

**APPLICATION TO THE MEDICINES CLASSIFICATION
COMMITTEE FOR
RECLASSIFICATION OF A MEDICINE**

**PROPOSAL FOR RECLASSIFICATION OF
FLURBIPROFEN 8.75mg LOZENGES
FROM PHARMACIST ONLY MEDICINE TO
PHARMACY MEDICINE**

29th July 2002

Submitted by:

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Commercial-in-Confidence

**PROPOSAL FOR RECLASSIFICATION OF
FLURBIPROFEN 8.75mg LOZENGES FROM RESTRICTED MEDICINE TO
PHARMACY MEDICINE**

BOOTS HEALTHCARE NEW ZEALAND LTD

July 2002

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**PROPOSAL FOR RECLASSIFICATION OF
FLURBIPROFEN 8.75mg LOZENGES FROM RESTRICTED MEDICINE TO
PHARMACY MEDICINE**

BOOTS HEALTHCARE NEW ZEALAND LTD

July 2002

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DETAILS OF COMPANY MAKING APPLICATION

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SPONSOR DECLARATION

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

.....
Sanya Ram

29th July 2002

1. EXECUTIVE SUMMARY

1.1 Purpose of the Application

The purpose of this application is to seek approval for Pharmacy Medicine (S2) classification of flurbiprofen lozenges (STREPFEN®, Boots) containing 8.75mg flurbiprofen per dosage unit. This is to be achieved by moving the current Pharmacist Only Medicine (S3) entry for flurbiprofen in divided throat preparations containing 10mg or less of flurbiprofen per dosage unit to Pharmacy Medicine (S2).

1.2 Arguments for the rescheduling

In New Zealand, STREPFEN lozenges were approved as a Pharmacist Only Medicine in February 1999 and have been available since February 1999. In Australia the classification of flurbiprofen throat lozenges was first considered by NDPSC at its meeting in February 2000 when it was determined that an S3 classification was appropriate for divided preparations containing 10mg or less of flurbiprofen per dosage unit. This decision, which was based on the safety profile of the lozenges and on the principles of Trans-Tasman Harmonisation, took effect in Australia in September 2000. STREPFEN lozenges were launched in February 2001, accompanied by consumer advertising as flurbiprofen is also included in Appendix H of the SUSDP.

The local post-marketing experience has confirmed that no new safety issues are likely to occur when STREPFEN is used in a non-prescription setting. In view of this period of Restricted Medicine availability, the company believes that it is now appropriate to request a Pharmacy Medicine classification for STREPFEN to align it with other products in this category.

Concerns about potential overuse and possibility of systemic side effects following use of STREPFEN lozenges are unwarranted for the reasons such as the self-limiting nature of the condition and the low daily dose of flurbiprofen. In addition, the contents of an entire box (140 to 210mg) will deliver less flurbiprofen than the daily dose used in the chronic setting (200mg to 300mg).

Since flurbiprofen lozenges were first available without prescription in February 1999, more than three years' marketing experience has been achieved in Australia/NZ. No safety concerns or evidence of misuse or abuse have arisen in this period, during which over 2.5 million lozenges have been sold in this region. This post marketing experience is in accord with the results of a specific pharmacy study which was undertaken by Boots in the UK.

The clinical data in support of the proven efficacy of STREPFEN lozenges has been evaluated by TGA, in contrast to other currently available products for which limited clinical data are available.

The Pharmacy Medicine availability of STREPFEN lozenges provides an alternative to currently available treatments for sore throat that include systemic analgesics as well as other lozenges containing ingredients such as simple emollients, local anaesthetics, antiseptics and benzydamine, another NSAID.

Sore throat is a common ailment that is usually treated by self-medication in the first instance. The choice of throat medications available in Pharmacy varies and few products have proven published clinical trial support material. The availability of STREPFEN as a Pharmacy Medicine product with proven efficacy and a good safety profile will provide consumers with a worthwhile additional self-selection choice.

1.3 Overall summary of supporting information

The enclosed application contains safety data accumulated by Boots Healthcare International in Periodic Safety Update Reports (PSURs). These reports cover the 24 month period to May 2001 and an additional report for the 12-month period to May 2002 will become available in July 2002. During the 24-month period of the available PSURs, almost 21 million STREPFEN lozenges have been supplied worldwide.

The company safety data is also augmented by reports from the Australian ADRAC and New Zealand CARM data bases. Comparative data are also supplied for benzydamine, a closely related comparative product.

This application also includes an extensive UK pharmacy study specifically conducted by Boots Healthcare International. The Boots Pharmacy Study, which involved over 7000 patients in an OTC setting, has shown that the AEs reported were mostly non-serious, transient and of minor clinical significance. The incidence and profile of events do not alter when the product is not used exactly as per the instructions on the pack. Similarly, those with common illnesses such as hypertension and asthma or taking commonly used drugs did not show an increase in GI or other relevant adverse event rates. There is no reason to believe that these findings will not continue in the Pharmacy Medicine setting.

1.4 Proposed labelling

Boots have designed a new label for STREPFEN. It is planned to utilise the identical pack in both Australia and New Zealand. The proposed new Pharmacy Medicine STREPFEN carton is supplied in Appendix 12.2 and the text of the current Pharmacist Only Medicine pack is shown in Appendix 12.1.

Major changes are to be seen in the layout of the text as well as some of the language. The package insert has been removed and relevant text incorporated onto the carton. The modifications have been achieved within the constraints of the current mandatory warning statements required by the SUSDP.

Packaging and Tamper Evidence

STREPFEN lozenges are currently available in packs of 16, although the maximum approved pack size is 24 lozenges. They are supplied in blister packs, which are inherently tamper-evident.

Warnings

The following warnings are included on the STREPFEN label:

- Check with your doctor or pharmacist before taking Strepfen if you suffer from asthma or have kidney, liver or heart problems, or if you are taking other medication (including aspirin or other anti-inflammatory drugs).
- Strepfen should not be taken during pregnancy.
- Do not use if you have or have ever had a stomach ulcer, or if you are allergic to aspirin, flurbiprofen or other anti-inflammatory drugs.

In addition, the dosage instructions include the following precautions:

- Do not take for more than 7 days
- If symptoms persist, see your doctor
- Not recommended for children under 12 years of age.

These warnings are all in line with the standard statements required for oral NSAID preparations.

In contrast, the label for DIFFLAM lozenges carries none of the NSAID warnings, nor does it carry any local anaesthetic warnings, despite the claimed local anaesthetic properties of benzydamine (DIFFLAM 2002). A copy of the DIFFLAM lozenge label is supplied as Appendix 12.4.

2. CURRENT SCHEDULING DETAILS

2.1 New Zealand

Flurbiprofen;	in throat lozenges containing 10mg or less per lozenge	Restricted
Flurbiprofen;	except in throat lozenges containing 10mg or less per lozenge	Prescription

2.2 Australia

SCHEDULE 4

FLURBIPROFEN **except** when included in Schedule 3.

SCHEDULE 3

FLURBIPROFEN in divided preparations for topical oral use containing 10mg or less of flurbiprofen per dosage unit.

APPENDIX H

FLURBIPROFEN

3. PROPOSED AMENDMENT TO SUSDP ENTRIES

3.1 New Zealand

Flurbiprofen;	in divided preparations for topical oral use containing 10mg or less per dosage unit.	Pharmacy Medicine
Flurbiprofen;	except when included in Pharmacy Medicine classification	Prescription

3.2 Australia

SCHEDULE 4 - Amendment

FLURBIPROFEN – amend entry to read

FLURBIPROFEN **except** when included in Schedule 2.

SCHEDULE 3 - Amendment

FLURBIPROFEN – delete entry

SCHEDULE 2 – New entry

FLURBIPROFEN in divided preparations for topical oral use containing 10mg or less of flurbiprofen per dosage unit.

APPENDIX H

FLURBIPROFEN – delete entry

4. BACKGROUND INFORMATION ON FLURBIPROFEN

Flurbiprofen is a propionic acid derivative NSAID, structurally related to ibuprofen. It possesses analgesic and antiinflammatory properties and has been in therapeutic use for over 20 years. It is used in daily doses of 150mg to 300mg primarily for the chronic treatment of musculoskeletal and rheumatic conditions, and for dysmenorrhoea and post-operative pain. Flurbiprofen is also increasingly used in the treatment of self-limiting conditions without medical supervision.

Worldwide, flurbiprofen is marketed in a range of dosage forms, including conventional and sustained release tablets, capsules, patches and suppositories for chronic indications that involve long-term administration. There are also suspensions and mouthwash preparations intended for short-term administration, some of which are available without prescription.

In Australia, flurbiprofen is available in lozenges for treatment of sore throats (S3) and in eye drops for treatment of intraoperative miosis (S4). These uses are further discussed in the next section.

4.1 Indications and presentations for non-prescription use

STREPFEN lozenges (flurbiprofen 8.75mg) are indicated for the symptomatic treatment of severe sore throats. The product is recommended for use in adults and children over 12 years of age. One lozenge is sucked every 3 to 6 hours, with a maximum of 8 lozenges per 24-hour period. Duration of treatment should not exceed 7 days and if symptoms persist, medical advice should be sought. The specific wording of the indications on the ARTG is as follows:

“Relief of pain, swelling and inflammation associated with severe sore throats”

A copy of the current STREPFEN Pharmacist Only Medicine (S3) label is supplied in Appendix 12.1. This label is approved for use in both Australia and New Zealand.

4.2 Indications and presentations for prescription use

Flurbiprofen tablets (50mg, 100mg) and sustained release capsules (200mg) are available on prescription in New Zealand and are known as FROBEN. In contrast, no oral (systemic) or topical preparations are available in Australia, with or without prescription. However, in Australia flurbiprofen is currently available in eye drops as a prescription-only product for the treatment of intraoperative miosis (OCUFEN®, flurbiprofen sodium 300mcg/mL).

4.3 Local marketing history

In New Zealand, STREPFEN lozenges was fully evaluated and approved in February 1999. In Australia, STREPFEN lozenges were fully evaluated by MEC in 1999-2000 and were approved for marketing in October 2000. An application to switch flurbiprofen lozenges to S3 was considered and approved by NDPSC at the February 2000 meeting. Marketing commenced in Australia in February 2001 and in New Zealand in February 1999. STREPFEN was approved as a Non-prescription product in both countries.

In the period to May 2001, over 2.6 million STREPFEN lozenges have been produced and delivered to the Australia/New Zealand market.

4.4 International history

Flurbiprofen was first registered in tablet and capsule presentations over 25 years ago. Dosage forms of 25mg, 50mg and 100mg were introduced in the UK in March 1977 and have subsequently been registered in all major European countries and territories, USA, New Zealand, South America, Asia and elsewhere. As such, flurbiprofen has been extensively used to treat both acute and chronic conditions, is well established as a prescription product, and is considered safe in single or multiple doses up to a maximum of 300mg daily. In recognition of the established use of flurbiprofen, the US FDA has issued a labelling guidance for generic manufacturers of flurbiprofen tablets (FDA, 1994)

As a Non-prescription product, the first approval was for a flurbiprofen mouthwash (25mg/10mL) in Italy in May 1998. The product, known as “Benactiv Gola”, is gargled in 10mL doses 2-3 times daily. The mouthwash is indicated for local inflammatory treatment in conditions of the throat, mouth and gums (tonsillitis, pharyngitis, stomatitis, and gingivitis both prior and subsequent top extraction of teeth and other dental and orthodontic interventions). In April 2001 an oral spray (2.5mg/mL) was approved in Italy for the same indications as the mouthwash.

Flurbiprofen first became available in a low dose lozenge presentation in New Zealand and Italy in 1999. STREPFEN or STREFEN (flurbiprofen 8.75mg) lozenges are now approved and available without prescription in UK, New Zealand, and in some European and Asian countries. In Italy, these lozenges are known as “Benactiv Pastiglie”. They are indicated for symptomatic treatment of sore throat. Approvals have also been gained in France, Germany, Portugal, Austria, Singapore and Ireland. Applications are pending in South Africa, Hungary, Romania, Slovak, Czech Republic and Russia.

A summary of the worldwide introduction of flurbiprofen lozenges is provided in Table 1 and some further details are provided in the discussion that immediately follows.

Table 1:
Summary of international Non-prescription introductions of flurbiprofen lozenges

Country	Prescription	Pharmacy
New Zealand	n/a	February 1999
Italy	n/a	April 1999
Thailand	n/a	October 1999
Poland	n/a	August 2000
Australia	n/a	February 2001
United Kingdom	August 1999	August 2002
Ireland	n/a	Q3 –2002

STREPFEN lozenges are also available in several European countries (eg France, Germany, Austria and Portugal), with a POM (prescription medicine) classification.

New Zealand

A registration application for flurbiprofen lozenges was lodged in New Zealand in September 1997. Neither Boots nor any other NZ sponsor lodged a specific “switch” or reclassification application in New Zealand in respect of the product. The NZ authorities assessed the available data on safety of flurbiprofen lozenges during the initial assessment of this product for registration and concluded that a Pharmacist-Only classification was appropriate.

United Kingdom

STREFEN lozenges were approved in UK in August 1999 as a prescription medicine and were launched into the market later that year. More recently, after review of a company-sponsored pharmacy-based post-marketing study, the MCA has reclassified the product to P (Pharmacy Medicine). The CSM recommended approval for the POM to P switch in June 2001, and after finalisation of the application, it is proposed to launch Non-prescription in the UK in August 2002.

Italy

In May 1998 the Italian Regulatory Authority approved a flurbiprofen (25mg/10mL) mouthwash, and lozenges were approved in May 1999. An oral spray formulation (2.5mg/mL) was approved in April 2001. All presentations have been approved as Non-prescription products.

4.5 Relevant data on post-marketing experience

In the two-year period from May 1999 to May 2001 over almost 21 million flurbiprofen lozenges have been sold worldwide. Of these, 1.8 million were supplied in Australia and 800,000 in New Zealand. Over 95% of these sales have been in Non-prescription markets, as shown in Table 2 below.

Table 2:
Worldwide sales of flurbiprofen lozenges

Period	No of Months	Rx sales*	OTC sales#	Total
17/05/99 to 16/11/99	6	643,776	2,993,792	3,637,568
17/11/99 to 16/05/00	6	316,224	3,432,464	3,748,688
17/11/00 to 31/05/01	12	149,952	13,185,216	13,335,168
GRAND TOTAL	24	1,109,952	19,611,472	20,721,424

* Product available on prescription only in UK during this period

All sales outside of UK are Non-prescription during this period

No major safety issues have arisen during this three-year period of post-marketing surveillance. There have been no market withdrawals, restrictions or failure to gain marketing approval in relation to safety aspects.

There have been no changes to contra-indications, precautions, warnings or adverse drug reactions in the company core data sheet. However, there have been changes made to the drug interactions section of the core data sheet.

Following a review of the literature, drug interactions between flurbiprofen and lithium and methotrexate have been removed from the company core data sheet for the flurbiprofen range of products. When considered in light of the relatively low daily dose of flurbiprofen (70mg per day, equivalent to eight lozenges), it was concluded that there is no evidence of a clinically significant interaction between flurbiprofen and either lithium or methotrexate.

4.6 Adverse drug reaction reports

The post-marketing data indicate that there is no evidence of abuse or misuse and there are no reported cases of overdose. Overall the safety data indicate that the flurbiprofen range of products is well tolerated and appropriately used by the population at large.

In the following sections, data are presented on the ADR reports for flurbiprofen lozenges available from the global data base of the Boots parent company as well as those on flurbiprofen available from the ADRAC and NZ CARM data bases

4.6.1 Global Data Base

Boots Healthcare International (BHI) has prepared several Periodic Safety Update Reports (PSURs) for the flurbiprofen range of products. These reports summarise the worldwide safety data and overall exposure to the products, in addition to documenting the international regulatory status, clinical trials and published studies on the drug.

In respect of the lozenge presentation, three such PSURs are currently available covering the period from May 1999 to May 2001, copies of which have been supplied to the NDPSC secretariat (PSUR 1999, 2000, 2001). Another PSUR covering the 12-month period to May 2002 will be available in July 2002 and can be made available to the NDSPC Secretariat upon request.

During the two-year period covered by BHI PSURs, the company has received a total of 5 serious and 2 non-serious spontaneous ADRs that were related to flurbiprofen (see Table 3 below).

Table 3

Summary of spontaneous flurbiprofen lozenge ADRs* in global Boots safety database

PSUR period	PSUR period (months)	Non-Serious ADRs	Serious ADRs	Sales volume
17/05/99 to 16/11/99	6	0	1	3,637,568
17/11/99 to 16/05/00	6	1	0	3,748,688
17/11/00 to 31/05/01	12	1	4	13,335,168
(cumulative)	24	2	5	20,721,424

* Spontaneous and regulatory reports related to flurbiprofen lozenge included

Four of the 5 serious reports occurred in one patient and arose in the PSUR for period ending May 2001. A 65 year old man experienced a "burst of heat" and severe sweating, (unlisted¹) as well as itching in the throat and the need to cough (listed²). The reporting pharmacist described these as serious. BHI assessed the causality as "possible" due to a temporal association however, the events may have been due to the condition being treated. This event is described in more detail in Appendix V of the PSUR for period ending May 2001. There was one (1) serious report of a gastro-

¹ Not listed in core data sheet

² Listed in core data sheet

intestinal haemorrhage, one (1) non-serious report of bronchospasm and one non-serious report of abdominal pain in the spontaneous reports. Full details of the cumulative safety data are supplied in Table 1 of the PSUR ending May 2001 (pages 11 to 15 of 31 – copy supplied as Appendix 12.3).

The global data base also contains reports of adverse events arising from clinical trials of flurbiprofen lozenges. These reports are discussed in more detail in the PSURs and in Section 7.8 below.

There have been no deaths reported in any connection with the administration of flurbiprofen lozenges.

4.6.2 Australia

Boots Healthcare has obtained a report from the ADRAC data base on all ADRS reported in connection with flurbiprofen and related compounds (ADRAC 2002). These reports are summarised in Table 4.

Table 4:

ADRAC reports on flurbiprofen (excluding eye preparations) and benzydamine (excluding creams and gels) for period to May 2002

Brand	2000	2001	2002 (to 05/02)	on file 11/72 to 05/02	Sole suspected
Flurbiprofen -Streptfen	N/A*	1	1	2	2
Benzzydamine -Difflam	3	1	0	33	22
-Difflam solution	0	0	0	2	2
-Difflam throat spray	1	0	0	2	2

*product not yet available

For the 12-month period to January 2002, approximately 1 million STREPFEN lozenges were sold in Australia and the corresponding figure for DIFFLAM lozenges was 9 million lozenges (source, IMS data).

The ADRAC reports indicate that for STREPFEN there was one report of hallucination in one patient during 2001. In 2002 (to May) there was a report of face oedema, paraesthesia, pruritus, tongue oedema and urticaria all in one patient. Neither of these reactions is included in the global data base of spontaneous reports discussed in Section 4.6.1. However, with the exception of hallucination, they have all been reported previously during clinical trials.

In addition to the ADRAC reports, the company has received one consumer report during 2001 where a young woman took a single lozenge for tonsillitis and developed shortness of breath, rash and blurred vision. Despite following up with the reporter, the Company was unable to gather sufficient details to document this suspect ADR. However, these reactions have all been reported previously in clinical trials.

By comparison, 5 suspect ADRs were reported for DIFFLAM (benzydamine) preparations during the same period (Jan 2000 to May 2002). Interestingly, all of these 5 reports concern lack of efficacy or decreased therapeutic response. DIFFLAM has been available in Australia since 1987. ADRs reported prior to 2000 include

anaphylactoid reaction, angioedema, abdominal pain, bronchospasm, tongue oedema, deafness and skin reactions including bullous eruptions and rash.

4.6.3 New Zealand

Boots Healthcare has obtained a report from the NZ CARM data base on all ADRS reported in connection with flurbiprofen and related compounds (CARM 2002). These reports are summarised below.

Table 5:
CARM reports on flurbiprofen and benzydamine products for period to March 2002

Brand	pre 1999	1999	2000	2001-2002	on file (to 31/03/02)
Flurbiprofen*	22	0	1	0	22
Benzydamine**	31	1	2	0	34

* all reports from systemic oral use in doses of 50mg or greater

** includes topical administration and oral doses of up to 200mg.

It should be noted that flurbiprofen tablets (50mg, 100mg) and sustained release capsules (200mg) are available in New Zealand and known as FROBEN.

In the 5-year period from May 1997 to May 2002, around 22.4 million DIFFLAM lozenges have been sold in New Zealand. In the period from February 1999 to May 2001, approximately 0.8 million STREPFEN lozenges have been supplied in New Zealand.

It is evident from review of these reports that there have been no ADRs reported for STREPFEN lozenges since their introduction in New Zealand in 1999. The single report in 2000 relates to melena (non serious) after an oral flurbiprofen dose of 200mg in conjunction with baclofen, cilazapril/hydrochlorothiazide, calcium carbonate and amitriptyline.

Of the 31 benzydamine non brand specific reports on file, 4 may be clearly identified as resulting from exposure to the lozenges. These reports include the following symptoms and reported outcomes:

- | | |
|-------------------------------------|-------------------|
| • urticaria, oedema, tachycardia | recovered |
| • dizziness, ataxia | recovered |
| • stomatitis, cheilitis, taste loss | not yet recovered |
| • stomatitis | outcome unknown |

The most common reactions reported for all presentations of benzydamine are:

- skin and appendages (11/31), including angioedema, pruritus, urticaria
- alimentary (8/31), including GI haemorrhage and perforated duodenal ulcer
- respiratory (7/31), including bronchospasm and dyspnoea
- cardiovascular (5/31), including tachycardia and cyanosis
- psychiatric (4/31) including hallucination, confusion and insomnia.

In the brand brand-specific ADR reports forwarded by CARM, 3 reports had been notified on Diffiam Lozenges. These reports include the following symptoms and reported outcomes:

- | | |
|--------------------------------------|----------------------------|
| • rash | outcome unknown |
| • erythema, pruritus, face oedema | outcome unknown |
| • depersonalisation, vision abnormal | recovered without sequelae |

5. **LABELLING AND PACKAGING**

Boots have designed a new label for STREPFEN. It is planned to utilise the identical pack in both Australia and New Zealand. The timing of this new label introduction is planned to coincide with the product's reclassification as a Pharmacy Medicine (S2). This new label design is presented and discussed below.

It should be noted that the revised label is yet to undergo formal assessment by Medsafe or TGA and this will be a necessary pre-requisite for its introduction.

The proposed new Pharmacy Medicine STREPFEN carton is supplied in Appendix 12.2 and the text of the current Pharmacist Only Medicine pack is shown in Appendix 12.1.

Major changes are to be seen in the layout of the text as well as some of the language. The modifications have been achieved within the constraints of the current mandatory warning statements required by the SUSDP. The package insert has been removed and relevant text incorporated onto the carton.

Packaging and Tamper Evidence

STREPFEN lozenges are currently available in packs of 16, although the maximum approved pack size is 24 lozenges. They are supplied in blister packs, which are inherently tamper-evident.

Warnings

The following warnings are included on the STREPFEN label:

- Check with your doctor or pharmacist before taking Strepfen if you suffer from asthma or have kidney, liver or heart problems, or if you are taking other medication (including aspirin or other anti-inflammatory drugs).
- Strepfen should not be taken during pregnancy.
- Do not use if you have or have ever had a stomach ulcer, or if you are allergic to aspirin, flurbiprofen or other anti-inflammatory drugs.

In addition, the dosage instructions include the following precautions:

- Do not take for more than 7 days
- If symptoms persist, see your doctor
- Not recommended for children under 12 years of age.

These warnings are all in line with the standard statements required for oral NSAID preparations.

In contrast, the label for DIFFLAM lozenges carries none of the NSAID warnings, nor does it carry any local anaesthetic warnings, despite the claimed local anaesthetic properties of benzydamine (DIFFLAM 2002). A copy of the DIFFLAM lozenge label is supplied as Appendix 12.4.

6. CURRENT AVAILABILITY OF OTHER PRODUCTS WITH SIMILAR BENEFITS

6.1 Benzydamine

Although there are numerous Non-prescription preparations for the treatment of sore throat, many of which are unscheduled, the most relevant comparators with similar benefits to STREPFEN are those based on benzydamine hydrochloride, which is also an NSAID with local anaesthetic actions (DIFFLAM 2002).

In New Zealand the classification of benzydamine is Pharmacy Medicine without exceptions.

Benzydamine-based products are all available in Australia as Pharmacy Medicine (S2) and the current SUSDP entry for benzydamine is:

Schedule 2

BENZYDAMINE in preparations for topical use³

Schedule 4

BENZYDAMINE **except** when included in Schedule 2:

In France, Germany, Sweden, Canada and Japan, benzydamine is available only on prescription (AESGP/WSMI, 2001).

The efficacy of benzydamine preparations as a treatment for painful oral conditions or sore throat does not appear to have undergone rigorous clinical testing in humans, although Martindale does mention two mouthwash studies in mucositis and oral ulcers with opposing conclusions. A meta-analysis recently published in the Cochrane library concluded that benzydamine preparations were not effective in the treatment of oral mucositis or associated pain in cancer patients receiving chemotherapy or radiotherapy (Worthington, HV *et al* 2002). In the treatment of acute sore throats, there are no studies on the efficacy of benzydamine throat lozenges. In addition, the limited evidence that does exist on the efficacy of the mouthwash (Wethington JF, 1985) requires confirmation.

For historical reasons, benzydamine preparations available in Australia were not required to have rigorous clinical data to support their indications and claims. In 1991 a number of products for treatment of sore throat were grandfathered on the ARTG, and therefore registration applications for subsequent products or formulations for these indications do not need to be supported by clinical data because the substance is considered to be "well characterised", at least in terms of the claims currently made for these products. In addition, on the basis of the published Product Information documents for DIFFLAM preparations, the original product registrations would appear to be based solely on evidence from animal models (DIFFLAM 2002).

Martindale reports that benzydamine is used topically on the skin in concentrations of 3-5% in painful musculoskeletal and soft tissue disorders and as a mouth wash or mouth spray in concentrations of 0.15% for the relief of inflammatory conditions of the mouth and throat. Martindale further reports that after administration by mouth the most

³ "Topical use" means application of a poison for the purpose of producing a localised effect on the surface of the organ or within the tissue to which it is applied.

common side-effects are gastrointestinal disturbances with numbness or a stinging sensation of the oral mucosa also reported.

In addition to various "house" brands, the major brands available are DIFFLAM and LOGICIN. All presentations are Pharmacy Medicines.

DIFFLAM LOZENGES

DIFFLAM lozenges containing 3mg benzydamine hydrochloride and cetylpyridinium chloride, have been available without prescription since 1987 and are provided as sugar-free lozenges in several different flavours (raspberry, eucalyptus and menthol, doublemint, honey & lemon and orange) in packs of 16 lozenges, and as anti-inflammatory cough lozenges combined with pholcodine and cetylpyridium chloride in packs of 24 lozenges.

More than 5.2 million packs of DIFFLAM (i.e. 83 million lozenges) have been sold in Australia in the period from January 1994 to April 2002 with the sales of DIFFLAM lozenges in the last 2 year period shown below (source, IMS data):

Jan 2000 – Dec 2000	Jan 2001 – Dec 2001
9,743,088 lozenges	8,540,576 lozenges

LOGICIN LOZENGES

These lozenges also contain benzydamine 3mg as well as lignocaine and dichlorobenzyl alcohol in three flavour variants. The product was first introduced in Australia in March 1999.

Following are the sales of LOGICIN lozenges in Australia for the past 2 year period (source, IMS data):

Jan 2000 – Dec 2000	Jan 2001 – Dec 2001
3,560,704 lozenges	2,723,520 lozenges

6.2 Analgesics

Several systemic analgesic products are approved by TGA for the treatment of sore throat. Current TGA registration guidelines specify the following indications for preparations containing aspirin, ibuprofen or paracetamol:

"For the temporary relief of pain (and discomfort) associated with ...sore throat..."(AGRD2, 2001)

No specific sore throat dosage recommendations appear in the TGA guidelines, therefore the usual analgesic dosage schedule is followed.

Anecdotally, gargling with aspirin or salt water is reported to relieve pain in some people. However, gargles in general have been poorly researched and no specific recommendations can be made regarding their use.

Small packs of aspirin or paracetamol preparations, whether or not they are labelled for the treatment of sore throat, are **unscheduled**.

6.3 Other Lozenges

Antibacterial sore throat treatments containing antiseptics, essential oils and emollients are all **unscheduled**. Brand leaders include STREPSILS and CEPACOL.

Local anaesthetics such as lignocaine and benzocaine may also be incorporated into lozenges for relief of pain and discomfort of sore throats. These preparations are primarily **Schedule 2**. Due to the numbing effects of the local anaesthetic, such products must carry the following warning:

“Do not take hot food or drink soon after using this product because it may burn your mouth.”

7. RISK-BENEFIT ANALYSIS

7.1 Pharmacokinetics

The absorption of flurbiprofen following oral tablet dosing is fairly rapid, almost complete and its extent is not influenced by food. Flurbiprofen binds extensively to plasma albumin. Metabolism is by hydroxylation and methylation, with some enantiomeric selectivity. Approximately 20% of the dose is excreted unchanged in the urine, with a further 60-70% excreted as acylglucuronides. Faecal elimination will also occur. The elimination half-life is approximately 4 to 5 hours and is almost 100% complete 24 hours after the last dose.

These pharmacokinetic parameters together with the low blood levels of flurbiprofen after consumption of STREPFEN lozenges, mean that accumulation of the drug does not occur after repeated dosing of the lozenges.

A comparative pharmacokinetic study (Nimmo, 1996) on flurbiprofen lozenges (5mg, 12.5mg) and tablets (12.5mg, 50mg) has demonstrated that the extent of flurbiprofen absorption from the dosage forms as measured by AUC is in proportion to the administered dose. Maximum blood levels after a single dose of flurbiprofen lozenge 12.5mg was 2.13 mcg/mL and the corresponding figure for the 5mg lozenge was 0.83mcg/mL. Apart from a slightly shorter T_{max} with the 12.5mg lozenge (0.63 hr) compared to the 12.5mg tablet (1.05 hr), there were no differences in overall disposition of the drug. These data are summarised in Table 6 below.

Table 6:
Summary of flurbiprofen pharmacokinetic variables (Study BH6001)

Pharmacokinetic Variable		Treatment			
		Tablets		Lozenges	
		12.5mg	50mg	12.5mg	5mg
AUC _(0-∞) (µg.h.ml ⁻¹)	Mean	8.99	34.28	8.33	3.64
	SD	4.3	16.6	3.8	1.6
C _{max} (µg.ml ⁻¹)	Mean	2.13	6.68	2.01	0.83
	SD	0.6	1.4	0.4	0.2
T _{max} (h)	Mean	1.05	1.73	0.63	0.66
	SD	0.9	1.0	0.2	0.2
Half life (h)	Mean	3.54	3.63	3.46	3.56
	SD	0.9	1.5	1.2	1.1

On the basis of these data, the expected C_{max} after 8.75mg is around 1.4mcg/mL. On a theoretical basis, if a patient took one lozenge every three hours (approximating to once

every half life) for 8 doses, the total accumulated flurbiprofen would be approximately 2 mcg/mL in the 24 hour period.

The reported maximum blood levels in healthy volunteers after a single 100mg dose of flurbiprofen in 15.2 mcg/mL, with 90% of the values between 10 and 22 mcg/mL (FDA, 1994). The NZ Data Sheet for FROBEN (flurbiprofen tablets) reports peak blood levels after a single dose of 100mg of 12.7mcg/mL (FROBEN, 1999)

7.2 Potential for inappropriate use

NATURE OF CONDITIONS OR AILMENTS BEING TREATED

Sore throat (pharyngitis, tonsillitis, laryngitis) is usually a self-limiting illness, whether due to viral or bacterial infection. Sore throat symptoms resolve within 3 days in 40% of people and within 1 week in 85% of people, irrespective of whether they are streptococcal positive or not (Del Mar C, 2000). Consumers are more than adequately equipped to self-medicate in this condition and indeed would rarely seek medical advice.

In view of the self-limiting nature of the condition, long-term use or misuse of flurbiprofen lozenges is unlikely.

REQUIREMENT FOR PROFESSIONAL ADVICE OR SUPERVISION

Due to the increasing popularity and non-prescription use of NSAIDs such as ibuprofen and diclofenac, consumers are more knowledgeable about the uses and limitations of this class of drugs. This awareness is complemented by responsible advertising and clear product labelling, all of which directs the consumer to seek the advice of their health care professional if in any doubt about the appropriateness of the product for them. As STREPFEN will be available as a Pharmacy Only product, the consumer has ready access to the pharmacist if necessary.

In addition, the potential drug interactions are not likely to result in significant harm due to the low blood levels of flurbiprofen and short-term use of the product (maximum 7 days).

7.3 Potential for abuse

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

7.4 Overdose

In the three-year period of post-marketing surveillance covered by the Boots PSURs (to May 2001), there have no reports of STREPFEN lozenge overdose. Moreover, from the Adverse Events reported, there is no evidence of overdose with either the lozenge or the mouthwash preparations.

Concerns about potential overuse and possibility of systemic side effects following use of STREPFEN lozenges are unwarranted for the following reasons:

- Max daily dose = 8 lozenges (70mg)
- One whole box: current market pack -16 lozenges = 140mg

maximum approved pack - 24 lozenges = 210mg

- Even if the contents of an entire box are consumed in one day, this is still within a safe daily dose (200-300mg); this dose is safely used in the long-term treatment of chronic conditions
- Pharmacy Medicine supply will guard against potential problems of misuse due to ready access to pharmacist for intervention if required.
- The self-limiting nature of sore throats means that there is limited potential for overuse or misuse.
- The presentation of the product as a lozenge prevents easy swallowing and is therefore a deterrent to deliberate or accidental over-consumption.

In addition, information available from the Boots Pharmacy Study also shows that improper use does not result in an increase in side effects (see Section 7.8).

Symptoms of flurbiprofen overdose may include nausea, vomiting, headache, drowsiness, blurred vision and dizziness. Treatment consists of gastric lavage and, if necessary, correction of serum electrolytes.

The FDA labelling guidance (FDA, 1994) reports effects of overdose with flurbiprofen tablets in children and adults. No deaths are reported. Drowsiness occurred after doses of up to 800mg in three young children, and semi-consciousness and elevated liver enzymes were reported in a 2 year-old. Adults have been reported to show no symptoms following doses of 3-5 grams. These data indicate that flurbiprofen is relatively safe in overdose.

7.5 Drug Interactions

There is limited potential for drug interactions occurring after use of STREPFEN lozenges due to the low dose (8.75mg) and the resultant very low blood levels.

In the two-year period of post-marketing surveillance covered by the Boots PSURs (to May 2001), there have been no reports of drug interactions with either the lozenge or the mouthwash flurbiprofen preparations. In addition, as stated in Section 4.5, the interactions section of the company core data sheet has been reviewed in light of post marketing experience.

Following a review of the literature, drug interactions between flurbiprofen and lithium and methotrexate have been removed from the company core data sheet for the flurbiprofen range of products. When considered in light of the relatively low daily dose of flurbiprofen (70mg per day, equivalent to eight lozenges), it was concluded that there is no evidence of a clinically significant interaction between flurbiprofen and either lithium or methotrexate. Nevertheless, the STREPFEN label does caution consumers who are taking concomitant medications to consult their health care professional.

Being a recently evaluated product, flurbiprofen lozenges carry all the NSAID-type precautions and warnings. In contrast, benzydamine throat preparations which were grandfathered on the ARTG, do not carry these NSAID warnings. The current label for DIFFLAM lozenges is supplied as Appendix 12.4.

The usual statements are to the effect that NSAIDs (as a class) should not be used in combination with

- aspirin or other NSAIDs – this may result in an increased incidence of adverse reactions
- Antihypertensives, since NSAIDs may diminish the effects of these drugs. There is limited evidence however of a reduction in the effect of diuretics

- Anti-coagulants – there is limited evidence of enhancement of oral anticoagulant effects
- Lithium and methotrexate – there is evidence for potential increase in plasma levels of both lithium and methotrexate administered in conjunction with NSAIDs.

However, the potential for these NSAID-type interactions needs to be balanced against the very low level of flurbiprofen encountered after use of STREPFEN lozenges. STREPFEN lozenges contain only 8.75mg of flurbiprofen and no more than 70mg of the drug is ingested in 24 hours. Interactions reported for flurbiprofen occur at daily doses of 200 to 300mg. The flurbiprofen blood levels that result after ingestion of STREPFEN lozenges are orders of magnitude lower than those that arise after ingestion of tablets for chronic indications. In addition, the short term use of STREPFEN in self-limiting conditions further mitigates any potential concerns for drug interactions. Lastly, the label warning on pack has been retained for people who are taking other medications to seek professional advice before using STREPFEN.

7.6 Hazard potential and likelihood of side effects

Clinical trials have shown that the most common side effect after STREPFEN lozenges is taste perversion. There is also the potential for inducing transient local irritation of the buccal mucosa. The most serious reaction that has been reported post-marketing is one case of gastro-intestinal haemorrhage.

Flurbiprofen does not adversely affect the ability to drive or operate machinery.

The usual side effects seen after long-term use of flurbiprofen tablets and capsules for chronic conditions are mostly gastro-intestinal effects and nausea. These effects are less likely to arise following short-term use of STREPFEN lozenges for a self-limiting condition like sore throat.

The pharmacokinetics of flurbiprofen, together with the low dose and short-term use of STREPFEN lozenges, result in next to no systemic accumulation of the drug. Similarly, there is limited potential for gastro-intestinal effects following use of STREPFEN lozenges.

Like all NSAIDs, flurbiprofen is not recommended for use in pregnancy. STREPFEN is appropriately labelled with contraindications to this effect.

7.7 Potential for masking or compromising medical management of a disease

As stated above, sore throat (pharyngitis, tonsillitis, laryngitis) is usually a self-limiting illness, whether due to viral or bacterial infection. Sore throat symptoms resolve within 3 days in 40% of people and within 1 week in 85% of people, irrespective of whether they are streptococcal positive or not (Del Mar C, 2000). However it is important that sore throats of non-viral origin and hence of a more serious nature can be recognised in a timely manner and not masked by excessive use of the lozenge.

With this in mind, and in accordance with other Non-prescription medicines, STREPFEN lozenges are indicated for short-term use (maximum 7 days), after which time the consumer is instructed to seek medical advice if symptoms persist. The small pack size also effectively limits the use to no more than a few days' treatment. In addition, the absence of a masking effect was demonstrated in the Boots Pharmacy Study (see Section 7.8).

In the pharmacy study TH9903 discussed below, there were five episodes reported of Quinsy throat, four in the flurbiprofen group and one in the aspirin group. (This incidence is in direct proportion to the treatment allocations). It is of note that in all of these cases, the symptoms were not masked. All subjects stopped taking the drug and sought and received further medical attention.

It may therefore be concluded that the potential for masking more serious conditions is no greater with flurbiprofen than with other currently available preparations for sore throat.

7.8 The Boots Pharmacy Study

Details of the study

Boots Healthcare International has conducted a post-marketing study in the UK in over 7000 patients (TH9903, Gibb IA and Veltri J, 2000). The study was conducted through UK pharmacies between January 2000 and June 2000.

The aim of this study was to quantify the safety of flurbiprofen 8.75mg lozenges, when used in a Non-prescription environment. The study compared the adverse event pattern of flurbiprofen 8.75mg lozenges with that of soluble aspirin 500mg for sore throat in a pharmacy setting. Other objectives were to determine the actual usage pattern of flurbiprofen 8.75mg lozenges in the Non-prescription setting and the ability of consumers to appropriately self-select the product.

A significant adverse event (AE) was defined in the protocol as a serious AE, or an AE which was moderate or severe in intensity, or an AE that resulted in the subject visiting their GP (or GP visit to the subject) or hospital casualty department, or an AE that resulted in permanent cessation of the study drug.

This was an open, randomised, multiple-dose, parallel group, actual use comparison of flurbiprofen 8.75mg lozenges with soluble aspirin 500mg tablets, in subjects attending a pharmacy with a sore throat. The professional expertise of the pharmacist was used to enrol the subjects and provide them with the study medication. Subjects were followed up a few days later by telephone using a trained nurse to interview them and record their experiences using the study medications.

Subjects aged 18 years and above were assigned to either flurbiprofen or aspirin in a 4:1 ratio by a computer-generated randomisation list. Subjects aged 12-17 years were assigned only to flurbiprofen. The dose of flurbiprofen was 8.75mg every 3-6 hours, with a maximum of 5 lozenges per 24 hours. The dose of soluble aspirin was 500 – 1000 mg dissolved in water every 4 hours, with a maximum of 4g per 24 hours.

7139 patients were enrolled, of which 6501 were analysed. 4918 were randomised to flurbiprofen and 1190 were randomised to aspirin. A further 393 patients 12-17 years received flurbiprofen lozenges, as specified in the protocol.

Safety Aspects

There was no difference between the randomised treatment groups in the incidence of serious AEs, with 0.28% in the flurbiprofen group and 0.17% in the aspirin group. No serious AEs were reported in the 12-17 year old population. Furthermore, there were no significant differences between the randomised treatment groups for significant gastrointestinal (GI) events; the rate was 3.6% for the flurbiprofen group and 3.3% for

the aspirin group. There were no GI bleeds in either group. In the non-randomised 12-17 year old population (all of whom received flurbiprofen), the rate was 3.1%.

Most of the GI events were classified as significant because the subject chose to permanently discontinue the study medication, as per the definition in the study protocol. Due to the self-limiting nature of sore throats, discontinuation of medication will not result in disease progression but rather be of benefit to the patient as exposure is minimised and the event resolves with minimal consequences for the subject.

Improper Use

Approximately 7.7% of subjects did not adhere precisely to the instructions on the Non-prescription product labelling. The most common type of improper use was failure to leave the required time interval between doses and use when their throat felt normal. These instances of improper use mostly occurred on a single occasion, or on one day, rather than consistently over several days. More importantly, a comparison of event rates in these subjects with event rates in subjects who adhered to the usage instructions shows that improper use was not associated with an increase in either the overall event rate or the treatment-related event rate.

The incidence of significant AEs in those who did not use flurbiprofen lozenges in complete accordance with the label instructions was 12.7% compared to 12.4% in those who used the lozenges as directed by the label. The incidence of significant AEs in those who used the lozenges when their throat felt normal was 5.8%.

Conclusion

The Boots Pharmacy Study has shown that the AEs reported were mostly non-serious, transient and of minor clinical significance. The incidence and profile of events do not alter when the product is not used exactly as per the instructions on the pack. Similarly, those with common illnesses such as hypertension and asthma or taking commonly used drugs did not show an increase in GI or other relevant adverse event rates. There is no reason to believe that these findings will not continue in the Pharmacy Medicine setting.

These results are in accord with post marketing experience in Australia, New Zealand and elsewhere where the product is available without prescription. It can therefore be concluded that flurbiprofen 8.75mg lozenges do not present a direct or indirect danger when used without medical supervision, and there appear to be no major safety issues with this product.

8. 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 Advertising Standards Authority Code for Therapeutic Advertising.

All advertising and promotion for STREPFEN in Australia would continue to be conducted in complete accordance with the ASMI voluntary code of conduct. A vital part of the marketing strategy for STREPFEN would be to educate the consumer regarding the responsible use of the product 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.

Boots Healthcare will continue its responsible education programme for healthcare professionals (doctors, pharmacists and dentists) as well as its programme for pharmacy assistants.

Boots Healthcare believes that the reclassification of STREPFEN to Pharmacy Medicine has the potential to provide benefits to the consumer through awareness and access to a safe and proven effective sore throat preparation compared to products that are currently available. It also provides the consumer with ready access to a wider choice than is currently available.

9. MONITORING AND CONSUMER EDUCATION

Treatment of acute sore throat pain is well understood by consumers, so there is little public education that is needed in terms of the condition itself. However, there may be some who need information about STREPFEN as a proven medication for the treatment of sore throat pain and swelling.

STREPFEN is currently advertised to the public because flurbiprofen is in Appendix H of the SUSDP. There will be no change in the way STREPFEN will be advertised as an Pharmacy Medicine. All advertising to consumers is rigorously controlled by various Advertising and broadcast codes. In fact the same controls exist whether the product is unscheduled or falls into Pharmacy Medicine (S2) or Pharmacist Only Medicine (S3) schedules. This ensures that all advertising remains appropriate, balanced and fully supportable.

The choice of throat medications available in Pharmacy varies and few of these products have proven published clinical trial support material. The availability of STREPFEN as a Pharmacy Medicine product with proven efficacy and a good safety profile will provide the consumer with a worthwhile additional self-selection choice.

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

- Consumers will be encouraged by advertising and via pack labelling to seek medical advice if symptoms worsen or persist for more than 7 days.
- 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.
- The Boots company Standard Operating Procedures ensure that all ADRs are recorded and reported on a global basis.

These company measures are further supported by general shifts in attitudes and expectations of health care professionals and of the community at large, such as:

- Doctors, pharmacists and pharmacy assistants are increasingly aware of the various alternative sources available to consumers to obtain medicines or, information about medicines (eg internet, grocery, health food store), and this awareness is also heightened by various forms of advertising. Therefore, they increasingly ask patients about their use of non-prescription medicines and take this into consideration in the overall patient treatment and monitoring plan.

- When consumers do attend a Health Care Professional (HCP) for any reason, it is therefore likely that history-taking will cover all medication use (including purchases of Non-prescription medicines for self-medication of sore throat pain) and that this will be recorded and noted, where relevant. This is the direction that the community is taking and professional educational campaigns increasingly remind HCPs of this.

Lastly, the availability of STREPFEN as a Pharmacy medicine ensures ready access to a pharmacist for advice and counselling if required.

10. CONCLUSION

The data in this application supports the reclassification of flurbiprofen 8.75mg lozenges as a Pharmacy Medicine product.

Sore throat is a common ailment that is usually treated by self-medication. Intervention by a health care professional is seldom sought, at least in the first instance.

The clinical data in support of the proven efficacy of STREPFEN lozenges has been evaluated by TGA, in contrast to other currently available products for which limited clinical data are available.

The Pharmacy medicine availability of STREPFEN lozenges provides an alternative to currently available treatments for sore throat that include systemic analgesics as well as other lozenges containing ingredients such as simple emollients, local anaesthetics, antiseptics and benzydamine, another NSAID.

The local and international post-marketing experience with flurbiprofen lozenges has confirmed the good safety profile of the product after widespread use in the general community.

The Boots Pharmacy Study has shown that the AEs reported were mostly non-serious, transient and of minor clinical significance. The incidence and profile of events do not alter when the product is not used exactly as per the instructions on the pack. Similarly, those with common illnesses such as hypertension and asthma or taking commonly used drugs did not show an increase in GI or other relevant adverse event rates.

These results are in accord with post marketing experience in Australia, New Zealand and elsewhere where the product is available without prescription. It can therefore be concluded that flurbiprofen 8.75mg lozenges do not present a direct or indirect danger when used without medical supervision, and there appear to be no major safety issues with this product.

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** Abstract, copy of full report available on request

12. APPENDICES

- 1 Current S3 STREPFEN label (Australia/New Zealand)
- 2 Proposed PHARMACY ONLY MEDICINE STREPFEN label
(Australia/New Zealand)
- 3 Cumulative Tables of all ADR reports for flurbiprofen lozenges to May
2001 (Table 1 - serious and Table 2 - non-serious)
- 4 Current PHARMACY ONLY MEDICINE DIFFLAM lozenges label

13. COPIES OF REFERENCES

Copies of references have been supplied to secretariat.