preparations would be Schedule 2.

Since 1997, fifteen reports of adverse reactions have been reported to ADRAC. These are mainly rash, bullous eruption, or other application site reaction, however there has also been 1 report of an irritated and bleeding mouth due to a consumer using the external gel product in the mouth instead of the mouth gel product. Two further reports related to taste perversion and dizziness accompanied by nausea and migraine.

5.4 Indomethacin

In New Zealand, indomethacin is scheduled as a Pharmacy Only Medicine for external use, in medicines containing 1% or less, except in medicines containing 1 milligram or less per litre or per kilogram.

In Australia, since 1994, external spray preparations of indomethacin have been Schedule 2 in preparations containing 1% or less of indomethacin. Effective March 2000, all external preparations of indomethacin, became Schedule 2.

Only two reports of adverse events have been reported to ADRAC (in 1997) and both these related to rash and bullous eruptions.

Note - from available data it appears that this product may no longer be available on the market.

5.5 Ketoprofen

In New Zealand, ketoprofen is scheduled as a Pharmacy Only Medicine for external use.

In Australia, Ketoprofen gel preparations (Orudis Gel) were rescheduled in August 1999 to Schedule 2 status.

In New Zealand, the major brands in the pharmacy are Voltaren with 42% market share, Rheumon 26%, Nurofen 6.73%, Oruvail 3%, and Metsal 2.9%. The major brands in Australia, in the pharmacy market are Voltaren with 48% market share, Feldene 9%, Difflam 6%, Metsal 5% and Dencorub 5%. These brands continue to be sold only through pharmacy despite the unscheduled classification. It is planned that Nurofen Gel will also only be sold through pharmacy outlets but the rescheduling will facilitate competitive ranging.

The major brands sold through grocery outlets are considered to be the more traditional methyl salicylate or menthol based products like, Goanna, Deep Heat, and Tiger Balm. Products containing shark cartilage and glucosamine appear to have moved from pharmacy outlets to alternate channels such as health food stores etc.

6. RISK BENEFIT RATIO

The Nurofen gel formulation does not contain any agent which has a potential sensitizing effect such as propylene glycol, lanolin, parabens or perfumes. It has the advantage of penetrating quickly without leaving any greasy residue on the skin. The sensation of cooling when applying a gel is also appreciated, particularly by patients with inflammatory pathologies.

Adverse reactions to Nurofen gel are expected to be minor and transient and mainly allergic skin reactions. The clinical benefit of a topical NSAID agent for the temporary relief of pain and inflammation associated with acute soft tissue injuries including sprains, strains and sports injuries outweighs the low level of risk associated with such topical preparations.

7. PUBLIC HEALTH CONSIDERATIONS

Boots Healthcare is an ethical pharmaceutical company dedicated to responsible marketing under the highest code of ethics and standards. In every respect the Company will adhere to and act within Codes laid down by the New Zealand Self-Medication Industry Association and the Code for Therapeutic Advertising..

The strategy of Boots Healthcare is to achieve market share for Nurofen Gel through shifts in consumer choice away from alternate external NSAIDs and other rubs.

All advertising and promotion for Nurofen Gel would continue to be conducted in complete accordance with the ASA code of conduct.

8. CONCLUSION

The data contained in this application supports the availability of ibuprofen external preparations as unscheduled products where professional advice is not necessarily required. Consumers can readily identify pain and inflammation associated with acute soft tissue injuries including sprains, strains and sports injuries and can choose the most appropriate product for their use, should an external preparation be required.

The clinical efficacy of Nurofen Gel (5% ibuprofen) has been approved by the TGA and Medsafe in New Zealand for the symptomatic relief of pain and inflammation associated with acute soft tissue injuries including sprains, strains and sports injuries.

The application of an external preparation provides an alternative to oral therapy and the action of massaging the preparation into the affected area can provide additional relief.

Patients can readily identify the problem and self-select suitable external preparations to manage this form of therapy.

The exemption from scheduling of ibuprofen external preparations would not lead to any greater consumer risk than currently available unscheduled preparations such as diclofenac and piroxicam. The likelihood of serious adverse events is extremely low with local skin reactions being the most common adverse event. Experience has shown that these resolve on stopping the treatment.

The availability of piroxicam, and diclofenac external presentations as unscheduled medicines suggests there should be no valid reason for ibuprofen external preparations to remain as Pharmacy Only (Schedule 2) and it is requested that these be also exempt from scheduling.

The exemption from scheduling will align New Zealand with the recent decision by the NDPSC to exempt ibuprofen from scheduling in preparations for topical use in Australia.

9. MONITORING AND CONSUMER EDUCATION

Boots Healthcare is committed to encouraging appropriate use of all medicines supplied for self-medication and has systems in place to record and trace any adverse events viz:

- Consumers will be encouraged by advertising and via pack labelling to seek medial advice if symptoms worsen, if there is no improvement after 7 days use or if new symptoms develop.

- As part of the ongoing marketing activities, consumers will be encouraged to report all problems to either their health care professional or to the company.

- Our company SOPs ensure that we record and report all ADRs on a global basis.

- Doctors, pharmacists and pharmacy assistants are increasingly aware of the various alternative sources available to consumers to obtain medicines (eg internet, grocery, health food store), or information about medicines, and this awareness is also heightened by various forms of advertising.

10. ATTACHMENTS

Proposed label and carton copy

11 REFERENCES

1. National Drugs and Poisons Schedule Committee, Record of the Reasons, 36th Meeting, October 2002, 77-79

2. Moore RA, Tramèr MR, Carroll D et al. Quantitative systematic review of externally applied non-steroidal anti-inflammatory drugs. Br Med J 1998; 316: 333-338.

3. Lopez. 1994 Multicentre double-blind trial with parallel groups comparing the efficacy and tolerance of ibuprofen gel versus a placebo in the treatment of uncomplicated ankle sprains. Study report IBU.JAGO 94.01 (*The full inhouse clinical report is available on request)*

4. Adroit 2000. Medicines Control Agency Adverse Drug Reactions Online Information Tracking: Drug Analysis Print. Ibuprofen. Topical Route. Report June 2000

5. Figueras A, Capella D, Castel JM et al. Spontaneous reporting of adverse drug reactions to non-steroidal anti-inflammatory drugs. A report from the Spanish system of Pharmacovigilance, including an early analysis of external and enteric-coated formulations. Eur J Clin Pharmacol 1994;47: 297-303.

6. Moore N *et al*, The PAIN study : Paracetamol, Aspirin and Ibuprofen New Tolerability study. Clin Drug Invest 1999 18(2) : 89-98

ATTACHMENTS

CARTON AND TUBE LABEL

A copy of the 50g labels follow.

Tube label (not to actual size)

Carton label (actual size)

REFERENCES