Reclassification of a Medicine for consideration by the Medicine Classification Committee

Application for the reclassification of flurbiprofen lozenges (8.75 mg flurbiprofen per lozenge) from Pharmacy Only Medicine to General Sale (Unscheduled) Medicine

30 June 2020

Submitted by:

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Executive Summary

This application seeks the reclassification of flurbiprofen in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit, when sold in the manufacturer's original pack containing not more than 16 dose units from Pharmacy Only to General Sale.

Flurbiprofen lozenges are a low-dose topical analgesic and anti-inflammatory medicine for the relief of pain, swelling and inflammation associated with sore throats. The use of flurbiprofen lozenges exposes the painful and inflamed mucosal region of the throat to the analgesic and anti-inflammatory actions of flurbiprofen(1) while minimising systemic exposure.(2)

The previous consideration of the down-scheduling of flurbiprofen lozenges to General Sale in 2010 was declined as the Committee were concerned that the dose form, presentation and proposed packaging would make it difficult for consumers to differentiate Strepfen from Strepsils and that such confusion could lead to consumers with contraindications to inadvertently take flurbiprofen.(3) Since 2010 the label for Strepfen lozenges has changed significantly introducing a medicines information panel at the back of the pack and very clear call out of the active ingredient on the front of the pack, in line with the requirements of TGO 92. The Australian TGO 92 labelling requirements were introduced to improve a consumer's understanding of the information on the label and represents current best practice. RB is of the view that these changes effectively address the concerns previously raised by the Committee and that there are no valid reasons not to proceed with this reclassification.

Since the previous review in 2010, there has been no significant change in the safety profile of topical oral flurbiprofen and the benefit/risk profile remains positive. The favourable safety profile is supported by substantial in-market experience, more than four decades globally and since 1999 in New Zealand and since 2001 in Australia. The estimated patient exposure to topical oral flurbiprofen exceeds [redacted] million patients globally, [redacted] in New Zealand and [redacted] in Australia.(4)

Sore throat is a very common condition with 89% of New Zealanders experiencing a sore throat at least once a year and 53% experiencing a sore throat at least once every 6 months.(5) In addition, the majority of acute sore throats in adults (85-95%) are viral and a self-limiting minor ailment which can generally be self-managed and resolved within a few days.(1, 6)

Sore throats are acute in nature and develop quickly which means consumers look for easily accessible relief. Pharmacies typically have limited opening hours whilst supermarkets and similar stores are usually open longer and provide greater access in which to purchase medications for minor self-limiting conditions.

Sales data demonstrates a growing preference for consumers purchasing medicated sore throat products in a grocery environment.(7)

Inflammation is the main cause of the pain associated with a sore throat and as such a localised anti-inflammatory treatment would be an appropriate option as it would act to relieve the pain at the site as well as manage the cause of the pain, the inflammation.(8)

Sore throat pain is often acute and severe in intensity(9, 10) and it can significantly impact health-related quality of life and everyday function.(11)

Pain is also the principle driver of people with sore throats seeking GP management.(12-14) Despite educational campaigns, GP visits for sore throat conditions often result in antibiotic

use. Australian research indicates that 30% of people who saw their GP for a sore throat were managed with an antibiotic.(13) New Zealand research indicates that 22.1% of patients surveyed had moderate to high feelings of entitlement to be prescribed antibiotics even for minor illnesses.(15) New Zealand has one of the highest rates of antibiotic use in the OECD, with the use of antibiotics increasing by 49% from 2006 to 2014.(16) The need to prevent antimicrobial resistance by reducing the inappropriate use of antibiotics is recognised by the New Zealand Ministry of Health.(17) It is acknowledged that new strategies are required to curb the use of antibiotics for minor, self-limiting ailments such as acute viral sore throats. One such strategy is to improve access to medications that effectively relieve painful sore throat.(14)

Lozenges are the most commonly used dosage form for the management of sore throats(18) and providing the public with wider access to a lozenge with both analgesic and anti-inflammatory activity has the potential to both improve self-management of sore throats and reduce the inappropriate use of antibiotics.

The Therapeutic Guidelines for management of Acute Pharyngitis/Tonsillitis recommends analgesics as a first-line approach for managing acute sore throat. Therapeutic Guidelines for the management of pain recommends that analgesics be used at the lowest effective dose for the shortest possible time.(6) Use of flurbiprofen lozenges to relieve the pain of acute sore throat is entirely consistent with these guidelines and the quality use of medicines. The flurbiprofen dose in lozenges is significantly lower than alternative General Sale oral NSAIDs, 8.75 mg flurbiprofen versus 200-400 mg ibuprofen, 300-1000 mg aspirin and other oral analgesics (paracetamol 500mg per tablet) which are also used to manage the pain of a sore throat.

The systemic exposure of flurbiprofen in a lozenge format is minimal and significantly lower than alternative oral analgesics (oral NSAIDs and paracetamol), as buccal absorption of flurbiprofen is low, with blood levels around 10% of those obtained from the same dose of flurbiprofen taken orally and swallowed.(2)

The proposed limited pack size of 16 dose units, represents 2 day’s therapy for patients taking the maximum dose (8 lozenges per day) compared to General Sale oral analgesics, ibuprofen where 24 units represents 4 day’s supply at the maximum dose and paracetamol 20 units representing 2.5 day’s supply.

The use of flurbiprofen lozenges in managing acute sore throat pain would present a better benefit/risk profile compared with use of systemic oral analgesics based on the minimal systemic absorption and the clinical efficacy of these lozenges.

The health benefits and suitability of flurbiprofen lozenges for General Sale is being recognised with EMA approving the down scheduling of topical oral flurbiprofen to unscheduled (General Sale) in Denmark and the Netherlands. In Australia an equivalent application was considered by the Advisory Committee on Medicines Scheduling at the March 2020 meeting with the interim decision being to make flurbiprofen lozenges (10 mg or less, for the treatment of adults and children over 12 years of age and in a primary pack containing not more than 16 dosage units) an unscheduled medicine, available for General Sale, from 1 October 2020.(19)

The evidence enclosed in this submission demonstrates that flurbiprofen lozenges do not need to be restricted to pharmacy only status given;

- Throat lozenges are generally the most common option used by consumers to relieve their sore throat.

- Consumers tend to visit grocery stores rather than pharmacy to buy lozenges to relieve their sore throats.
- Consumers are well equipped to self-manage their sore throat.
- Advice from a pharmacist is not required (and in fact generally not sought) for purchase of flurbiprofen or other throat lozenges.
- Minimal systemic absorption results in a favourable safety profile which would be better than an oral analgesic.
- Labelling clearly differentiates Strepfen from Strepsils and includes all of the required warning statements that are also mandated for oral NSAIDs that are available as General Sale medicines.

Part A

1. International Non-proprietary Name of the medicine.

Flurbiprofen

2. Proprietary name(s).

Strepfen

3. Name and contact details of the company / organisation / individual requesting a reclassification.

[redacted]

Reckitt Benckiser (New Zealand) Pty Limited

Postal address: Level 47 / 680 George Street Sydney NSW 2000, Australia

Phone: [redacted]

Email: [redacted]

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

Flurbiprofen 8.75 mg lozenges

5. Pack size, storage conditions and other qualifications.

Manufacturer's original pack containing not more than 16 dose units. Larger pack sizes are not subject to this reclassification application and are proposed to remain as Pharmacy Only medicines.

Store below 25^{o}C.

Qualifications: for use by adults and children over 12 years of age.

6. Indications for which change is sought.

Flurbiprofen 8.75 mg lozenges - for the relief of pain, swelling and inflammation associated with severe sore throats.(20)

7. Present classification of the medicine.

The current classification of flurbiprofen is summarised in Table 1. The classification of flurbiprofen 8.75 mg lozenges is Pharmacy Only.

Table 1: Current classification of flurbiprofen

Ingredient	Conditions (if any)	Classification
Flurbiprofen	**except** in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit	Prescription
Flurbiprofen	in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit	Pharmacy Only

8. Classification sought.

The classification sought is flurbiprofen in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit, when sold in the manufacturer's original pack containing not more than 16 dose units from Pharmacy Only to General Sale.

If accepted the proposed classification of flurbiprofen is summarised in Table 2.

Table 2: Proposed classification of flurbiprofen

Ingredient	Conditions (if any)	Classification
Flurbiprofen	**except** in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit	Prescription
Flurbiprofen	in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit **except** when specified in General Sale	Pharmacy Only
Flurbiprofen	in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit, when sold in the manufacturer's original pack containing not more than 16 dose units	General sale

9. Classification status in other countries (especially Australia, UK, USA, Canada).

Globally flurbiprofen lozenges are available in 73 countries. In the majority of these countries they are available for self-selection in pharmacy.

The lozenges are available for General Sale as unscheduled medicines in four countries including two recent down-scheduling in Europe, specifically in Denmark and the Netherlands. Other countries with general sale access are Botswana and Iraq. See Table 3 below for scheduling status in comparable markets.

Table 3: Scheduling status of topical oral flurbiprofen in comparable markets

Country	Legal status of medicine
Austria	OTC
Australia	OTC (Schedule 2), Interim ACMS decision is GSL from 1 October 2020
Belgium	OTC - Behind the Counter
Denmark	GSL
Germany	OTC
Italy	OTC
Netherlands	GSL
Sweden	OTC
Switzerland	OTC
United Kingdom	P

GSL, general sales list; OTC, over-the-counter; P, pharmacy.

In Australia the current scheduling status for flurbiprofen in preparations for topical oral use when in divided preparations containing 10 mg or less of flurbiprofen per dosage unit or in undivided preparations containing 0.25 per cent or less, or 10 mg or less per dose of flurbiprofen is Schedule 2 (Pharmacy Only). An equivalent application for the reclassification of flurbiprofen lozenges of small pack sizes (not more than 16 dose units) as an unscheduled medicine was considered by the Advisory Committee on Medicines Scheduling at the March 2020 meeting. The interim decision is to make flurbiprofen lozenges (10 mg or less, for the treatment of adults and children over 12 years of age and in a primary pack containing not more than 16 dosage units) an unscheduled medicine, available for General Sale, from 1 October 2020.(19)

In the United Kingdom, flurbiprofen lozenges have been approved for use since August 1999. They were originally classified as a prescription medicine and have been classified as a P (Pharmacy) medicine since June 2001.

In the United States of America, flurbiprofen in eye drops and tablets are prescription medicines. It was first entered as a prescription drug in 1985. No information could be found regarding the availability of oromucosal flurbiprofen preparations in the USA.(21)

In Canada, flurbiprofen or its salts was entered on the Prescriptions Drugs List in December 2013 as a product for human use.(22)

10. Extent of usage in New Zealand and elsewhere (e.g., sales volumes) and dates of original consent to distribute.

Flurbiprofen 8.75 mg lozenges are for the relief of pain, swelling and inflammation associated with acute severe sore throats. Sore throat is a very common condition with 89% of New Zealanders experiencing a sore throat at least once a year and 53% experiencing a sore throat at least once every 6 months.(5) In addition, the majority of acute sore throats in adults (85-95%) are viral and a self-limiting minor ailment which can generally be self-managed and resolved within a few days.(1, 6)

Flurbiprofen lozenges are available as a self-select over-the-counter medicines in pharmacies in most countries and based on its excellent benefit/risk profile access is becoming wider with the recent down scheduling occurring in two EU countries, Denmark and the Netherlands.

In New Zealand Strepfen Lozenges were approved as Pharmacist Only medicines in February 1999 and have been available in New Zealand since this date, representing more than 20 years in market experience. In 2002 at the 28th meeting of the Medicines Classification Committee flurbiprofen lozenges were recommended to be reclassified to Pharmacy Only medicines. Hence for the vast majority of time, flurbiprofen lozenges have been available in New Zealand for self-selection within pharmacy.

During this time, there has been substantial consumer experience with flurbiprofen lozenges. Over the past two years (2018-2019) more than [redacted] day's supply of flurbiprofen lozenges have been sold in New Zealand.

Flurbiprofen lozenges have been available in Australia as Schedule 2 (Pharmacy Only) medicine since 2003 with no safety issues emerging despite limited pharmacist involvement in its sale. During this time over 302 thousand lozenges have been sold in Australia.(4)

Globally, consumer use of flurbiprofen lozenges is extensive with over [redacted] million lozenges sold since 1999. The total patient exposures for all oromucosal flurbiprofen formulations is estimated to be in excess of [redacted] million since launch to 14 April 2019.(4)

11. Local data or special considerations relating to New Zealand (if applicable).

There are no additional local or special considerations relating to New Zealand.

12. Labelling or draft labelling for the proposed new presentation(s).

The previous consideration of the down-scheduling of topical oral flurbiprofen (lozenges) to General Sale in 2010 was declined as the Committee were concerned that the dose form, presentation and proposed packaging would make it difficult for consumers to differentiate Strepfen from Strepsils and that such confusion could lead to consumers with contraindications to inadvertently take flurbiprofen. At this meeting the committee indicated that this would be reconsidered if the company provided "data confirming that consumers clearly differentiated and understood the differences between Strepfen and cough and cold unmedicated preparations such as Strepsils."(3)

Since this time, the label for Strepfen lozenges have been amended and now complies with TGO 92, representing current best practice. Since 2010 the label for Strepfen lozenges has changed significantly introducing a medicines information panel at the back of the pack and very clear call out of the active ingredient on the front of the pack, in line with the requirements of TGO 92. The Australian TGO 92 labelling requirements were introduced to improve a consumer's understanding of the information on the label and represents current best practice. RB is of the view that these changes effectively address the concerns previously raised by the Committee. The new (Pharmacy Only) Strepfen Lozenge label is illustrated in Appendix 1 and Figure 1 and the previous 2010 label is shown in Appendix 2 and Figure 2 and a current Strepsils label is shown in Figure 3.

As TGO 92 represents current best practice and these standards have been applied to Strepfen packaging we believe that these previous concerns have been addressed and that additional consumer research is not necessary. Note that the primary aims of TGO 92 labelling are to avoid consumer confusion and minimise medication errors.

A comparison of the TGO 92 approved label (Figure 1) with the 2010 label (Figure 2) illustrates that key information of the product label has been enhanced, including:

- The active ingredient and strength are clearly displayed in the new label. It is in a large, dark font (the same colour as the brand name) on a white background; versus the 2010 label where the active ingredient and strength were in a white font reversed out of a coloured background.
- The intended use for “SEVERE SORE THROAT RELIEF” has been added to front of pack. This is in a highlight box, again in a dark font on a white background so that consumers can quickly and clearly identify that this product is for severe sore throats. This information was on front of pack in 2010, but as a smaller bullet point linked to anti-inflammatory action. This enables consumers to quickly differentiate Strepfen from Strepsils and when to consider its use versus other lozenges, be they medicated or unmedicated lozenges.
- The anti-inflammatory action of Strepfen lozenges is now stated twice on front of pack, while previously it was only stated once. This enhances the differentiation between Strepfen and other sore throat lozenges with different actives.
- In addition, a medicines information panel has been added to the back of the pack which very clearly calls out warnings associated with the use of this product as well as the active ingredient, uses, and directions for use (see Appendix 1).

A comparison of the TGO 92 approved label (Figure 1) with the Strepsils Honey and Lemon label (Figure 3) illustrates that the two labels are distinctly different.

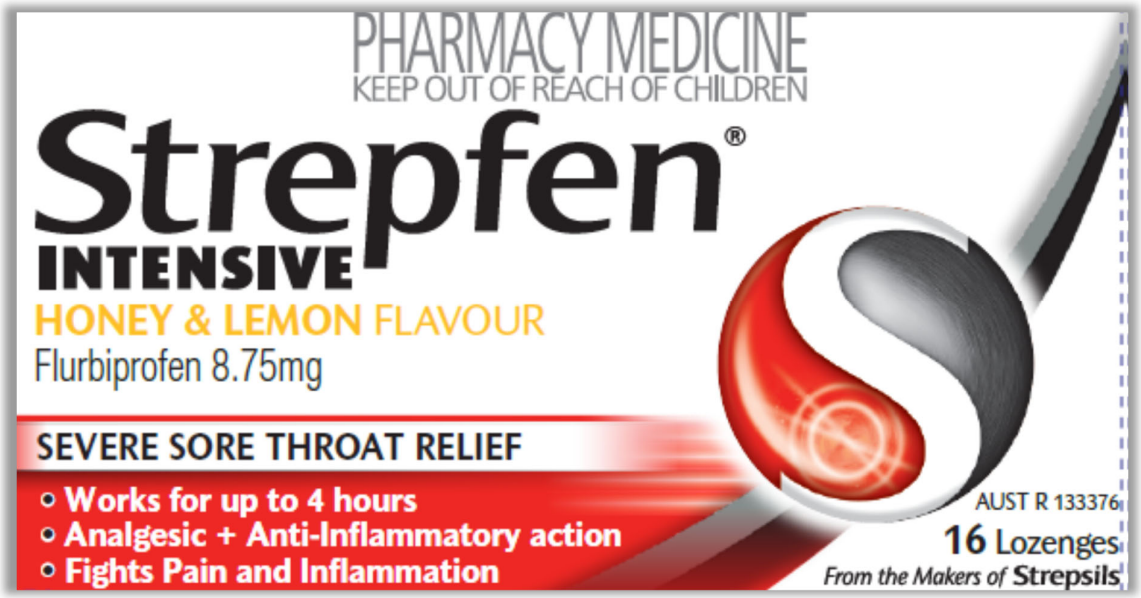
- The active ingredients for both Strepfen and Strepsils are clearly identified. They are in a large dark font on a white background. This makes it very clear that the active ingredients are different.
- The intended use are clearly communicated. For Strepfen this is clearly differentiated by the use of the word INTENSIVE under the brand name and “SEVERE SORE THROAT RELIEF” on front of pack in highlight box. For Strepsils the use is similarly called out for “sore throat relief” in a highlight box as well as “soothes throat discomfort”. This enables consumers to quickly differentiate Strepfen (for severe sore throats) from Strepsils (for milder sore throats) and when to consider Strepfen versus other lozenges.
- The anti-inflammatory actions of Strepfen lozenges is stated twice on front of pack.
- In addition, medicines information panels on the back of the pack are distinctly different with the additional warnings associated with Strepfen clearly and appropriately communicated.

This label clearly differentiates Strepfen from Strepsils, and the risk of confusion has been mitigated. Given the Strepfen labelling provided at Figure 1 is the current Medsafe approved label available for self-selection in pharmacy alongside Strepsils lozenges one can assume that the presentation is deemed sufficiently differentiated from other lozenges and that consumers can distinguish between them.

However, if it was taken by a person with a contraindication, the risk of an adverse outcome is minimal as oromucosal flurbiprofen is locally absorbed and has minimal systemic absorption and as such it has an excellent safety profile(4). The proposed small pack size for Strepfen flurbiprofen lozenges represents 2 day’s supply hence limiting patient exposure. Data from the Periodic Safety Update Report indicates that adverse events resulting from the use of oromucosal flurbiprofen (lozenges or sprays) by people with a history of gastric ulcers with is very rare, with an event rate of 0.000024254%.(4)

Please note, if this submission is accepted, the label for the Strepfen lozenges General Sale packs (16 units) will essentially be the same as the current TGO 92 label (Appendix 1) with the “Pharmacy Medicine” mandatory information removed.

Figure 1: Strepfen Intensive Honey and Lemon current (2020) TGO 92 label



MEDICINE INFORMATION

ACTIVE INGREDIENT (per Lozenge)

- Flurbiprofen 8.75mg.

USES

✓ For relief of pain, swelling and inflammation associated with severe sore throat.

WARNINGS

! Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.
Do not use: x if you have stomach ulcer, impaired kidney function or heart failure **x** if you are allergic to flurbiprofen or other anti-inflammatory medicines **x** if you are trying to become pregnant or during the first 6 months of pregnancy except on the doctor's advice. Do not use at all during the last 3 months of pregnancy **x** in children under the age of 12.
Do not use this product with other products containing flurbiprofen, aspirin or other anti-inflammatory

WARNINGS (cont.)

medicines or with medicine that you are taking regularly unless a doctor or pharmacist has told you to.
Unless a doctor has told you to, do not use: x if you have asthma. **x** for more than a few days at a time.
! Stop taking and see your doctor immediately if you get an allergic reaction.
! If symptoms persist talk to your doctor or pharmacist.
Contains: sugars and honey

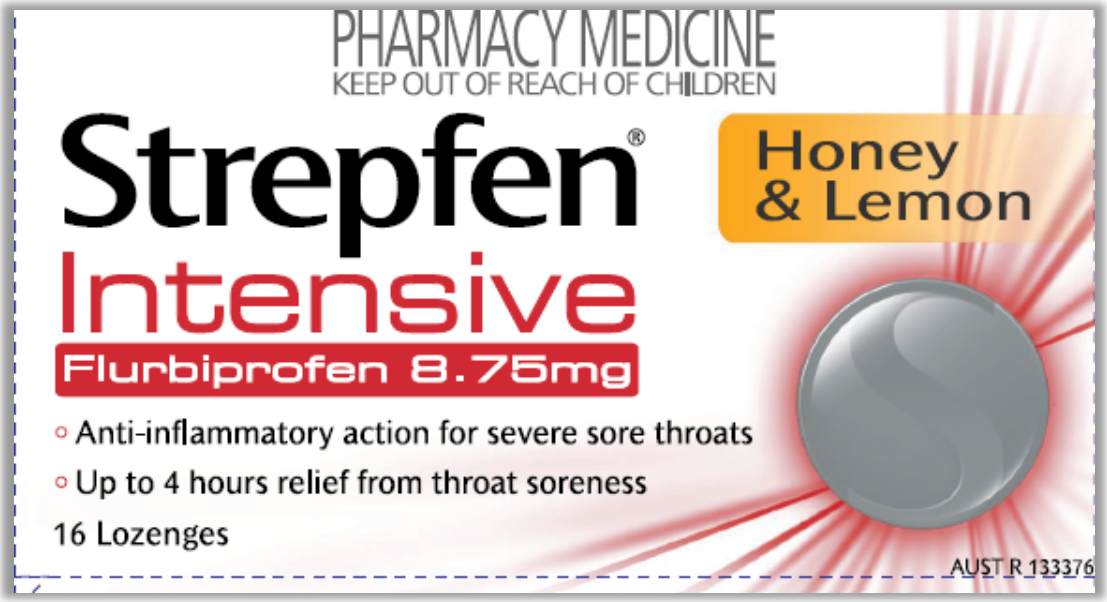
DIRECTIONS FOR USE

Adults and children over 12 years
✓ Suck one lozenge slowly every 3 to 6 hours as needed.
✓ Move lozenge around the mouth occasionally as you suck it.
! Do not take more than 8 Strepfen Intensive lozenges in 24 hours.

OTHER INFORMATION

- Store below 25°C.
- Do not use if foil seal is broken.
- Supplied by Reckitt Benckiser.

Figure 2: Strepfen Intensive Honey and Lemon 2010 label



Anti-inflammatory action:

Strepfen Intensive lozenges are a breakthrough in the treatment of painful and swollen sore throats.

Strepfen Intensive lozenges:

- Provide fast, effective pain relief without numbing.
- Contain the anti-inflammatory and analgesic flurbiprofen.
- Work for up to 4 hours to relieve throat soreness.
- Help eliminate painful swelling and tenderness of the throat.

Directions: Adults and children over 12 years

- Suck one lozenge slowly every 3 to 6 hours as needed. Move the lozenge around the mouth occasionally as you suck it. Do not take more than 8 Strepfen Intensive lozenges in any 24-hour period.
- Not recommended for children under 12 years of age.
- If symptoms persist, talk to your pharmacist or doctor.

Check with your pharmacist or doctor before use:

- If you are receiving regular treatment with other medications.
- If you have asthma. Most asthmatics can take Strepfen Intensive, but if you are sensitive to aspirin or other anti-inflammatory medicines, do not take this product. If you are unsure, ask your doctor or pharmacist for advice.

Do not take:

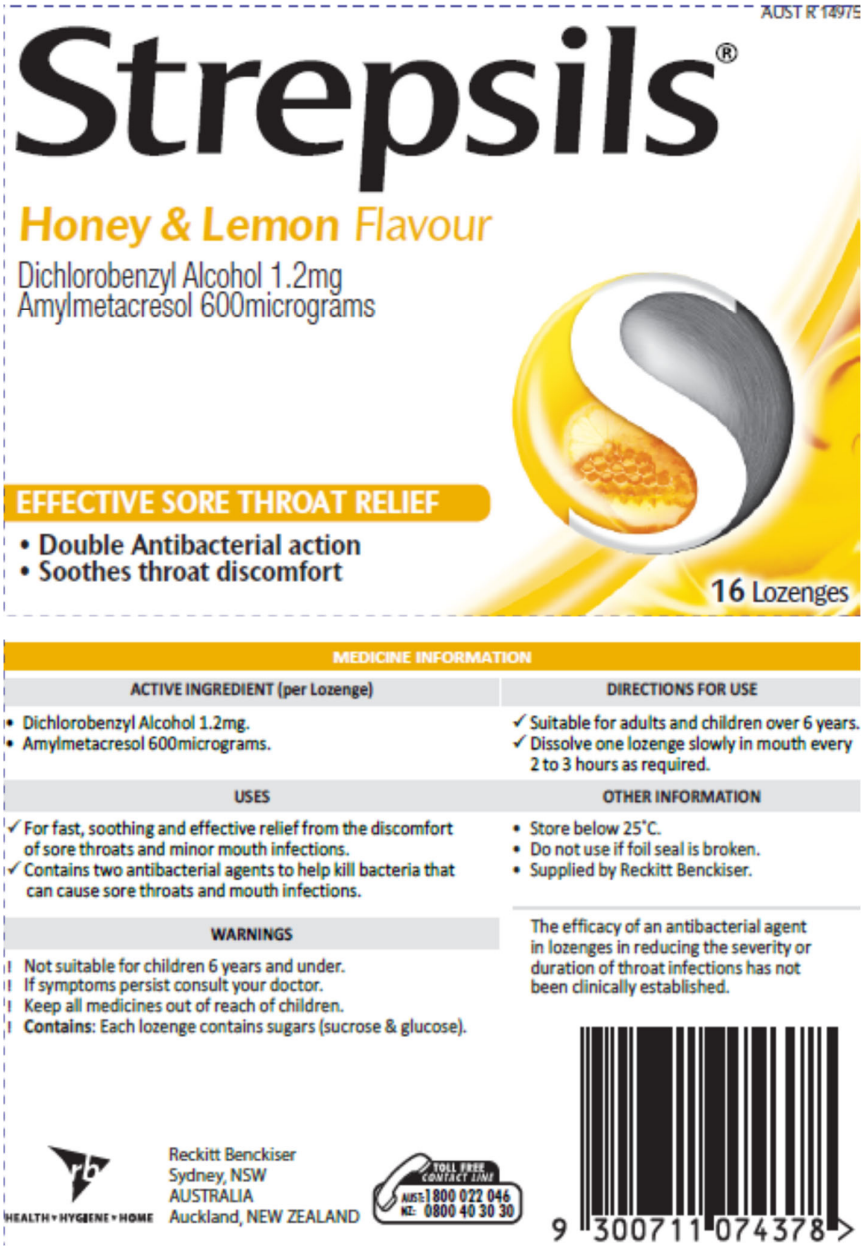
- In the presence of stomach ulcer or other stomach disorders, impaired kidney function or heart failure.
- If you are allergic to aspirin, flurbiprofen or other anti-inflammatory medicines. If you get an allergic reaction, stop taking and see your doctor immediately.
- During pregnancy except with your doctor's advice.
- In the last 3 months of pregnancy.
- For more than 3 days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.

This product is gluten free. Contains sugars and honey.

Do not use if foil seal is broken.
Store below 25°C.

Made in UK

Figure 3: Strepsils Soothing Honey and Lemon



13. Proposed warning statements (if applicable).

Flurbiprofen lozenges is for the relief of pain, swelling and inflammation associated with acute severe sore throat. This is a minor ailment with symptoms that can easily be recognised and are unlikely to be confused by the consumer with other more serious diseases or conditions. Treatment can be managed by the consumer without the need for medical or pharmacist intervention. Australian consumer research shows that the majority of consumers (64%) self-manage their sore throat.(18) There are multiple products for the symptomatic relief of sore throats available in supermarkets and other non-pharmacy retailers. These therapies include demulcents with or without other actives such as

antiseptics, local anaesthetics, or analgesics, as well as oral analgesics including aspirin, ibuprofen and paracetamol. Hence, it is well established that consumers can identify and self-manage sore throats.

The warning statements proposed for flurbiprofen lozenges as a General Sale medicine are identical to the current warning statements for their self-selection within pharmacy. These statements are consistent with those for oral NSAIDs, such as ibuprofen, which are available for General Sale.

The medicines information panel clearly stipulates how to use the product and highlights the contraindications, warnings and precautions as per the requirements of Medsafe and Australia's Therapeutic Goods Administration. Given the Strepfen labelling provided at Figure 1 is the current Medsafe approved label available for self-selection in pharmacy and has warning statements equivalent to those for other General Sale oral NSAIDs, one can assume that it is also appropriate for self-selection in General Sale.

The warning statements on the Strepfen label (below) are the same as those for oral OTC NSAIDs and clearly alerts consumer to the contraindications and precautions for use :

- Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.
- Do not use:
    - if you have stomach ulcer, impaired kidney function or heart failure
    - if you are allergic to flurbiprofen or other anti-inflammatory medicines
    - if you are trying to become pregnant or during the first 6 months of pregnancy except on the doctor's advice. Do not use at all during the last 3 months of pregnancy
    - in children under the age of 12.
- Do not use this product with other products containing flurbiprofen, aspirin or other anti-inflammatory medicines or with medicine that you are taking regularly unless a doctor or pharmacist has told you to.
- Unless a doctor has told you to, do not use:
    - if you have asthma
    - for more than a few days at a time.
- Stop taking and see your doctor immediately if you get an allergic reaction.
- If symptoms persist talk to your doctor or pharmacist.

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

The proposed changes will only apply to locally acting oromucosal preparations containing flurbiprofen 10 milligrams or less per dosage unit, in packs of 16 dose units or less. The only products in New Zealand that would be affected by this change are Strepfen lozenges which are available in two flavours, honey and lemon and orange.

Part B

1. Indications and dose

− What is the medicine indicated for, and for which indication(s) is the reclassification application for?
− What is the evidence that the proposed indication is an OTC indication ie, that the diagnosis and treatment can be understood by the consumer; that the risks of inappropriate treatment can be minimised?
− What is the treatment population for the indication (age; gender etc.)?

− *What is the dose and dose frequency of the medicine for this indication?*

Flurbiprofen 8.75 mg is indicated for the relief of pain, swelling and inflammation associated with severe sore throat. The reclassification application is for this same indication.

Sore throat is a very common condition with 89% of New Zealanders experiencing a sore throat at least once a year and 53% experiencing a sore throat at least once every 6 months.(5) In addition, the majority of sore throats in adults (85-95%) are viral and self-limiting minor ailments which are resolved within a few days.(1, 6) Guidelines recommend the self-management of acute sore throat.(6)

There are several products (therapeutic and non-therapeutic) for the symptomatic relief of sore throats available for self-selection in supermarkets, other non-pharmacy retailers and pharmacy. These therapies include locally acting lozenges containing demulcents with or without other actives such as antibacterial, antiseptics, local anaesthetics, and analgesics (e.g. benzydamine another topical NSAID), as well as oral analgesics including aspirin, ibuprofen and paracetamol. Given these products are available in a General Sale setting one can conclude that it is well established and accepted that consumers can identify and self-manage sore throats. In addition, Australian research has shown that the majority of consumers self-manage their sore throat and do not discuss this with a healthcare professional.(18) As such consumers feel well informed and capable of self-managing their sore throat. The risk of consumers confusing their condition with a more serious disease or condition is very small.

Self-limiting viral infections are the most common cause of sore throats. Streptococcus pyogenes (group A streptococcus) causes approximately 10% of sore throats in adults.(6) These bacterial infections are generally self-limiting, and the risk of complications is very low in developed countries.(13) In addition, General Sale flurbiprofen lozenges are proposed to be available in only a small pack size, 16 lozenges, which represents two day's therapy. The product contains appropriate warning statements, "If symptoms persist, talk to your pharmacist or doctor." Hence, if the sore throat is due to a bacterial infection that may require antibiotics the delay in therapy would be minimal and would also be aligned with clinical practice which is focused on delaying initial antibiotic use for sore throats.(6, 23-25)

Flurbiprofen lozenges are a low-dose topical oral NSAID that has been available in New Zealand since 1999. The risk profile is well defined. Since reclassification for flurbiprofen was last considered in 2010, there has been no significant change in the safety profile of flurbiprofen and the benefit/risk profile remains positive.(4) In addition, a search of the Suspected Medicine Adverse Reaction Search (SMARS) database from 1 January 2000 to 25 April 2020 identified only one suspected adverse event with oral flurbiprofen, and none with flurbiprofen lozenges. This reinforces its excellent safety profile and that consumers can appropriately use this therapy. Over this same time period, there have been 16 reports of 27 suspected adverse reactions with benzydamine (a locally acting nonsteroidal anti-inflammatory drug) which is available in lozenges as a General Sale medicine in New Zealand.(26)

Packaging for flurbiprofen lozenges, contains the same warning statements as applied to General Sale oral NSAIDs. Hence, any potential health risks associated with flurbiprofen lozenge use has been effectively and appropriately addressed with packaging and labelling. The labelling clearly calls out that the lozenges are not to be used for more than a few days at a time and if symptoms persist to talk to a pharmacist or doctor. Pack size has been limited to 2 day's supply further minimising any risk to the consumer.

The treatment population for these indications is for both males and females who are aged 12 years or older.

The dosing instructions for flurbiprofen lozenges are:

- Suck one lozenge slowly every 3 to 6 hours as needed.
- Move lozenge around the mouth occasionally as you suck it.
- Do not take more than 8 Strepfen Intensive lozenges in 24 hours.

2. Presentation

− What is the proposed dose form and strength of the medicine to be reclassified? Is this the same for all indications?
− What disposal considerations need to be made for the medicine?
− How practical and easy to use is the proposed presentation?

The dosage form and strength subject to this reclassification is 8.75 mg lozenges. This is the same dosage form and strength for all indications.

In terms of disposal consideration, the proposed General Sale pack size being limited to up to 16 dose units, represents 2 day's therapy. It is unlikely that there will be any significant disposal considerations associated with this small pack size.

Lozenges are the most commonly used dosage form for the management of sore throats.(18) Medicated (including other locally acting NSAIDs) and non-medicated lozenges to manage sore throats are widely available for General Sale. Hence, these previous reclassification decisions acknowledge that lozenges are a practical and easy to use format for the self-management of sore throats.

3. Consumer benefits

− What is the history of this medicine's use for the proposed indication(s) ie, number of users; number of countries used in?
− To what extent is this medicine used for the proposed indication(s) ie, duration of use; frequency of use?
− What is the evidence that improved access is beneficial for the individual?
− What is the evidence of improved consumer involvement in their health?
− What are the benefits from a consumer viewpoint?

In New Zealand Strepfen Lozenges were approved as Pharmacist Only medicines in February 1999 and have been available in New Zealand since this date, representing more than 20 years in market experience. In 2002 at the 28th meeting of the Medicines Classification Committee flurbiprofen lozenges were recommended to be reclassified to Pharmacy Only medicines. Hence for the vast majority of time, flurbiprofen lozenges have been available for self-selection within pharmacy in New Zealand.

Globally flurbiprofen lozenges are available in 73 countries. In the majority of these countries they are available for self-selection in pharmacy. The lozenges are available for General Sale as unscheduled medicines in four countries including two recent down-scheduling in Europe, specifically in Denmark and the Netherlands and was considered for reclassification for General Sale in Australia at the March ACMS meeting. The interim decision at the March ACMS was to make flurbiprofen lozenges (10 mg or less, for the treatment of adults and children over 12 years of age and in a primary pack containing not more than 16 dosage units) an unscheduled medicine, available for General Sale, from 1 October 2020.

Globally the total patient exposures for all topical oral flurbiprofen is estimated to be in excess of [redacted] million since launch to 14 April 2019. Since its launch in New Zealand the estimated patient exposure for all oromucosal flurbiprofen formulations is in excess of [redacted] patients.(4)

As there is only a single indication for flurbiprofen lozenges, for the relief of pain, swelling and inflammation associated with severe sore throat, it is expected that 100% of the use of flurbiprofen lozenges is for this indication. In addition, data collected from the Periodic Safety Update Report indicates that off label use that results in an adverse event, which includes use in children aged under 12 years, is a rare event with only 9 cases documented.(4)

Consumer benefits

Flurbiprofen lozenges have an equivalent or better benefit/risk profile than systemic oral analgesics and their use is consistent with clinical guidelines.

Flurbiprofen is a weak, monoprotic carboxylic acid (pKa 4.2), structurally related to ibuprofen.(2) As a non-steroidal anti-inflammatory substance, it has an anti-inflammatory effect when applied directly to the throat.(1) Buccal absorption of flurbiprofen is low, with blood levels around 10% of those obtained from the same dose taken orally and swallowed.(2)

Flurbiprofen lozenges are for the relief of pain, swelling and inflammation associated with sore throats. The pain of a sore throat is due to inflammation, hence the therapeutic principle behind the use of flurbiprofen is to expose the painful and inflamed mucosal region of the oropharynx, oral cavity and tonsils to the analgesic and anti-inflammatory actions of flurbiprofen, while minimising systemic exposure. People using this lozenge are exposed to a very small, localised dose of flurbiprofen. The maximum daily dose of flurbiprofen lozenges is 70 mg (from 8 lozenges) which is less than a quarter of the maximum flurbiprofen oral dose of 300 mg.(27) The low dose of flurbiprofen lozenges results in minimal systemic adverse events.(4) The Therapeutic Guidelines for management of Acute Pharyngitis/Tonsillitis recommend analgesics as a first line approach for managing acute sore throat.(6) Guidelines on the management of pain and the use of analgesics recommend using the lowest effective dose for the shortest possible time.(6) Expanding access to flurbiprofen lozenges is entirely consistent with these guidelines and enhances the benefit/risk profile compared to the use of systemically acting oral analgesics which are available for General Sale.

The minimal systemic absorption of flurbiprofen lozenges along with the proposal to limit the pack size to 16 dose units, representing 2 day's therapy for patients taking the maximum dose (8 lozenges per day) and efficacy of topical flurbiprofen in relieving severe acute sore throat contribute to the favourable benefit/risk profile.(28, 29)

Wider access to flurbiprofen lozenges is aligned with the quality use of medicines

Sore throat in the vast majority of cases is a self-limiting condition which can be easily identified and self-managed by consumers.(1, 6) Australian consumer research has shown that the majority (64%) of sore throat sufferers do not consult a healthcare professional when they have a sore throat, but manage their sore throat with options available for self-selection.(18)

Current unscheduled options to treat sore throats include:

- Non-medicated lozenges and mouthwashes, for which there is no clinical data as to their effectiveness when used alone.(30)
- Medicated lozenges and throat sprays containing antiseptics, anaesthetics, and/or analgesics provide some pain relief, but do not address the underlying inflammation that often causes painful pharyngitis and tonsillitis(6, 31) and are therefore unlikely to be as effective as flurbiprofen lozenges which has anti-inflammatory action.(9, 32)
- Oral paracetamol, which has no/minimal anti-inflammatory activity(33)

- Oral NSAIDs such as ibuprofen and aspirin.

Australian research has shown that the most commonly used therapies to manage sore throats are lozenges, with 63% of consumers surveyed indicating that they used lozenges for relief of their sore throats.(18)

Flurbiprofen lozenges are a locally acting, low-dose NSAID which due to its local application to the site of inflammation(32) demonstrates minimal systemic absorption. Systemic exposure is very low due to minimal systemic absorption from the oral mucosa approximately 10% of the equivalent oral dose.(2) The small pack size limits use to 2 days, which is less than that for General Sale oral analgesics. Sixteen dose units represents 2 day's flurbiprofen therapy compared to paracetamol 20 units representing 2.5 day's supply and ibuprofen 200 mg tablets 24s which represents 4 day's therapy.

Clinical trials have confirmed that the pain relief provided by flurbiprofen lozenges is clinically meaningful.(9, 10, 28, 29) It is well accepted that a change in pain of at least 12-13 mm using a 100 mm Visual Analogue Scale (VAS) is clinically meaningful.(34, 35) Therefore, the 47% and 59% reduction in sore throat pain intensity observed in two placebo controlled (or in effect demulcent controlled) clinical trials represent a highly clinically meaningful result.(28, 29)

Therefore, giving consumers wider access to unscheduled flurbiprofen lozenge, with its targeted, localised analgesic and anti-inflammatory actions, will provide access to a more effective topical oral (lozenge) therapy that not only relieves the pain of an acute sore throat but also reduces the inflammation which is the cause of the pain.(8)

Flurbiprofen lozenges have demonstrated clinically meaningful better pain relief than the demulcent effects of non-medicated lozenges

Viral pharyngitis and tonsillitis are the most common causes of sore throat in patients of all ages. Sore throat is a self-limiting condition that is characterised by pain, especially on swallowing, and inflammation of the larynx or pharynx and tonsils.(6)

Clinical studies have shown that acute sore throat pain is often severe in intensity(9, 10) and can result in functional impairment of simple daily activities including swallowing, talking, eating meals, sleeping and working.(11)

The efficacy of flurbiprofen 8.75 mg lozenges has already been evaluated and confirmed by the regulatory authorities including Medsafe and Therapeutic Goods Administration for the "relief of pain, swelling and inflammation associated with severe sore throats."(20)

This effectiveness has been established in multiple placebo-controlled trials. However, in these trials placebo is not an inactive intervention, but represents the demulcent effects of non-medicated lozenges, equivalent to many unscheduled lozenges available for people to manage sore throats. In these comparisons, flurbiprofen lozenges have consistently demonstrated superiority over the demulcent-only lozenges. In one trial, flurbiprofen 8.75mg lozenges demonstrated statistically significant reductions in pain (from 22 minutes), in difficulty swallowing (by 20 minutes), and the sensation of a swollen throat (at 1 hour) vs placebo. These statistically significant separations from placebo represent differentiation from demulcent effects and progression to nociceptive pharmacologic action.(10) Therefore, flurbiprofen lozenges represents a more effective treatment option than many of the current unmedicated lozenges that are available for General Sale.

In addition, clinical trials have confirmed that the pain relief provided by flurbiprofen lozenges is clinically meaningful. It is well accepted that a change in pain of at least 12-13 mm using a 100 mm Visual Analogue Scale (VAS) is clinically meaningful.(34, 35) Therefore, the 47%

and 59% reduction in sore throat pain intensity observed in two placebo controlled (or in effect demulcent controlled) clinical trials represent a highly clinically meaningful result.(28, 29)

As previously highlighted, a survey of consumers identified that the most commonly used format to relieve sore throats are lozenges.(18) Expanding access of flurbiprofen lozenges will provide consumers shopping for throat lozenges in a grocery store a treatment which has both local analgesic and anti-inflammatory actions, in a format that consumers clearly prefer further enabling effective and timely self-management of the pain of an acute sore throat.

The need for pain relief is a major driver of GP consultations and subsequent inappropriate antibiotic use

Most people who experience sore throats self-manage their condition. Despite this, sore throat remains one of the top 10 reasons for visiting a GP.(36) A survey conducted in the UK in 2010-2011 found that 13% of sore throat episodes led to a GP consultation, with the strongest driver of GP consultations being the experience of severe pain. Despite public health initiatives to raise awareness of the over prescribing/use of antibiotics in the treatment of minor respiratory tract infections such as acute viral sore throats, 57% of people who consulted their GP about their sore throat received antibiotics. The authors of this study indicated that to curb antibiotic use for sore throats, strategies should focus on reducing initial GP consultations. Given that the strongest driver of GP consultation was pain, improved access to effective treatments of acute sore throat pain has the potential to curb GP consultations and inappropriate antibiotic use.(14)

Similarly, a Belgian survey of patients visiting the GP for an acute sore throat identified the need for pain relief as the second most common reason for the GP consultation, with 84.5% of people surveyed listing this as an important reason for this consultation. In addition, the need for pain relief was the strongest predictor for the person's hope to receive antibiotics. This indicates that people who visit a GP for an antibiotic script for their sore throat are often in fact seeking pain relief.(12)

An international survey, that included 428 respondents from Australia, also found similar associations between the severity of sore throat pain and antibiotic use. In this survey four of the five symptoms associated with antibiotic use were related to pain or inflammation; 'swollen, tight/inflamed throat', 'burning, painful throat', 'stabbing, sharp pain' and 'cut throat' (a descriptor for severe discomfort).(13) Of concern is that amongst the Australian cohort surveyed, 30% of people used antibiotics for their last sore throat episode and the mean pain/discomfort score associated with this episode was 2.3 on a 5 point categorical scale (1 = dull/annoying, 2 = sore/troublesome, 3 = hurting/miserable, 4 = aching/intense, 5 = throbbing/unbearable). Eleven percent more Australians used antibiotics than the surveyed population from other countries and the Australian use of antibiotics was the third highest amongst the 12 countries surveyed.(13) This research is consistent with other data that demonstrate Australia continues to be a high prescriber of antibiotics, compared with other Organisation for Economic Cooperation and Development (OECD) countries.(23)

This issue is also highly relevant in New Zealand as the use of antibiotics has increased by 49% from 2006 to 2014, with New Zealand having one of the highest rates of antibiotic use in the OECD, higher than that in Australia.(16) The need to prevent antimicrobial resistance by reducing the inappropriate use of antibiotics is recognised by the New Zealand Ministry of Health(17) and this indicates that there is an ongoing public health need to address the overuse of antibiotics for acute viral sore throats.

Relying on pharmacist intervention to help minimise visits to the GP and hence use of antibiotics for viral sore throats has not been effective despite numerous education campaigns and publications on this matter. Research by Shephard and colleagues (2016) was conducted between October and December 2009 with essentially the same range of treatment options for sore throats (unscheduled and OTC) that are available today. Even though pharmacists or pharmacy assistants were the most commonly consulted about the management of sore throats, 30% of all Australians surveyed used antibiotics for their last sore throat.(13) Hence, it does not seem justifiable to limit availability of flurbiprofen lozenge to Pharmacy if the appropriate conversations with consumers are not occurring.

Moreover, 64% of consumers are self-managing their sore throat, without consulting a healthcare professional before purchasing a product. When a sore throat lozenge is purchased from a pharmacy, the pharmacist is involved in only 42% of the purchases.(18) Therefore, the opportunity for pharmacist intervention to help curb inappropriate antibiotic use is limited and insufficient to address the ongoing public health need.

Antibiotic prescribing is often not related to clinical need; new strategies are needed to encourage self-management of acute sore throats and to help minimise unnecessary GP consultations and subsequent antibiotic use.

Doctors are well aware that antibiotics do not help most acute sore throat sufferers.(37) A Cochrane systematic review has confirmed the limited clinical benefits of antibiotics in this setting with the number needed to treat to prevent one sore throat at week one being 21, with antibiotics shortening the duration of symptoms by approximately 16 hours.(38) Clinical guidelines recommend limiting antibiotic use to patients at high risk of complications such as those with existing rheumatic heart disease or scarlet fever, or those at risk of rheumatic fever.(6)

Despite this knowledge, overuse of antibiotics to manage acute sore throat continues.(16, 23)

GP prescribing of antibiotics is often not driven by clinical need alone, but by a complex interplay of perceived clinical need, perceived patient pressure for antibiotics, clinical uncertainty and the desire to maintain a good relationship with the patient.(14, 37) Research indicates that 22.1% of those New Zealanders surveyed had moderate to high feelings of entitlement to be prescribed antibiotics even for minor illnesses.(15) This creates pressure on GPs to prescribe antibiotics even if they may not benefit the patient.

This ongoing public health need to limit inappropriate antibiotic use requires the implementation of new strategies. Expanding access to effective pain management treatments for acute sore throats, as is proposed by this application, has the potential to help reduce unnecessary GP consultations for sore throats and subsequent antibiotic use.(14)

Note, in Australia an equivalent rescheduling application was considered by the Advisory Committee on Medicines Scheduling at the March 2020 meeting. The evaluation of this application concluded that “the net benefits of broadening the availability of flurbiprofen to the general sale level with restrictions placed on age and dosage form combined with warning labels outweighs the potential risks associated with improper use.” The interim decision was to make flurbiprofen lozenges (10 mg or less, for the treatment of adults and children over 12 years of age and in a primary pack containing not more than 16 dosage units) an unscheduled medicine, available for General Sale, from 1 October 2020.(19)

4. Contraindications and precautions

− What are the contraindications for the medicine and how easy are they to identify and prevent?

− What are the precautions for this medicine and how easy are these to understand?

− Does the medicine have a low therapeutic index?
− What class effects need to be considered and what are the risks?
− What are the risks of the medicine being used in an OTC environment?
− What other drug interactions need to be considered?
− What food and/or drink interactions need to be considered?
− Are there any other restrictions when taking the medicine ie, driving restrictions or operating machinery?
− Are there any special populations where exposure to the medicine needs to be restricted?

Contraindications

The contraindications for flurbiprofen lozenges are essentially the same as for oral NSAIDs such as ibuprofen which has a long and safe history of use as a General Sale medicine.

Consumers are advised on pack not to use flurbiprofen lozenges:

- If you have stomach ulcer, impaired kidney function or heart failure
- If you are allergic to flurbiprofen or other anti-inflammatory medicines
- If you are trying to become pregnant or during the first 6 months of pregnancy except on the doctor's advice. Do not use at all during the last 3 months of pregnancy
- In children under the age of 12
- Do not use this product with other products containing flurbiprofen, aspirin or other anti-inflammatory medicines or with medicine that you are taking regularly unless a doctor or pharmacist has told you to.
- Unless a doctor has told you to, do not use:
    - if you have asthma.
    - for more than a few days at a time.
- Stop taking and see your doctor immediately if you get an allergic reaction

As these contraindications are essentially the same as those for ibuprofen 200 mg which is available for General Sale (in packs up to 4 day's supply) it is clear that previous scheduling reviews have concluded that these contraindications are easily identified and understood by consumers and inappropriate use/ misuse is mitigated by appropriate labelling.

Precautions

The precautions associated with the use of flurbiprofen lozenges are essentially the same as those for other oral NSAIDs such as ibuprofen 200 mg which is available for General Sale. Please refer to contraindications section above, for those patient groups who are advised to not use flurbiprofen lozenges.

Many of these precautions arise from clinical use of NSAIDs in the prescription setting, where use is at higher doses for prolonged periods of time. It is well accepted that the short-term use of NSAIDs such ibuprofen in lower doses used in the OTC setting has an excellent safety profile.(39-41)

Importantly the risk associated with the use of flurbiprofen lozenges would be expected to be lower than with other General Sale NSAIDs such as aspirin as the flurbiprofen lozenge is a low-dose topical oral NSAID and systemic exposure is minimal due to relatively low absorption from the oral mucosa (10% of the equivalent dose of a flurbiprofen tablet).(2)

The precautions for flurbiprofen lozenges are equivalent to those for aspirin and ibuprofen 200 mg which is available for self-selection as General Sale medicine. It is therefore clear

that previous scheduling reviews have concluded that these precautions can be easily identified and understood by consumers.

Wide therapeutic index

Flurbiprofen lozenges has a wide therapeutic index, an excellent safety profile and its action is localised to the throat(1) given its relatively low absorption from the oral mucosa.(2) There is no evidence to suggest that the toxicity or safety profile of flurbiprofen lozenges has changed over time. This is supported by safety data from the latest Reckitt Benckiser Periodic Safety Update Report (PSUR). This update covers the reporting period of the 15 October 2018 to 14 April 2019. During this period, the patient exposure to topical oral flurbiprofen is estimated at over [redacted] million patients with over 80% being exposed to the lozenge formulations. There have been no new important, potential or identified risks associated with use of flurbiprofen lozenges (or other topical oral formulations) during this reporting period.(4)

In addition, the cumulative global data since November 1976 indicate no new safety concerns have been identified and that the incidence of adverse events is very low with 4,516 adverse events reported from over [redacted] million patient exposures.(4)

Data from the New Zealand Suspected Medicine Adverse Reaction Search (SMARS) database for the period of 1st January 2000 to 25th April 2020 also supports the good safety profile of flurbiprofen lozenges. During this period there have been no reported adverse events with flurbiprofen lozenges and only one reported case for any use of flurbiprofen, a case of melena in a female taking oral flurbiprofen. During this same time period there have been 16 reports of 27 adverse events associated with the use benzydamine, a topical oral NSAID, available for General Sale in New Zealand.(26)

Class effects

The main class effects that need to be considered are those associated with the use of NSAIDs, such as aspirin and ibuprofen which are both available as General Sale medicines, such as the risk of gastrointestinal side effects.

As previously stated, the safety risk associated with flurbiprofen lozenges would be expected to be lower than with these other oral NSAIDs as the systemic exposure following the use of flurbiprofen lozenge is minimal due to its relatively low absorption from the oral mucosa (10% of the equivalent dose of a flurbiprofen tablet).(2) In addition, limiting the pack size to 16 dose units, equivalent to 2 day's supply, is shorter than that for General Sale oral NSAIDs which is of the order of 4 day's supply.

Data from the Periodic Safety Update Report indicates that adverse events resulting from the use of topical oral flurbiprofen (lozenges or sprays) by people with a history of gastric ulcers is very rare, with an event rate of 0.000024254% since the product was first launched globally in 1976.(4)

In addition, the packaging for flurbiprofen lozenges contains essentially the same warning statements as other oral NSAIDs, hence the risk of class effects is addressed by the product label.

Risks of the medicine used in the OTC setting

In RB's view, there is minimal risk associated with use of flurbiprofen lozenges for the following reasons:

- Sore throats are self-limiting conditions that can be and are commonly managed without doctor or pharmacist intervention.

- Consumers are well informed and equipped to manage sore throats and sore throat pain.
- The risk of confusing sore throats with more serious conditions is small and addressed with labelling directions that instructs consumers to seek pharmacist or doctor advice if their symptoms persist.
- General Sale pack size is limited to 16 dose units, equivalent to 2 day's supply. Hence prolonged use without seeking medical advice is unlikely to occur and the risk is lower than with other General Sale oral NSAIDs which are available in pack sizes equivalent to 4 day's supply.
- The systemic exposure to the active ingredient is lower with flurbiprofen lozenges, than that with other General Sale oral NSAIDs or paracetamol due to the low systemic bioavailability from the oral mucosa.(2)
- Flurbiprofen lozenges has an excellent safety profile, with the current PSUR indicating that the benefit/risk profile remaining positive.(4)
- Packaging for flurbiprofen lozenges contains the same warning statements as applied to General Sale oral NSAIDs. Hence, any potential health risks associated with flurbiprofen lozenge use in the General Sale setting has been effectively and appropriately addressed with packaging and labelling.

Drug interactions

There is minimal risk of clinically significant drug interactions associated with the General Sale use of flurbiprofen lozenges.

Potential drug interactions are those that are common for any oral NSAID. The main potential interaction of concern is the concomitant use with aspirin or another NSAID. This can occur with other NSAIDs that are available for General Sale and this risk is being managed in equivalent fashion with appropriate warning statements on the product packaging and clearly identifying that Strepfen has anti-inflammatory action on front of pack.

Data from the Periodic Safety Update Report indicates that adverse events resulting from the concomitant use of topical oral flurbiprofen (lozenges or sprays) with aspirin or other NSAIDs is extremely rare, with an event rate of 0.00000117% since the product was first launched globally in 1976.(4)

In addition, if this use was to occur the risk of harm is expected to be lower than that for other oral NSAIDs available for General Sale, as the pack size is smaller (2 versus 4 day's supply) and the systemic NSAID exposure is low due to flurbiprofen's low oral mucosal absorption.(2)

Food/drink interactions

There are no relevant food or drink interactions.

Other restrictions

There are no additional restrictions regarding the use of flurbiprofen lozenges.

Special populations where exposure to the medicine needs to be restricted

Patient groups that should not take flurbiprofen lozenges are the same groups that cannot take other NSAIDs such as aspirin and ibuprofen which are available for self-selection as General Sale medicines. These groups are listed on the product packaging and are patients with:

- Stomach ulcers

- Impaired kidney function
- Heart failure
- If you are trying to become pregnant or are pregnant
- Children under the age of 12.

The effectiveness of warning statements about who should not use flurbiprofen lozenges is indicated with safety data from the PSUR. Between 10 November 1976 and 14 April 2019, use during pregnancy that resulted in an adverse event was extremely rare, with only 13 cases reporting use during the first or second trimesters (event rate relative to cumulative exposures of 0.000001383%) and only 12 cases in the third trimester (event rate of 0.000001277%).(4)

Events amongst people with other comorbidities that should avoid using flurbiprofen lozenges is also extremely rare with adverse event rates of:(4)

- 0.000024254% in people with current or a history of gastric ulcers
- 0.000003085% for renal impairment and use in patients with renal failure
- 0.000007446% for cardiovascular disease and use in patients with cardiac failure.

Similarly, there is an extremely low risk of adverse events due to the use of flurbiprofen in children aged under 12 years of age. There have been 9 such reports that resulted in an adverse event of which 8 were non-serious. As flurbiprofen is not indicated in children it is not possible to determine the overall exposure in children, however the cumulative exposure exceeds [redacted] million patients.(4)

If use was to occur by people with these conditions, the risk associated with the use of flurbiprofen lozenges would be expected to be lower than with other NSAIDs available for General Sale, such as aspirin, as the flurbiprofen lozenge is a low-dose locally acting NSAID and systemic exposure is minimal due to relatively low absorption from the oral mucosa (10% of the equivalent dose of a flurbiprofen tablet).(2)

In addition, the use in people from 12 years is based on the patient population included in the clinical trials for flurbiprofen. This age limit is not based on any specific safety concerns for use in younger children. Safety issues are unlikely in children as other oral NSAIDs, such as ibuprofen, have a well-established tolerability and safety profile in children that is similar to placebo(42) and topical flurbiprofen in lozenge format is a low-dose localised NSAID.

5. Undesirable effects

− What are the known undesirable effects and the frequencies of these? Do these vary for special populations?
− What are the risks and consequences of known undesirable effects?
− Are there any significant safety concerns for the medicine under review?
− Have there ever been any withdrawals of the medicine or other regulatory actions taken for safety reasons (during a time period or in a specific jurisdiction)?
− Are there any withdrawal effects following cessation of use of the medicine?

Extensive data on the safety of flurbiprofen lozenges have been presented and evaluated in the previous application for down-scheduling in both New Zealand and Australia.

Australia's National Drugs and Poisons Schedule Committee (NDPSC) evaluation of this data in 2010 came to the following conclusions:(43)

> "Use of flurbiprofen lozenges in Australia and NZ had been associated with an excellent safety profile, and there was no expectation that a shift from Schedule 2 to exempt would result in any additional problems."

> "The spontaneous reporting rate of adverse events (AE) has been very low, and post-marketing surveillance suggested that the lozenge formulation was very safe in OTC use. There was no reason to expect that a shift to general availability would be associated with any significant change in the safety profile."

Since 2010, there have been no signals that would indicate a change in the excellent safety profile of flurbiprofen lozenges. The current Periodic Safety Update Report indicates that there have been no new important, potential or identified risks associated with use of flurbiprofen lozenges (or other oromucosal formulations) and that the benefit/risk profile remains positive.(4)

The cumulative global data since November 1976 indicates a very low incidence of adverse events associated with topical oral flurbiprofen use. Since launch patient exposures exceeds [redacted] million, with only 4,516 adverse events reported.(4)

The favourable safety profile is further supported by the absence of any adverse events reported for flurbiprofen lozenges in New Zealand for the period of 1st January 2000 to 25th April 2020.(26) During this same time period there have been 16 reports of 27 adverse events associated with the use benzydamine (e.g. Difflam lozenges, sprays or mouthwash), a topical oral NSAID available for General Sale in New Zealand.(26)

The low incidence of adverse events is also supported by Australian post-marketing surveillance data. Since its launch in Australia in 2001 until 1st June 2019 there have only been 4 adverse events recorded in the Database on Adverse Event Notifications for flurbiprofen lozenges (See Table 4), compared to 31 cases for benzydamine hydrochloride (Difflam).(44)

Table 4: Adverse events reported for flurbiprofen lozenges in Australia(44)

Year	Case report
2001	A 46-year-old male reported hallucinations following use of Strepfen (product not stated)
2002	A 40-year-old female reported face oedema, paraesthesia, pruritus, tongue oedema and urticaria following use of Strepfen (product not stated)
2009	A female (age not stated) reported chest discomfort, condition aggravated, dizziness and hypersensitivity following use of Strepfen
2014	A 14-year-old female reported pruritic rash following use of Strepfen

There is no evidence to indicate that the adverse events occur at a higher incidence in special populations.

Flurbiprofen lozenges have not been withdrawn from any market due to safety concerns related to the active ingredient.

There are no withdrawal effects following the cessation of flurbiprofen lozenges.

6. Overdose

− Is there a potential for overdose of the medicine?
− What are the consequences of overdose of the medicine?
− Are there any reports of overdose of the medicine?

Like all other NSAIDs, flurbiprofen is not known to have the potential for abuse and therefore the potential for intentional overdose is negligible.

The maximum proposed pack size for General Sale flurbiprofen lozenges is 16 dose units. Even if an accidental overdose was to occur and all lozenges were taken at once, the clinical consequences would be minimal as the dose of flurbiprofen in each lozenge is low and with limited systemic exposure. Each lozenge contains 8.75 mg; a pack contains 140 mg flurbiprofen which is lower than the usual daily dose of oral flurbiprofen of between 150 and 300 mg.(27)

Products containing flurbiprofen for the symptomatic relief of sore throats have been available in New Zealand since 1999 and in Australia since 2001. There has been no evidence of misuse, abuse or illicit use to date and no reports in the Suspected Medicine Adverse Reaction Search (SMARS) database or the TGA's Database on Adverse Event Notifications.(26, 44)

The risk of overdose is negligible. The Reckitt Benckiser PSUR lists 1 report of 'intentional overdose', 11 reports of 'accidental overdose' and 25 reports of 'overdose' for all oromucosal dosage forms of flurbiprofen. During this period patient exposures exceeded [redacted] million.(4)

7. Medication errors and abuse/misuse potential

− Would reclassification affect the risk of unnecessary use?
− Is the medicine be provided with necessary tools to allow correct dosing eg, liquids supplied with a measuring device?
− What are the reported medication errors post-market?
− What are the reported cases of abuse/misuse/accidental overdose?
− How would reclassification affect import considerations?
− What is the addiction potential of the medicine?

Unnecessary use

Flurbiprofen 8.75 mg lozenges are for the relief of pain, swelling and inflammation associated with acute severe sore throats. Sore throat is a very common condition with 89% of New Zealanders experiencing a sore throat at least once a year and 53% experiencing a sore throat at least once every 6 months.(5)

The majority of sore throats in adults (85-95%) are viral and self-limiting minor ailments which are resolved within a few days.(1, 6) As flurbiprofen's actions are limited to its anti-inflammatory and analgesic properties, its availability as a General Sale medicine is unlikely to result in unnecessary use.

Necessary tools

Lozenges are the most commonly used dosage form for the relief of sore throats(18), hence consumers are familiar with how to use them to manage a sore throat.

Flurbiprofen lozenges have the potential for inducing transient local irritation of the buccal mucosa. Moving the lozenge around in the mouth whilst sucking can reduce these effects, and the labelling for flurbiprofen lozenges gives clear instructions to move the lozenge

around the mouth as follows: “Suck one lozenge slowly every 3 to 6 hours as needed. Move the lozenge around the mouth occasionally as you suck it.”

These instructions appear to be effective as data from the post-marketing surveillance databases and the PSUR indicates that flurbiprofen lozenges have an excellent safety profile.(4, 26, 44)

Potential for medication errors

The Reckitt Benckiser PSUR for the period up to 14 April 2019 indicates that there is a negligible risk of medication errors with flurbiprofen lozenges. Medication errors were classified as incorrect route of administration [2 cases], overdose [2 cases], administered to patient of inappropriate age [2 cases], use in unapproved indication [4 cases], product use issue [1 case], underdose [2 cases] and wrong technique in product usage [1 case]. All 14 adverse events associated with medication errors were non-serious indicating that on the rare occasions when a medication error has occurred, the risk of harm is negligible.(4)

Addiction, misuse, abuse, accidental overdose

Like other NSAIDs, flurbiprofen is not known to have the potential for abuse or addiction.

The Reckitt Benckiser PSUR lists one report of dependence and no reports of addiction for all topical oral dosage forms of flurbiprofen since 10 November 1976. During this period patient exposures exceeded [redacted] million. This demonstrates the risk of dependence/addiction is negligible.(4)

During the same reporting period, the PSUR lists 6 reports of ‘intentional misuse’ for all dosage forms of flurbiprofen again demonstrating that the risk of inappropriate use and misuse is negligible.(4)

The risk of accidental overdose is also negligible with 11 reports of ‘accidental overdose’ since 10 November 1976.(4)

The maximum proposed pack size for General Sale flurbiprofen lozenges is 16 dose units. Even if an accidental overdose was to occur and all lozenges were taken at once, the clinical consequences would be minimal as the dose of flurbiprofen in each lozenge is low and with limited systemic exposure. Each lozenge contains 8.75 mg; a pack contains 140 mg flurbiprofen which is lower than the usual daily dose of oral flurbiprofen of between 150 and 300 mg.(27)

Import considerations

This reclassification to General Sale would not impact any import considerations. Please note that an equivalent application for reclassification has been applied for in Australia and was considered by the Advisory Committee on Medicines Scheduling at the March 2020 meeting. The interim decision was to classify flurbiprofen lozenges (10 mg or less, for the treatment of adults and children over 12 years of age and in a primary pack containing not more than 16 dosage units) as an unscheduled medicine, available for General Sale, from 1 October 2020.(19)

8. Communal harm and / or benefit

− What are the possibilities of community harm resulting from wider use of the medicine in question (eg, the development of antibiotic resistance in bacteria or increased immunisation rates)?
− What are the possibilities of community benefit resulting from wider use of the medicine in question (eg, greater herd immunity as a result of improved access to a communicable disease vaccine)?

Not applicable. Pain is a personal and subjective experience and effective management varies from individual to individual. The risks and benefits have been addressed elsewhere in the submission.

9. Integrated benefit-risk statement

A summary of the reclassification benefits
− A summary of the reclassification risk of harm
− A summary of the need for the medicine at the classification proposed
− Precedent – how are other medicines in the same class classified?

From the information provided, it is clear that low-dose flurbiprofen lozenges (8.75 mg) are a safe and well-tolerated medication, providing effective short-term relief for patients with a sore throat. The overall benefit-risk profile of flurbiprofen lozenges remains positive with more than 40 years in market experience globally.(4)

The previous consideration of the reclassification of topical oral flurbiprofen (lozenges) was declined as there were concerns for potential inappropriate use by people with contraindications. However, it was also acknowledged that this risk could be managed by appropriate labelling that clearly differentiated Strepfen from other medicated preparations such as Strepsils.(3)

Since this consideration, there has been a decade of self-selection availability of Strepfen lozenges within pharmacy in New Zealand and not a single adverse event recorded on the Suspected Medicine Adverse Reaction Search database.(26) In addition, data from the Periodic Safety Update Report indicates that adverse events resulting from the use of topical oral flurbiprofen (lozenges or sprays) by people with a history of gastric ulcers is very rare, with an event rate of 0.000024254% since the product was first launched globally in 1976.(4) This indicates that consumers with contraindications can self-select the appropriate product and/or that flurbiprofen has an excellent safety profile that is enhanced by its pharmacological actions being essentially limited to local effects(1) and given its low systemic bioavailability from oromucosal absorption.(2)

In addition, since the previous consideration, the label for Strepfen lozenges have been amended to comply with TGO 92. As TGO 92 represents current best practice and that the primary aims of TGO 92 labelling are to avoid consumer confusion and medication errors we believe that these previous concerns have been addressed and support the reclassification of flurbiprofen lozenges to General Sale.

The data presented in this submission, continues to support that there is little risk associated with this proposed reclassification, but that there are benefits, both for the individual and at the public health level.

Lozenges are the most commonly used dosage form for the management of sore throats and providing the public with wider access to a more effective analgesic/anti-inflammatory lozenge has the potential to improve self-management of this common condition.

Pain is also the principle driver of people with sore throats seeking GP consultation, which in 30% of cases results in antibiotics being used.(13) New strategies which reduce GP visits are required to curb the use of antibiotics for minor, self-limiting ailments including sore throats. The reclassification of flurbiprofen lozenges to General Sale is one such strategy.

In addition, flurbiprofen has a well-established safety profile and can be supplied with acceptable safety without access to health professional advice.

In terms of precedent, lozenges that contain NSAIDs for oromucosal use, benzydamine are available for General Sale in New Zealand without any pack size limitations. These lozenges are used for the same indication as flurbiprofen, the relief of sore throats. Although it is difficult to assess the relative safety of different medications from adverse event databases, since January 2000 there have been no reports of adverse events with flurbiprofen lozenges in New Zealand, while there have been 16 reports for benzydamine.(26) This suggests that flurbiprofen lozenges have a good safety profile which is suitable for General Sale availability.

In terms of precedent, oral NSAIDs, aspirin and ibuprofen, are indicated for the management of sore throat pain and these are available as General Sale medicines in New Zealand in larger pack sizes that deliver larger systemic exposures than proposed for flurbiprofen lozenges. Hence, the risks for harm is lower with flurbiprofen lozenges than oral NSAIDs that are available for General Sale. This indicates that flurbiprofen lozenges have a good benefit/risk profile which is suitable for General Sale availability.

10. Risk mitigating strategies

− Are there any risk mitigation strategies required? If so, what risk mitigation strategies are required eg, healthcare professional education; integration of care; consumer information to be provided etc?
− What is the evidence that these proposed risk mitigation strategies would be effective?
− What post-market surveillance activities would be carried out?
− Is the proposed reclassification supported by professional bodies?

The proposed reclassification poses negligible change in risk as alternative therapies oral NSAIDs that are used to manage sore throats are used in higher doses, deliver higher systemic NSAID exposures and are available in larger pack sizes than that proposed for flurbiprofen lozenges.

The label for Strepfen lozenges has been amended to comply with TGO 92. TGO 92 represents current best practice and has been developed to avoid consumer confusion and medication errors. This includes clear warning statements as to who should avoid using this medication. This amended label is an effective risk mitigation strategy and supports the reclassification of flurbiprofen lozenges to General Sale.

As the risk of harm associated with this reclassification is negligible, no additional risk-mitigation strategies or additional post-marketing surveillance studies are proposed.

Conclusion

From the information provided, it is clear that flurbiprofen in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit, when sold in the manufacturer's original pack containing not more than 16 dose units is a safe and well-tolerated medication, that provides effective relief of sore throat pain and is suitable for reclassification to General Sale.

Flurbiprofen has a wide therapeutic index and a favourable benefit/risk profile, which is equivalent or better than other General Sale oral NSAIDs due to its localised action and low systemic exposure.

The updated labelling complies with TGO 92 and clearly differentiates Strepfen from Strepsils. As it is TGO 92 compliant, the risk of consumers with contraindications inadvertently using flurbiprofen lozenges is minimised. In addition, evidence from the PSUR indicates that even if this was to occur that the risk of harm is negligible.(4)

The availability of flurbiprofen lozenges in limited pack sizes (≤ 16 dose units) as a General Sale medicine will benefit consumers giving them easier access to an effective localised therapy and has the potential to reduce the inappropriate use of antibiotics for common viral throat infections.

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Appendix 1: Current Flurbiprofen Lozenge Label

Strepfen®
INTENSIVE
HONEY & LEMON FLAVOUR

PHARMACY MEDICINE
KEEP OUT OF REACH OF CHILDREN

Strepfen®
INTENSIVE
HONEY & LEMON FLAVOUR
Flurbiprofen 8.75mg

SEVERE SORE THROAT RELIEF

- **Works for up to 4 hours**
- **Analgesic + Anti-Inflammatory action**
- **Fights Pain and Inflammation**

AUST R 133376

16 Lozenges

From the Makers of **Strepsils**

This product is gluten free

Reckitt Benckiser
Sydney, NSW
AUSTRALIA
Auckland, NEW ZEALAND

HEALTH ▸ HYGIENE ▸ HOME

TOLL FREE CONTACT LINE
AUST: 1800 022 046
NZ: 0800 40 30 30

<9371 1777>

Lane 1 Lane 2 Lane 3

EXP.

Lane 1 Lane 2 Lane 3

B

3086638

Strepfen® INTENSIVE HONEY & LEMON FLAVOUR

MEDICINE INFORMATION

ACTIVE INGREDIENT (per lozenge)

- Flurbiprofen 8.75mg.

USES

✓ For relief of pain, swelling and inflammation associated with severe sore throat.

WARNINGS

! Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.

Do not use: x if you have stomach ulcer, impaired kidney function or heart failure **x** if you are allergic to flurbiprofen or other anti-inflammatory medicines **x** if you are trying to become pregnant or during the first 6 months of pregnancy except on the doctor's advice. Do not use at all during the last 3 months of pregnancy **x** in children under the age of 12.

Do not use this product with other products containing flurbiprofen, aspirin or other anti-inflammatory medicines or with medicine that you are taking regularly unless a doctor or pharmacist has told you to.

Unless a doctor has told you to, do not use: x if you have asthma. **x** for more than a few days at a time.

! Stop taking and see your doctor immediately if you get an allergic reaction.

! If symptoms persist talk to your doctor or pharmacist.

Contains: sugars and honey

DIRECTIONS FOR USE

Adults and children over 12 years

✓ Suck one lozenge slowly every 3 to 6 hours as needed.

✓ Move lozenge around the mouth occasionally as you suck it.

! Do not take more than 8 Strepfen Intensive lozenges in 24 hours.

OTHER INFORMATION

- Store below 25°C.
- Do not use if foil seal is broken.
- Supplied by Reckitt Benckiser.

Appendix 2: 2010 Flurbiprofen Lozenge Label

PHARMACY MEDICINE

KEEP OUT OF REACH OF CHILDREN

Strepfen®

Intensive

Honey & Lemon

Flurbiprofen 8.75mg

- Anti-inflammatory action for severe sore throats
- Up to 4 hours relief from throat soreness

16 Lozenges

AUST R 133376

Lane 1 Lane 2 Lane 3

EXP.

Lane 1 Lane 2 Lane 3

<9371 1777>

Reckitt Benckiser

Reckitt Benckiser
44 Wharf Road, West Ryde,
NSW 2114, AUSTRALIA.
Auckland, NEW ZEALAND.

TOLL FREE CONTACT LINE
AUST: 1800 226 766
NZ: 0508 731 234

Anti-inflammatory action:

Strepfen Intensive lozenges are a breakthrough in the treatment of painful and swollen sore throats.

Strepfen Intensive lozenges:

- Provide fast, effective pain relief without numbing.
- Contain the anti-inflammatory and analgesic flurbiprofen.
- Work for up to 4 hours to relieve throat soreness.
- Help eliminate painful swelling and tenderness of the throat.

Directions: Adults and children over 12 years

- Suck one lozenge slowly every 3 to 6 hours as needed. Move the lozenge around the mouth occasionally as you suck it. Do not take more than 8 Strepfen Intensive lozenges in any 24-hour period.
- Not recommended for children under 12 years of age.
- If symptoms persist, talk to your pharmacist or doctor.

Check with your pharmacist or doctor before use:

- If you are receiving regular treatment with other medications.
- If you have asthma. Most asthmatics can take Strepfen Intensive, but if you are sensitive to aspirin or other anti-inflammatory medicines, do not take this product. If you are unsure, ask your doctor or pharmacist for advice.

Do not take:

- In the presence of stomach ulcer or other stomach disorders, impaired kidney function or heart failure.
- If you are allergic to aspirin, flurbiprofen or other anti-inflammatory medicines. If you get an allergic reaction, stop taking and see your doctor immediately.
- During pregnancy except with your doctor's advice.
- In the last 3 months of pregnancy.
- For more than 3 days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.

This product is gluten free. Contains sugars and honey.

Do not use if foil seal is broken.

Store below 25°C. Made in UK

0227937

Strepfen® Intensive Honey & Lemon