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

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Table of Contents

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 and when labelled only for the treatment of adults and children over 12 years 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 reclassification of flurbiprofen lozenges to General Sale in 2020 was declined as the Committee considered the submission was deficient in New Zealand specific data and that it did not take into account the prevalence of acute rheumatic fever in New Zealand and the risk posed by increasing the availability of a medicine that could potentially mask the symptoms of a sore throat and potentially impact the incidence of untreated streptococcal throat infections, through delayed detection and diagnosis.(3)

The current application addresses the issues raised by the Committee at the 65th meeting. This application demonstrates that:

1. Flurbiprofen lozenges are unlikely to mask the symptoms of a Streptococcal A sore throat infection.
2. Acute rheumatic fever is predominantly a clinical issue in children aged younger than 12 years, and flurbiprofen lozenges are not indicated for use in this age group.
3. Current health initiatives to address the prevalence of acute rheumatic fever in New Zealand are working and hence this risk is mitigated by these initiatives. This is evident by lower incidences of first time rheumatic fever from 2014 to 2019 than in 2010.(4) In addition, New Zealand research of parents in at risk regions found high levels of awareness of rheumatic fever and that 9 in 10 parents indicated that the best way to manage their child’s sore throat was to see a doctor or nurse straight away, which is consistent with the public health initiatives.(5) There is no evidence to indicate that the effectiveness of these initiatives would be compromised by the General Sales availability of flurbiprofen lozenges.
4. There are anti-inflammatory lozenges (containing benzydamine hydrochloride) that are currently available as General Sale medicine. Benzydamine hydrochloride lozenges have similar effectiveness to flurbiprofen lozenges in the relief of sore throat pain.(6) As the actions and efficacy are comparable, the risk of masking the symptoms of a Streptococcal A sore throat infection is at face value at least equivalent. However, benzydamine hydrochloride lozenges are approved for use in younger children from 6 years of age while for flurbiprofen approval for use is in children 12 years or older. Therefore, benzydamine hydrochloride lozenges can be used by almost all children with the greatest risk of developing acute rheumatic fever (aged 5 to 14 years).(7-9) As benzydamine hydrochloride lozenges are classified as a General Sale medicine, the reasonable conclusion is that the benefit/risk profile is favourable and the risk of delaying the management of Streptococcal A throat infections in at risk populations is minimal. Given that flurbiprofen lozenges cannot be used by children aged under 12 years, the vast majority of children at greatest risk of acute rheumatic fever cannot use these lozenges and therefore there is negligible risk of delaying the management of Streptococcal A throat infections in these children. For those children aged 12 to 14 years the risk is the same as for

General Sale benzydamine hydrochloride lozenges. Hence, the risk posed by the reclassifying flurbiprofen lozenges to General Sale is lower than the risk posed by benzydamine lozenges.

5. New Zealand specific consumer research has demonstrated that the majority of consumers are aware that sore throats can be a serious illness and that most New Zealanders have heard about rheumatic fever, with 96% awareness amongst Māori and Pacific Islanders. This research also identified that the current management of sore throats by consumers is unlikely to delay the diagnosis of Streptococcal A sore throat infections. The majority of consumers seek medical advice if the sore throat persisted for more than 2 days. Importantly, 2 in 3 parents of children with a sore throat which has persisted for more than 2 days would seek medical advice. If the child's sore throat was accompanied by other symptoms such as a fever or pus almost all parents would seek medical advice with it being highest at 93% amongst Māori and Pacific Islanders (who are at greatest risk). Of most significance, was the finding that after reading the label for Strepfen lozenges, 9 in 10 people would seek medical advice if their sore throat persisted for more than 2 days. Hence, this New Zealand specific research has demonstrated that given the current health initiatives which raise awareness about acute rheumatic fever, New Zealanders, are very conscious that a sore throat may become serious. As such the risk of masking a serious medical condition, Streptococcal A sore throat infection, is effectively managed by current educational campaigns and current warning statements on pack. In addition, awareness and comprehension of the appropriate actions is consistently higher for the cohort at risk, Māori and Pacific Island people.(10)

The previous consideration of the reclassification of topical oral flurbiprofen (lozenges) also raised concerns for potential inappropriate use of flurbiprofen lozenges by people with contraindications and concerns that consumers may not clearly differentiated Strepfen from other medicated preparations such as Strepsils. The Committee indicated that the lack of New Zealand research demonstrating that consumers could differentiate Strepfen from Strepsils made it difficult for them to overcome their reservations.(11)

A recent label discernment study confirmed that New Zealand consumers can in fact differentiate Strepfen lozenges from Strepsils lozenges and that they understand the difference in the active ingredients and indications.(10)

- Anti-inflammatory action was correctly attributed to Strepfen by 80% of consumers and 83% of Māori and Pacific Island people.
- Anti-bacterial action was correctly attributed to Strepsils by 75% of consumers and 78% of Māori and Pacific Island people.
- Use for the management of severe sore throats was correctly attributed to Strepfen by 83% of consumers and 85% of Māori and Pacific Island people.

Sore throats are 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.(12) In addition, the majority of acute sore throats in adults (85-95%) are viral, self-limiting minor ailment which can generally be self-managed.(1, 13)

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.(14)

Sore throat pain is most often acute and when severe in intensity(15, 16) it can significantly impact health-related quality of life and everyday function.(17)

Pain is also the principal driver of people with sore throats going to see their GP.(18-20) Despite educational campaigns, GP visits for sore throat conditions often result in antibiotic use.(19) 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.(21) 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.(22) The need to prevent antimicrobial resistance by reducing the inappropriate use of antibiotics is recognised by the New Zealand Ministry of Health.(23) 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.(20)

Lozenges are the most commonly used dosage form for the management of sore throats(24) 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.(13) 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 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. In addition, the proposed General Sale pack size is 16 dosage units, representing 2 days' therapy, supporting short term use and the need to seek medical attention if a sore throat persists for more than a few days (as per pack instructions).

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 hours providing greater access to medications for managing the symptoms of minor self-limiting conditions.

Sales data demonstrates a growing preference for consumers purchasing medicated sore throat products in a grocery environment.(25) New Zealand research indicates that 64% of consumers will purchase a medication for a sore throat from grocery or convenience stores.(10) Hence, there is a consumer need and public health benefit for providing General Sales access for flurbiprofen lozenges.

Flurbiprofen lozenges are available as a self-select over-the-counter medicines in pharmacies in most countries, based on its excellent benefit/risk profile it is available as a General Sales medicine in Australia, Denmark, and the Netherlands.

In 2020, the Australian Advisory Committee on Medicines Scheduling (ACMS) indicated that the net benefits of broadening the availability of flurbiprofen to general sale with restrictions

placed on age and dosage form combined with warning labels outweighs the any potential risks associated with misuse. The Committee indicated that flurbiprofen lozenges have the potential to improve the self-management of sore throats and that the low bioavailability of the lozenge preparation will minimise the known drug interactions and contraindications. Consequently the ACMS concluded that flurbiprofen lozenges are able to be supplied at the general sales level, with reasonable safety, without the need for access to health professional advice.(26) Since its availability as an unscheduled medicine over [redacted] days' supply of flurbiprofen lozenges have been sold in in Australia. During this time as an unscheduled medicine there have been no reports of adverse events for Strepfen (flurbiprofen) lozenges in the Database on Adverse Event Notifications,(27) indicating that consumers can safely use this medication in the General Sale environment.

Excluding the issue of the risk of acute rheumatic fever in Māori and Pacific peoples in specific impoverished regions of New Zealand (which has been specifically addressed in Part A, Section 11) we believe that the findings of the Advisory Committee on Medicines Scheduling are applicable to the general New Zealand population.

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.
- The majority of New Zealand consumers will purchase medications to manage sore throats from non-pharmacy retailers, e.g., supermarkets and convenience stores(10)
- Consumers are well equipped to self-manage their sore throat.(10)
- Advice from a pharmacist is generally not sort for purchase of medicated lozenges to relieve acute sore throat.
- 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 remains positive.(12)
- Labelling clearly differentiates Strepfen from Strepsils(10) and includes all of the required warning statements that are also mandated for oral NSAIDs that are available as General Sale medicines.
- Consumer research indicates that people understand that Strepfen is an anti-inflammatory medicine and should not be taken with other anti-inflammatory medicines.(10)
- The risk of delaying the treatment of Streptococcal A throat infections and thus increasing the risk of rheumatic fever is not substantive. There are substantial public health campaigns in place educating at risk groups about acute rheumatic fever and New Zealand research indicates that these campaigns are effective and parents of at risk children know to take their child to a doctor or nurse if they develop a sore throat.(5)
- Māori and Pacific Islander people have a high awareness of rheumatic fever and if their child had a sore throat that persisted for more than 2 days or was accompanied by other symptoms associated with Streptococcal A infection the vast majority (93%) would seek medical advice(10) in a manner consistent with local guidelines.(9)
- The proposed General Sale pack size is limited to 16 dose units, equivalent to 2 days' supply. Hence prolonged use without seeking medical advice is unlikely to occur.

- Anti-inflammatory lozenges containing benzydamine hydrochloride are already available as general sale medicines in New Zealand hence precedent has already been set on the benefit risk profile.

Reckitt's believes that this application supports 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 and when labelled only for the treatment of adults and children over 12 years from Pharmacy Only to General Sale. However, if the Committee after considering this application still has some reservations about the use in adolescents and the risk of rheumatic fever, Reckitt proposes that the General Sales classification of flurbiprofen lozenges be restricted to adults (aged 18 years or older) thereby effectively eliminating any risk regarding streptococcal A sore throat infections and acute rheumatic fever. In this situation the proposed wording for the reclassification would be; 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 and when labelled only for the treatment of adults aged 18 years or over.

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]

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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.(28)

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 and when labelled only for the treatment of adults and children over 12 years 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 and when labelled only for the treatment of adults and children over 12 years	General sale

As specified previously if the Committee does not agree that the risk in relation to diagnosis of acute rheumatic fever in Māori and Pacific peoples is equivalent for General Sale flurbiprofen lozenges vs benzydamine hydrochloride lozenges, Reckitt proposes that the wording of the General Sale classification be adjusted to, '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 and when labelled only for the treatment of adults aged 18 years or over'.

Under these circumstances the proposed classification of flurbiprofen is summarised in Table 3.

Table 3: Alternative 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 and when labelled only for the treatment of adults aged 18 years or over	General sale

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

Globally flurbiprofen lozenges are available in 70 countries.(29) 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 five countries including the most recent down-scheduling in Australia. Other countries with general sale access are Denmark, the Netherlands, Botswana, and Iraq. See Table 4 below for scheduling status in comparable markets.

Table 4: Scheduling status of topical oral flurbiprofen in comparable markets

Country	Legal status of medicine
Austria	OTC
Australia	GSL
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 divided preparations containing 10 mg or less of flurbiprofen per dosage unit when in a primary pack containing not more than 16 dosage units; and when labelled only for the treatment of adults and children over 12 years is unscheduled (General Sale). In reaching this decision in 2020, the Advisory Committee on Medicines Scheduling (ACMS) indicated that the net benefits of broadening the availability 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. In addition, the low bioavailability of the lozenge preparation will minimise the known drug interactions and contraindications. That committee concluded that flurbiprofen lozenges have the potential to improve the self-management of sore throats and that they are able to be supplied at the general sales level, with reasonable safety, without any access to health professional advice.(26)

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.(30)

In Canada, flurbiprofen or its salts was entered on the Prescriptions Drugs List in December 2013 as a product for human use.(31)

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.(12) 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, 13)

Flurbiprofen lozenges are available as a self-select over-the-counter medicines in pharmacies in most countries and are available as General Sale medicines in Australia, Denmark, and the Netherlands, based on its excellent benefit/risk profile.

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, there is at least 20 years in market experience with, flurbiprofen lozenges available for self-selection in pharmacy.

During this time, there has been substantial consumer experience with the use of flurbiprofen lozenges. From 2018 to July 2022 more than [redacted] days' 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 and with smaller pack sizes (≤ 16 dosage units) available as an unscheduled medicine (General Sale) since October 2020. Since its availability as an unscheduled medicine over [redacted] days' supply of flurbiprofen lozenges have been sold in in Australia. During this time as an unscheduled medicine there have been no reports of adverse reports for Strepfen (flurbiprofen) lozenges in the Database on Adverse Event Notifications,(27) indicating that consumers can safely use this medication in the General Sale environment.

Globally, consumer use of flurbiprofen lozenges is extensive with over [redacted] billion lozenges sold since 1999. The total patient exposures for all oromucosal flurbiprofen formulations is estimated to be in excess of [redacted] billion since launch to 3 February 2022.(29)

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

The previous consideration by the MCC for the down-scheduling of flurbiprofen lozenges to General Sale was in 2020. At that time the Committee considered that the submission was deficient in 'New Zealand specific' data and that it did not take into account the prevalence of acute rheumatic fever in New Zealand and the risk posed by increasing the availability of a medicine that could potentially mask the symptoms of a severe sore throat as such potentially delaying the detection and treatment of streptococcal throat infections.(3)

Reckitt recognises acute rheumatic fever is a health issue and clinical priority in New Zealand. The burden of this risk is almost entirely restricted to Māori and Pacific Island children living in the most impoverished regions of New Zealand.(32) As flurbiprofen lozenges are not indicated for use in children under 12 years of age, much of the concerns

raised by the Committee in 2020 are not warranted as flurbiprofen cannot be used by the majority of children at greatest risk (aged 5 to 12 years).(7-9). In addition, New Zealand research of parents in at risk regions found high levels of awareness of rheumatic fever. Nine out of ten parents surveyed indicated that the best way to manage their child's sore throat was to see a doctor or nurse straight away, which is consistent with the public health initiatives that are effectively addressing this issue.(5)

Reckitt's believes that the information provided in this section of the application supports 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 and when labelled only for the treatment of adults and children over 12 years from Pharmacy Only to General Sale. However, if the Committee after considering this still has some concerns regarding the potential risks associated with a reclassification to General Sales, Reckitt proposes that the General Sales classification of flurbiprofen lozenges be restricted to adults (aged 18 years or older) effectively eliminating any risk regarding streptococcal sore throat and acute rheumatic fever in children.

Streptococcal A sore throat is associated with multiple symptoms and severe pain all of which are unlikely to be masked by the use of flurbiprofen lozenges.

The majority of sore throats are due to viral infections. It is estimated that in adults 10% of sore throats are due to Streptococcal A infections and in children it ranges between 15 to 30%.(9)

New Zealand data indicates that the peak age for Streptococcal A infections presenting to general practitioners is 0-4 years and 5-9 years for hospital presentations.(33) As flurbiprofen lozenges are not approved for use in children under 12 years of age there is negligible risk that flurbiprofen lozenges will be used by the consumer cohort with the highest incidence of these infections. This is supported by a NZ label discernment research where 90% of New Zealanders, and 91% of Māori and Pacific Island people, stating that Strepfen could not use in children under 12 years.(10)

In addition, New Zealand research confirmed that the risk of Streptococcal A related disease was lowest for adults aged 20–59 years,(33) the typical user of General Sale medicines.

Although it is difficult to differentiate between Streptococcal A sore throat and a viral sore throat based on symptoms alone, a Streptococcal A sore throat has a clinical presentation that is broader than simply a painful sore throat. With Streptococcal A throat infections there is an abrupt onset of illness with sore throat, malaise, fever, and headache. It is often accompanied by nausea, vomiting, and abdominal pain. The tonsils and pharynx are inflamed. A greyish white exudate on the tonsils is common. Throat pain is typically severe and is associated with difficulty swallowing.(34, 35)

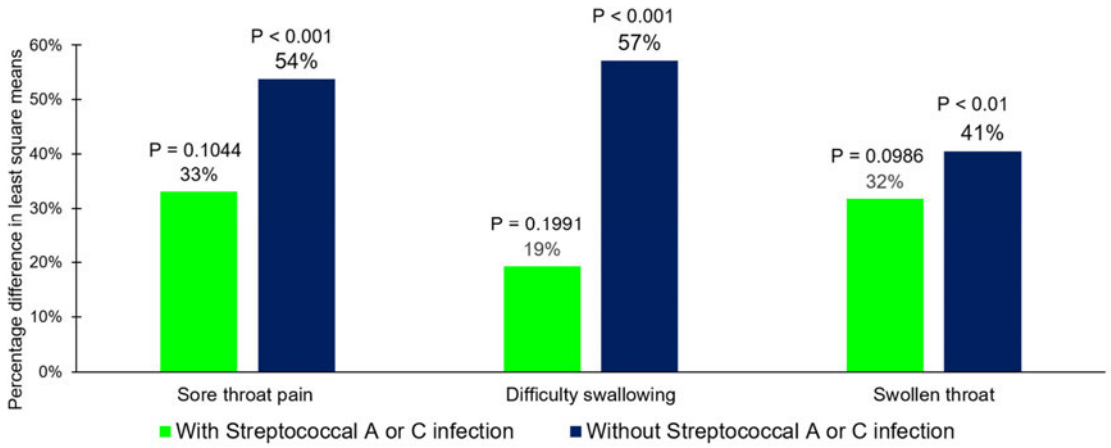
A systematic review on assessing Streptococcal A sore throats indicated that the most useful symptom for predicting if a person's sore throat is due to Streptococcal A is the presence of tonsillar or pharyngeal exudate.(35)

Flurbiprofen is an effective, topical analgesic that is useful for the relief of localised pain and inflammation within the throat. However, its use will not relieve the other symptoms associated with Streptococcal A sore throats, including tonsillar or pharyngeal exudates, malaise, fever, headache, nausea, vomiting or abdominal pain.

In addition, as Streptococcal A sore throats tend to cause severe pain, the relative clinical effectiveness of flurbiprofen lozenges is likely to be less in this subset of sore throats. This was demonstrated in a pooled analysis of two placebo controlled trials conducted in patients

with or without Streptococcal A or C throat infections. Symptomatic relief tended to be lower in patients with confirmed Streptococcal A or C infections compared to those with sore throats without Streptococcal A or C infections (see Figure 1).(36)

Figure 1: Percentage change in patient-reported symptoms over 24 hours(36)



This data suggests that even from a pain relief perspective, patients with Streptococcal A sore throats will experience modest pain relief with flurbiprofen lozenge use, but it will not eliminate pain to the extent that symptoms will be masked and therefore the use of these lozenges are unlikely to delay clinical assessment.

Importantly, the Strepfen label discernment research has demonstrated that 9 in 10 consumers understand that if symptoms of a sore throat persist for more than 2 days whilst using Strepfen lozenges that they should seek medical advice. Even though 3% of consumers indicated that they would continue to use Strepfen lozenges on day 3 only 1% would do this and not seek medical advice. This indicates that the current label for Strepfen is understood by New Zealanders including those at risk of rheumatic fever, Māori and Pacific Island people, and that its use is unlikely to mask or delay treatment of Streptococcal sore throats.(10)

This same research also examined how New Zealanders currently manage sore throats in general. If a sore throat in a child was persisting for more than 2 days and was accompanied by other symptoms such as fever or pus, 93% of Māori and Pacific Island people would seek medical advice. Also, in this situation the continued use of a medicated lozenge was low, being 4% if the child was under 12 years and was 11% for children aged 12 to 14 years. Note, in these older children no (0%) Māori and Pacific Island people indicated that they would continue to use medicated sore throat lozenges and not seek medical advice. It is also important to note that other therapies that are available for General Sales such as paracetamol, ibuprofen, sore throat gargles and unmedicated throat lozenges (e.g. Vicks, Throaties) would also be used to manage the sore throat in this situation,(10) hence reclassifying Strepfen lozenges to General Sales does not pose any increased risk to that which is already deemed acceptable for these other therapies.

Acute rheumatic fever is predominantly a clinical issue in children aged younger than 12 years and flurbiprofen lozenges are not for use in children under 12 years of age.

The clinical need to promptly assess a sore throat to determine if it is due to a Streptococcal A infection to prevent acute rheumatic fever is predominantly a paediatric issue in high risk patient populations, i.e., specifically amongst Māori and Pacific Island children, aged 5-14 years residing in the most deprived areas of New Zealand.(32) We acknowledge that public

health initiatives on the prevention of acute rheumatic fever include a broader range of children, aged from 4 to 19 years,(9) however the clinical need is greatest for younger children in the 5 to 12 year old age bracket as indicated by several key facts:

- New Zealand guidelines indicate that the peak age for acute rheumatic fever is around 8 years old.(37)
- The median age for acute rheumatic fever in New Zealand is 12 years (2010-2013).(38)
- The rate of primary rheumatic fever (in 2018) was highest in children aged 5–9 years (15.9 per 100,000), followed by those aged 10–14 years (15.4 per 100,000).(7)
- The rate of primary rheumatic fever (in 2019) was highest in children 10–14 years (21.1 per 100,000) followed by those aged 5–9 years (7.2 per 100,000). Noting that in 2019 there were overall fewer cases of rheumatic fever than in 2018.(8)
- 94.7% of first time hospital admissions from rheumatic fever in New Zealand in 2019 were amongst children aged 5 to 14 years.(4)
- School-based sore throat clinics focus on year 1-8 students, that is ages 5 to 13 years.(9)

Taken together, it is clear that the vast majority of those at risk of acute rheumatic fever are children aged under 12 years, and as flurbiprofen lozenges are contraindicated in this age group, the risk of delaying the assessment and diagnosis of Streptococcal A throat infections due to flurbiprofen lozenge use is avoided in the patient population at greatest risk.

Strepfen label discernment research indicated that 9 in 10 people understood that Strepfen could not be used in children under 12 years,(10) hence the risk of use in this cohort is mitigated with existing labelling.

The prevalence of acute rheumatic fever has not increased since 2010, and targeted public health measures are making effective progress in addressing acute rheumatic fever in the communities at greatest risk

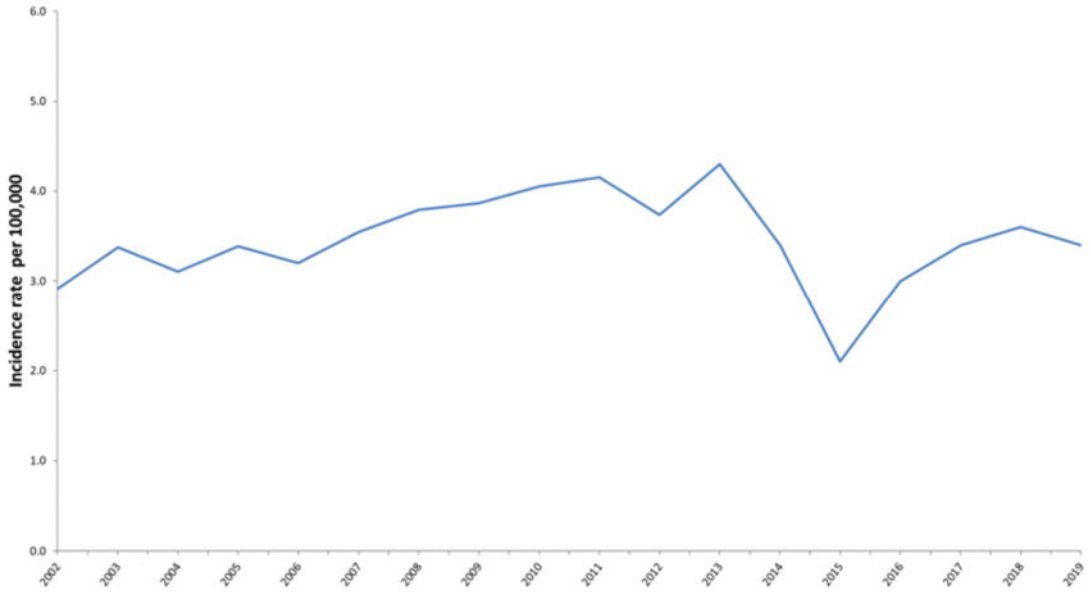
In the Committee's 2020 deliberations there is a statement to the effect that since the classification of flurbiprofen was last considered in 2010 there is now more evidence around the prevalence of acute rheumatic fever in New Zealand. For clarity, the excerpt we refer to is as follows:

> "The Committee noted that although the submission addresses the issues raised by the Committee in 2010, the submission is deficient in New Zealand specific data and does not take into consideration the New Zealand context particularly noting that there is now a more substantive body of evidence around the prevalence of acute rheumatic fever in New Zealand."(3)

Although the minutes do not disclose what the discussions were around this "more substantive evidence", one implication is that prevalence of acute rheumatic fever has increased since 2010 and/or the clinical issue has deteriorated, and therefore more conservative measures are warranted from a medicine's classification perspective. However, the data gathered since 2010 does not suggest that the public health issue has deteriorated, but that it has improved.

Between 2010 and 2019 the incidence of people diagnosed with rheumatic fever for the first time (as assessed by hospitalisation rates) has decreased in New Zealand (See Figure 2). Amongst Māori people this incidence (first time hospitalisations) was more than 30% lower in 2019 compared to 2010, however the incidence was higher for people of Pacific Island ethnicity.(4)

Figure 2: First episode rheumatic fever hospitalisations, annual rate per 100,000, New Zealand, 2002–2019(4)



As noted previously, this risk is greatest amongst Māori and Pacific Island school aged children. 90% of children at greatest risk are in schools with clinics that can conduct prompt assessments of sore throats for Streptococcal A infections.(39)

These school-based screening programs are effective in reducing the prevalence of acute rheumatic fever. An assessment of the effectiveness of these programs amongst children aged 5 to 13 years (conducted from 2010 to 2016) demonstrated a 58% reduction in the rate of acute rheumatic fever from 88/100,000 to 37/100,000 (P = 0.008).(39, 40)

The effectiveness of these school-based and community-based initiatives is also acknowledged within the current Rheumatic Fever New Zealand Guidelines for Group A Streptococcal Sore Throat Management Guideline 2019.(9)

In addition, New Zealand research conducted amongst parents/care givers of children who were diagnosed with either definite, probable, or possible/borderline rheumatic heart disease during a school-based echocardiographic screening programme and matched controls found that almost all respondents had heard of rheumatic fever (rates > 90%). In addition, there was high levels of sore throat awareness. Importantly parents of children in these risk groups knew about the need to promptly seek medical attention if their child has a sore throat. 89% of parents of a child who had an abnormal echocardiograph and 83% of the matched controls indicated that the best way to manage their child's sore throat was to see a doctor or nurse straight away. This research also indicated that lozenge use as the best way to manage their child's sore throat was very low at 2% for those with an abnormal echocardiograph and 7% in the matched controls.(5) This indicates that the public health campaigns instituted to date are working and there is no evidence that the increased availability of flurbiprofen lozenges would not compromise this.

Given the positive gains that have been made since 2010 in relation to awareness and understanding of rheumatic fever amongst all New Zealanders indicates that reclassification of flurbiprofen lozenges to a General Sales medicine will not minimise these efforts.

We also note that the New Zealand government in May 2019 allocated $12 million over 4 years to improve the prevention and management of rheumatic fever, primarily in the

Auckland region where most cases occur. This $12 million is in addition to the $5 million allocated per year until 2022 across the 11 district health boards with a high incidence of rheumatic fever so they can continue to deliver a balanced mix of rheumatic fever prevention activities to address rheumatic fever and reduce rheumatic fever rates. This targeted investment is addressing this health issue and this well-defined health issue should not impede the benefits of wider access to flurbiprofen lozenges for the majority of New Zealanders.

In addition, New Zealand consumer research on sore throats investigated the awareness of rheumatic fever and found that 87% of New Zealanders and 96% of Māori and Pacific Island people had heard about rheumatic fever. The quality of awareness was higher amongst Māori and Pacific Island people, with 66% understanding that a sore throat could lead to the development of rheumatic fever. In addition, most (93%) understood that rheumatic fever was a moderate to potentially serious medical condition in children.(10)

Flurbiprofen lozenges have tighter age restrictions than other anti-inflammatory lozenges that are currently available as General Sales medicines and poses less risk of masking the symptoms of Streptococcal A throat infections in at risk children

In New Zealand, there are other anti-inflammatory lozenges available as General Sales medicines, specifically the NSAID, benzydamine hydrochloride.(41) Given the perceived risk of flurbiprofen lozenges masking symptoms of strep A are potentially due to its anti-inflammatory action, this perceived risk currently exists due to the availability of General Sale anti-inflammatory lozenges. One can assume that the MCC is comfortable with this current level of risk.

A head-to-head randomised, single-blind clinical trial has compared the efficacy of single doses of flurbiprofen 8.75 mg (Strepfen) and benzydamine hydrochloride 3 mg (Difflam) lozenges for the relief of sore throats. In this study, both lozenges provided similar levels of pain relief ($P = 0.5666$) and reductions in pain intensity ($P = 0.2396$) with no significant differences observed for these primary endpoints or any of the secondary study endpoints.(6)

As both mediations have the same anti-inflammatory and analgesic actions and have comparable efficacy, the risk of masking the symptoms of a Streptococcal A sore throat is at face value equivalent. However, unlike flurbiprofen lozenges that are for use in children 12 years or older, benzydamine hydrochloride lozenges can be used in children 6 years and older. Therefore, the current level of risk is greater for benzydamine hydrochloride lozenges than that posed by the reclassification of flurbiprofen lozenges as benzydamine hydrochloride lozenges can currently be used by almost all children with the greatest risk of developing acute rheumatic fever (those aged 5 to 14 years)(7-9) while flurbiprofen lozenges cannot be used in children aged under 12 years.

This risk associated with General Sales availability of benzydamine hydrochloride 3 mg (Difflam) is accentuated by the fact that the purchase these lozenges is [redacted] times higher than that for Strepfen, both amongst New Zealanders in general and amongst Māori and Pacific Island people. Noting that the higher purchase rates for Difflam lozenges corresponds with higher awareness and experience with these lozenges than for Strepfen lozenges.(10)

To the best of our knowledge none of the New Zealand research on acute rheumatic fever have raised the issue of analgesic or lozenge usage as a risk factor impeding the prompt identification of Streptococcal A throat infections and/or management of rheumatic fever

The New Zealand health authorities and other researchers have devoted much effort to understanding the risk factors for acute rheumatic fever and strategies to address this health issue. To the best of our knowledge not a single report or guideline has raised self-management of sore throats with analgesics (either systemic or topical) as an impediment to the prompt assessment of sore throats in at risk people. Given the breadth of research done on this issue in New Zealand, if such analgesic use was a significant contributor to increasing the risk, one would expect it to be mentioned in the guidelines or other Ministry of Health reports or published research.

For example, the 2011 guidelines on the management of Streptococcal A sore throats for the prevention of acute rheumatic fever specifically considered patient barriers to going to the GP to have a sore throat assessed amongst high risk patients. Barriers to assessment noted in these guidelines included:(42)

- The severity of the sore throat, e.g., patients had to be quite sick before considering seeing a doctor
- Financial barriers, e.g., it was too expensive to go the doctor every time they were sick or going to the doctor was not perceived to be good value for money
- Patients did not like taking medications for their illnesses
- Differences in the experiences Māori patients have with GP practices, compared to non-Māori patients.

Kljakovic and Crampton (2005) investigated the GP management of sore throats in New Zealand and how this had changed over time. These researchers found that the overall presentation to GPs for sore throats had remained unchanged, but that there was a relative increase in GP consultations amongst Māori people (any age) and Pacific Island patients aged 5 to 14 years.(43) Again this is a positive sign of improved care amongst people with a high risk of acute rheumatic fever.

The General Sale use of lozenges to manage sore throats is consistent with New Zealand guidelines

New Zealand guidelines on the management of sore throats is stratified according to the risk of acute rheumatic fever. For the majority of New Zealanders, who have a low risk of acute rheumatic fever, minimising swabs for Streptococcal A, antibiotic stewardship and minimising inappropriate prescribing are primary management aims.(9) In these people, the self-directed use of analgesics including the short-term use of flurbiprofen lozenges is consistent with Ministry of Health recommendations for the management of general sore throats(44) and has the potential to support antibiotic stewardship.

This guidance also provides specific advice on when people should seek medical attention, specifically if the person experiences any of the following:(44)

- a sore throat that lasts more than a few days
- difficulty swallowing
- your tonsils are enlarged or coated
- a high temperature (above 39°C)
- swelling in your neck
- earache or joint pain.
- If your child is Māori or Pacific, aged 4 to 19 years, lives in certain parts of the North Island, and has a sore throat.

The short-term use of flurbiprofen lozenges is clearly communicated on pack with consumers directed not to use the lozenges for more than a few days without doctor's advice and if symptoms persist to see your doctor or pharmacist. Hence, existing labelling is

supporting the safe and quality use of this medication which will not be altered by a reclassification to a General Sale medicine.

Strepfen label discernment research has confirmed the effectiveness of the label in ensuring appropriate use. 9 in 10 consumers understood that if symptoms of a sore throat persisted for more than 2 days whilst using Strepfen lozenges that they should seek medical advice. Even though 3% of consumers indicated that they would continue to use Strepfen lozenges on day 3 only 1% would do this and not seek medical advice. Importantly data amongst Māori and Pacific Island people also indicated that they would seek medical advice at equivalent rates. This indicates that the use of Strepfen lozenges is unlikely to delay the treatment of Streptococcal sore throats.(10)

This research also investigated how New Zealanders currently manage sore throats in general. If a sore throat in a child was persisting for more than 2 days and was accompanied by other symptoms such as fever or pus, 93% of Māori and Pacific Island people would seek medical advice.(10) Therefore, the people at greatest risk are managing sore throats in a manner consistent with local guidelines and reclassifying Strepfen lozenges to General Sales will not alter this risk.

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

Previous considerations 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.”(11)

The subsequent consideration in 2022 acknowledged that these labelling issues were addressed in the application, but it was considered deficient due to the lack New Zealand specific data and the application did not account for the issue of rheumatic fever.(3) These concerns have been addressed in this application. Section 11 above has addressed rheumatic fever and the findings of New Zealand specific label research are presented here.

New Zealand label discernment research demonstrated that consumers could differentiate Strepfen lozenges for Strepsils lozenges, including:(10)

- Anti-inflammatory action was correctly attributed to Strepfen by 80% of consumers and 83% of Māori and Pacific Island people.
- Anti-bacterial action was correctly attributed to Strepsils by 75% of consumers and 78% of Māori and Pacific Island people.
- Use for the management of severe sore throats was correctly attributed to Strepfen by 83% of consumers and 85% of Māori and Pacific Island people.
- The ages for which the two different lozenges are indicated was correctly attributed by more than 80% of consumers. That is Strepfen cannot be used in children under 12 years of age was correctly attributed to Strepfen by 80% of consumers and 83% of Māori and Pacific Island people. Similarly, Strepsils can be used by children aged over 6 years was correctly attributed to Strepsils by 83% of consumers and 84% of Māori and Pacific Island people.

The Strepfen lozenges label complies with the TGA labelling requirements specified by TGO 92. The TGO 92 labelling requirements were introduced to improve a consumer’s understanding of the information on the label and represents current best practice. Reckitt is

of the view that these changes effectively address the concerns previously raised by the Committee. The current (Pharmacy Only) Strepfen Lozenge label is illustrated in Figure 3 and a current Strepsils label is shown in Figure 4.

Figure 3: Strepfen Intensive Honey and Lemon current (2022) 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

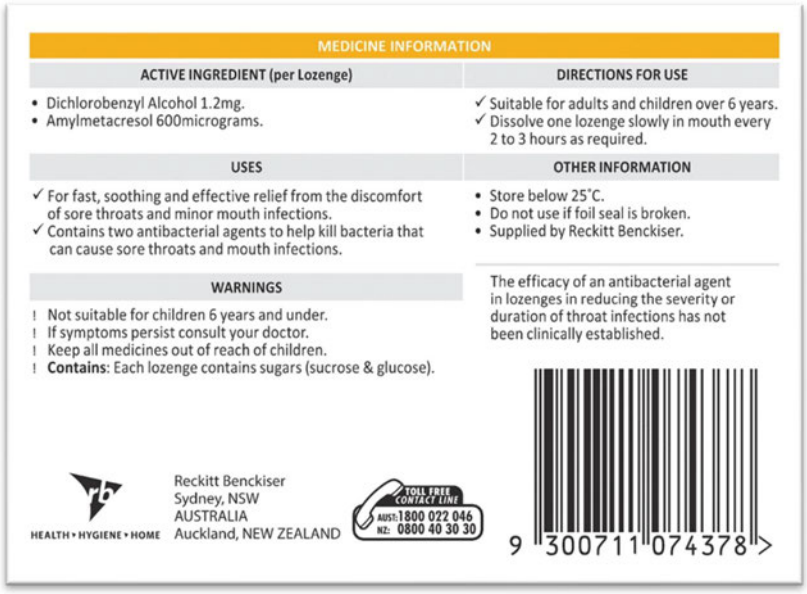
DIRECTIONS FOR USE

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 4: Strepsils Soothing Honey and Lemon



A comparison of the TGO 92 approved label (Figure 3) with the Strepsils Honey and Lemon label (Figure 4) 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 is 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 are stated twice on front of pack.

- The medicines information panels on the back of the pack are distinctly different with the additional warnings associated with Strepfen clearly and appropriately communicated.

In addition, both packs have physical different dimension with the Strepsils range of lozenges being in a larger (squarer) front of pack than Strepfen. The front facing of Strepfen lozenges 60 mm high by 111 mm wide, while for Strepsils it is 80 mm high by 111 mm wide. Hence these different front facings add to the product differentiation.

This label clearly differentiates Strepfen from Strepsils, and the risk of confusion has been mitigated. Given the Strepfen labelling provided at Figure 3 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.

If Strepfen lozenges were taken by a person with a contraindication, the risk of an adverse outcome is minimal as oromucosal flurbiprofen is locally absorbed, has minimal systemic absorption and has an excellent safety profile.(29) This was specifically acknowledged by the ACMS when deciding to reschedule flurbiprofen lozenges to an Unscheduled Medicine in 2020.(26) In addition, the proposed small pack size for Strepfen flurbiprofen lozenges represents 2 days' 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 specific warning or precaution is very rare. Event rates in such groups are:(29)

- 0.000000263% for patients with active or history of gastric ulcers
- 0.000000032% for use during pregnancy (first or second trimester)
- 0.000000026% for use during pregnancy (last trimester)
- 0.000000129% for use in children aged under 12 years of age
- 0.000000144% for use in patients with cardiovascular disease or cardiac failure
- 0.000000016% for use in patients with renal impairment or renal failure
- 0.000000018% for concomitant use with other NSAIDs.

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 (Figure 3) with the "Pharmacy Medicine" mandatory information removed.

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. Consumer research shows that the majority of consumers (64%) self-manage their sore throat.(24)

There are multiple products for the symptomatic relief of sore throats available in supermarkets and other non-pharmacy retailers. These therapies include lozenges with or without therapeutic active ingredients such as antiseptics, local anaesthetics, or anti-inflammatory agents such as benzydamine hydrochloride lozenges, as well as oral analgesics including aspirin, ibuprofen, and paracetamol. New Zealand research indicates that products to manage a sore throat are commonly purchased from non-pharmacy retailers with 64% of people purchasing them from a supermarket or convenience store.(10) Hence, it is well established that consumers can identify and self-manage sore throats and there is a consumer need to have access to these therapies as General Sales medicines.

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 3 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.

These warning statements are effective with the vast majority of consumers understanding the directions. For example, New Zealand label discernment research reported that 91% of people understood that Strepfen lozenges could not be used by children aged under 12. It is noteworthy the label discernment on this issue were the same for Māori and Pacific Island people.(10)

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.(12) 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, 13) New Zealand Ministry of Health guidance supports the self-management of acute sore throat in the general population including the short-term use of lozenges.(44)

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 anti-inflammatory analgesics (benzydamine hydrochloride), 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, consumer research has shown that the majority of consumers self-manage their sore throat and do not discuss this with a healthcare professional.(24) 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 small.

Self-limiting viral infections are the most common cause of sore throats. According to the National Heart Foundation of New Zealand, group A Streptococcus causes approximately 10% of sore throats in adults and in children it ranges between 15 to 30%.(9) These bacterial infections are generally self-limiting, and the risk of complications is low in the general New Zealand population. The risk of developing acute rheumatic fever is essentially limited to Māori and Pacific Island people residing in the most deprived areas of New Zealand(32) and the special considerations regarding these risks and the relevance to this reclassification application has been addressed in Part A, Section 11.

General Sale flurbiprofen lozenges are proposed to be available in only a small pack size, 16 lozenges, which represents two days' supply. 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 is aligned with New Zealand guidelines on rheumatic fever and Streptococcal sore throat management that indicate that for people with a low risk of acute rheumatic fever, minimising throat swabbing, unnecessary antibiotic treatment and healthcare expenditure are the management aims.(9) In addition, New Zealand research has shown that when managing sore throats in children, if the symptoms persisted for more than 2 days the majority of people, including Māori and Pacific Island people would seek medical advice and if the sore throat was associated with other symptoms such as a fever and pus, 93% would seek medical advice.(10) Hence the at risk groups are taking actions consistent with New Zealand guidelines.(9)

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 the availability of flurbiprofen lozenges in New Zealand, there has been no significant change in the safety profile of flurbiprofen and the benefit/risk profile remains positive.(29) In addition, a search of the Suspected Medicine Adverse Reaction Search (SMARS) database from 1 January 2000 to 5 September 2022 identified only one suspected adverse event with oral flurbiprofen, and none with flurbiprofen lozenges. In comparison, 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.(45) This reinforces the excellent safety profile of flurbiprofen lozenges compared with benzydamine containing lozenges which are available as a GSL medicine. In addition, it reinforces the fact that consumers can appropriately use this Strepfen lozenges.

The ability of consumers to safely use flurbiprofen lozenges in a General Sale environment is further supported by Australian data. Since its availability as an Unscheduled medicine over [redacted] days' supply of flurbiprofen lozenges have been sold in Australia. During this time there have been no reports of adverse events for flurbiprofen lozenges in the Database on Adverse Event Notifications.(27)

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 days' 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.

The ability of New Zealand consumers to comprehend these instructions was confirmed in the label discernment research with 90% of people understanding that these lozenges are not for use in children under 12 years of age and 93% correctly identifying that the maximum recommended daily dose being ≤ 8 lozenges/day.(10)

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 days' 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.(24) Medicated (including other locally acting anti-inflammatory lozenges) and non-medicated sore throat lozenges are widely available for General Sale in New Zealand supporting the position that lozenges are a practical and easy to use format for the self-management of sore throats. In addition, 64% of New Zealanders purchase medications to manage a sore throat from grocery outlets or convenience stores.(10)

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. During this time, there has been substantial consumer experience with flurbiprofen lozenges. From 2018 to July 2022 more than [redacted] days' supply of flurbiprofen lozenges have been sold in New Zealand

Globally flurbiprofen lozenges are available in 70 countries.(29) 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 five countries including the most recent down-scheduling in Australia. Other countries with general sale access are Denmark, the Netherlands, Botswana and Iraq.

Globally, consumer use of flurbiprofen lozenges is extensive with over [redacted] billion lozenges sold since 1999. The total patient exposures for all oromucosal flurbiprofen formulations is estimated to be in excess of [redacted] billion since launch to 3 February 2022.(29)

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 rare with an event rate of 0.000000129%.(29)

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 target 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.(46) The low dose of flurbiprofen lozenges results in minimal systemic adverse events.(29) New Zealand guidance on the self-management of a sore throat in the general population supports the use of lozenges for symptomatic relief.(44) The Therapeutic

Guidelines for management of Acute Pharyngitis/Tonsillitis recommend analgesics as a first line approach for managing acute sore throat.(13) Guidelines on the management of pain and the use of analgesics recommend using the lowest effective dose for the shortest possible time.(13) 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 days' therapy for patients taking the maximum dose (8 lozenges per day) and the efficacy of topical flurbiprofen in relieving severe acute sore throat contribute to the favourable benefit/risk profile.(47, 48)

The ACMS in reaching its' decision to schedule flurbiprofen lozenges as an Unscheduled medicine indicated that the net benefits of broadening the availability 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. In addition, the ACMS determined that flurbiprofen lozenges have the potential to improve the self-management of sore throats and that the low bioavailability of the lozenge preparation will minimise the known drug interactions and contraindications. Consequently, it was agreed by the committee that flurbiprofen lozenges are able to be supplied at the general sales level, with reasonable safety, without any access to health professional advice.(26) The rationale for this decision is supported by post-marketing Australian data. Since its availability as an Unscheduled medicine, there has been an increase in the use of flurbiprofen lozenges with no reports of adverse reports in the Database on Adverse Event Notifications.(27)

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, 13) 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.(24)

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.(25) New Zealand research indicates that 64% of consumers will purchase a medication for a sore throat from grocery or convenience stores.(10) Hence, there is a consumer need and public health benefit in providing General Sales access for flurbiprofen lozenges.

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.(49)
- Medicated lozenges and throat sprays containing antiseptics, anaesthetics, but do not address the underlying inflammation that often causes painful pharyngitis and tonsillitis(13, 50) and are therefore unlikely to be as effective as flurbiprofen lozenges which has anti-inflammatory action.(15, 51)
- Anti-inflammatory lozenges, that have comparable efficacy to flurbiprofen lozenges.(6)
- Oral paracetamol, which has no/minimal anti-inflammatory activity.(52)
- Oral NSAIDs such as ibuprofen and aspirin.

Consumer 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.(24)

Flurbiprofen lozenges are a locally acting, low-dose NSAID which due to its local application to the site of inflammation(51) 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 days' flurbiprofen therapy compared to paracetamol 20 units representing 2.5 days' supply and ibuprofen 200 mg tablets 24s which represents 4 days' therapy.

Clinical trials have confirmed that the pain relief provided by flurbiprofen lozenges is clinically meaningful.(15, 16, 47, 48) 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.(53, 54) 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.(47, 48)

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.(14)

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.(13)

Clinical studies have shown that acute sore throat pain is often severe in intensity(15, 16) and can result in functional impairment of simple daily activities including swallowing, talking, eating meals, sleeping and working.(17)

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."(28)

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.(16) 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.(53, 54) 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.(47, 48)

As previously highlighted, a survey of consumers identified that the most commonly used format to relieve sore throats are lozenges.(24) As 64% New Zealanders purchase medications to manage sore throats from supermarkets or convenience stores(10) expanding access of flurbiprofen lozenges will provide these consumers with a treatment that 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.(55) 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 in the general population.(20)

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.(18)

An international survey 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).(19) 19% of people used antibiotics for their last sore throat episode and the mean pain/discomfort score associated with this episode was 2.8 on a 5 point categorical scale (1 = dull/annoying, 2 = sore/troublesome, 3 = hurting/miserable, 4 = aching/intense, 5 = throbbing/unbearable).(19)

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.(22) The need to prevent antimicrobial resistance by reducing the inappropriate use of antibiotics is recognised by the New Zealand Ministry of Health(23) and this indicates that there is an ongoing public health need to address the overuse of antibiotics for acute viral sore throats amongst the vast majority of the population that have a low risk of acute rheumatic fever.

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, 19% of people surveyed used antibiotics for their last sore throat.(19) 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.(24) Therefore, the opportunity for pharmacist intervention to help curb inappropriate antibiotic use is limited and insufficient to address the ongoing public health need.

Importantly, research amongst Māori and Pacific Islander people, who have an increased risk of rheumatic fever indicates, that the General Sales availability of flurbiprofen would not increase the risk of Streptococcal A sore throats being mismanaged due to this reclassification. These patient groups have a high awareness of rheumatic fever and if their child had a sore throat persisted for more than 2 days or was accompanied by other symptoms associated with Streptococcal A infection the vast majority (93%) would seek medical advice.(10) See Part A, Section 11 for additional information on this issue.

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.(56) 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.(57) New Zealand guidelines support the aim of limiting antibiotic use in patients with a low risk of rheumatic fever.(9)

Despite this knowledge, antibiotic use in New Zealand is high compared to international standards with a significant proportion used to manage acute viral upper respiratory tract infections where there is no clinical benefit.(22)

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.(20, 56) 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.(21) 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 in the general population(20) without compromising the appropriate use of antibiotics in high risk populations.(10)

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 days' 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.(58-60)

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 1 July 2017 to 3 February 2022. During this period, the patient exposure to topical oral flurbiprofen is estimated at over [redacted] billion patients with over 66% 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.(29)

In addition, the adverse events recorded during the most recent reporting period indicate no new safety concerns have been identified and that the incidence of adverse events is very low with 1469 adverse events reported from almost [redacted] billion patient exposures.(29)

Data from the New Zealand Suspected Medicine Adverse Reaction Search (SMARS) database for the period of 1st January 2000 to 5th September 2022 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 hydrochloride, a topical oral NSAID, available for General Sale in New Zealand.(45)

Flurbiprofen's wide therapeutic index supports its self-selection use a General Sale medicine. This is supported by Australian data since its availability as an Unscheduled medicine. During this period over [redacted] days' supply of flurbiprofen lozenges have been sold in in Australia and there have been no reports of adverse reports for flurbiprofen lozenges in the Database on Adverse Event Notifications.(27)

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 days' supply, is shorter than that for General Sale oral NSAIDs which is of the order of 4 days' 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 0.000000263% since the product was first launched globally in 1976.(29)

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 Reckitt's view, there is minimal risk associated with use of flurbiprofen lozenges in an OTC or GSL setting 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.
- There are substantial public health campaigns in place educating at risk groups about acute rheumatic fever and New Zealand research indicates that these campaigns are effective and parents of at risk children know to take their child to a doctor or nurse if they develop a sore throat(5)
- For the majority of the New Zealand population, who have a low risk of rheumatic fever, the risk of confusing sore throats with more serious conditions is negligible and addressed with labelling directions that instructs consumers to seek pharmacist or doctor advice if their symptoms persist.
- For Māori and Pacific Islander people living in the most impoverished regions of New Zealand who are at risk of developing rheumatic fever(32) research supports Reckitt's position that the General Sales availability of flurbiprofen would not increase the risk of Streptococcal A sore throats being mismanaged due to this reclassification. Māori and Pacific Islander people have a high awareness of rheumatic fever and if their child had a sore throat persisting for more than 2 days or if the sore throat was accompanied by other symptoms associated with Streptococcal A infection the vast majority (93%) would seek medical advice(10) in a manner consistent with local guidelines.(9)
- General Sale pack size is limited to 16 dose units, equivalent to 2 days' supply. Hence prolonged use without seeking medical advice is unlikely to occur.
- The systemic exposure to the active ingredient is low with flurbiprofen lozenges, as there is minimal systemic absorption and action is local and targeted.(2)
- Flurbiprofen lozenges has an excellent safety profile, with the current PSUR indicating that the benefit/risk profile remains positive.(29)
- 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.

In addition**,** there are already anti-inflammatory lozenges (benzydamine hydrochloride) available as General Sale medicines. These lozenges have comparable efficacy to flurbiprofen lozenges(6) therefore the risk of potentially masking a more serious medical condition is one the committee would have considered in relation to these lozenges and one which already exists. This perceived risk of delaying medical treatment for Strep A throat would be higher for benzydamine hydrochloride than for flurbiprofen as these lozenges can be used from 6 years of age and therefore could be used Māori and Pacific Island children with the highest risk of rheumatic fever (aged 5 to 14 years)(9) compared to use from 12 years old with flurbiprofen lozenges.

As previously stated, if the Committee is concerned that the risk associated with flurbiprofen is greater than what can only be assumed to be the acceptable risk posed General Sale benzydamine hydrochloride lozenges, Reckitt believes that this can be managed by adjusting the proposed classification for use by adults aged 18 years or older, thus eliminating use in children.

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.

These warning statements are effective with the vast majority of consumers understanding the directions. For example, New Zealand label discernment research with Strepfen lozenges found that 80% of consumers, and 83% of Māori and Pacific Island people researched, understood that Strepfen lozenges were anti-inflammatory.(10)

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 0.000000018% since the product was first launched globally in 1976 through to February 2022.(29)

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 days' 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

Flurbiprofen lozenges are not indicated for use in children under 12 years of age.

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 3 February 2022, the rate of adverse events in these patient cohorts is very rare, with following event rates:(29)

- 0.000000263% for patients with active or history of gastric ulcers
- 0.000000016% for use in patients with renal impairment or renal failure
- 0.000000144% for use in patients with cardiovascular disease or cardiac failure
- 0.000000032% for use during pregnancy (first or second trimester)
- 0.000000026% for use during pregnancy (last trimester)
- 0.000000129% for use in children aged under 12 years of age
- 0.000000018% for concomitant use with other NSAIDs.

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(61) and topical flurbiprofen in lozenge format is a low-dose local-acting NSAID. In addition, New Zealand label discernment research indicates than 90% of people and 91% of Māori and Pacific Island people understood that Strepfen lozenges were not for use in children aged under 12 years of age.(10)

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.

In 2020, the Australian Advisory Committee on Medicines Scheduling in exempting flurbiprofen lozenges (≤16 dose units) from the schedule indicated that flurbiprofen lozenges are able to be supplied at the general sales level, with reasonable safety, without any access to health professional advice.(26)

The favourable safety profile of flurbiprofen lozenges is supported by safety data from the latest Periodic Safety Update Report, with no new important, potential or identified risks associated with use of flurbiprofen lozenges (or other topical oral formulations) reported. The benefit/risk profile for flurbiprofen lozenges remains positive (29)

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 5th September 2022.(45) 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.(45)

The low incidence of adverse events is further supported by Australian post-marketing surveillance data. Since its launch in Australia in 2001 until 30th August 2022 there have only been 4 adverse events recorded in the Database on Adverse Event Notifications for flurbiprofen lozenges (See Table 5), compared to 56 cases for benzydamine hydrochloride. In addition, since flurbiprofen lozenges have been sold in Australia as an Unscheduled medicine, there have been no reports of adverse events in the Database on Adverse Event Notifications,(27) indicating that consumers can safely use this medication in the General Sale environment.

Table 5: Adverse events reported for flurbiprofen lozenges in Australia(27)

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

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 significant safety concerns under review.

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 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.(46)

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.(27, 45)

The risk of overdose is negligible. The Reckitt PSUR lists 1 non-serious report of 'intentional overdose', 9 reports of 'accidental overdose' (of which 7 were non-serious) and 25 reports of 'overdose' (of which 20 were non-serious) for all oromucosal dosage forms of flurbiprofen. During this period patient exposures exceeded [redacted] billion.(29)

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.(12)

The majority of sore throats in adults (85-95%) are viral and self-limiting minor ailments which are resolved within a few days.(1, 13) 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(24), 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.(27, 29, 45)

Potential for medication errors

The Reckitt PSUR for the period up to 3 February 2022 indicates that there is a negligible risk of medication errors with topical oral flurbiprofen. Since 10 November 1976 there have been 147 non-serious medication errors and 38 serious medication errors with an extremely low overall event rate of 0.000000486%. Medication errors include administration errors, accidental exposures, accidental overdose, use for unapproved indication, use when contraindicated, underdosing, and use of expired product.(29)

Addiction, misuse, abuse, accidental overdose

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

The Reckitt PSUR lists two reports 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] billion. This demonstrates the risk of dependence/addiction is negligible.(29)

During the same reporting period, the PSUR lists 7 reports of ‘intentional misuse’ for all dosage forms of flurbiprofen again demonstrating that the risk of inappropriate use and misuse is negligible.(29)

The risk of accidental overdose is also negligible with 9 reports of ‘accidental overdose’ since 10 November 1976.(29)

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.(46)

Import considerations

This reclassification to General Sale would not impact any import considerations.

This reclassification to General Sale would improve the long-term viability of this product in New Zealand as it would allow the use of a New Zealand/Australian harmonised pack in New Zealand.

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 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.(29)

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

Pain is the principle driver of people with sore throats seek GP consultation, which in 30% of cases results in antibiotics being used.(19) Amongst the vast majority of New Zealanders

with a low risk of rheumatic fever, increased access to effective pain relief for sore throats has the potential to reduce the inappropriate use of antibiotics for this minor, self-limiting ailment.

Amongst Māori and Pacific Islander people living in the most impoverished regions of New Zealand who are at risk of developing rheumatic fever(32) research indicates that the General Sales availability of flurbiprofen would not increase the risk of Streptococcal A sore throats being mismanaged or treatment being delayed due to this reclassification. Māori and Pacific Islander people have a high awareness of rheumatic fever and if their child had a sore throat which persisted for more than 2 days or was accompanied by other symptoms associated with Streptococcal A infection (such as a fever or exudate) the vast majority (93%) would seek medical advice(10) in a manner that is consistent with local guidelines.(9)

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.(11)

Strepfen label discernment research has confirmed that New Zealand consumers can differentiate Strepfen lozenges from Strepsils lozenges:(10)

- Anti-inflammatory action was correctly attributed to Strepfen by 80% of consumers and 83% of Māori and Pacific Island people.
- Anti-bacterial action was correctly attributed to Strepsils by 75% of consumers and 78% of Māori and Pacific Island people.
- Use for the management of severe sore throats was correctly attributed to Strepfen by 83% of consumers and 85% of Māori and Pacific Island people.

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

The excellent safety profile of flurbiprofen lozenges is reflected by the facts that there has been more than 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.(45) Similarly there have been no adverse events reported in Australia since its availability as an Unscheduled medicine since 1 October 2021.(27)

In addition, data from the Periodic Safety Update Report indicates an extremely low rate of adverse events including amongst people who should avoid use due to comorbidities.(29) 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)

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.

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. These lozenges have comparable efficacy as analgesics for the relief of sore throat pain.(6) 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.(45) This suggests that flurbiprofen lozenges have a good safety profile which is suitable for General Sale availability.

With respect to the risk of masking more serious medical condition, the main issue to be considered is the risk of acute rheumatic fever. This risk in New Zealand is effectively limited to Māori and Pacific Island people residing in the most deprived areas of New Zealand.(32) As both benzydamine and flurbiprofen lozenges have the same anti-inflammatory and analgesic actions and have comparable efficacy,(6) the risk of masking the symptoms of a Streptococcal A sore throat is at face value equivalent. However, benzydamine lozenges can be used in children 6 years and older which means that it can be used by almost all children with the greatest risk of developing acute rheumatic fever (those aged 5 to 14 years)(7-9). As the use of flurbiprofen lozenges is limited to adults and children aged 12 years or older, the risk posed by the reclassification of flurbiprofen lozenges is lower than the current and acceptable risk associated with General Sale benzydamine.

Market research indicates that the General Sales availability of flurbiprofen would not increase the risk of Streptococcal A sore throats being mismanaged or treatment being delayed due to this reclassification. This research confirmed that Māori and Pacific Islander people have a high awareness of rheumatic fever and recognise that a sore throat can be a serious medical condition. The vast majority of Māori and Pacific Islander people indicated that if their child had a sore throat that persisted for more than 2 days or was accompanied by other symptoms such as fever and pus (symptoms associated with Streptococcal A infection) the vast majority (93%) would seek medical advice(10) which is consistent with National Heart Foundation guidelines.(9)

In terms of precedent, as indicated above NSAID containing lozenges such as benzydamine are already available as General Sale medicines in New Zealand in larger pack sizes than proposed for flurbiprofen lozenges. This indicates that flurbiprofen lozenges have a good benefit/risk profile which is suitable for General Sale availability.

The suitability of flurbiprofen lozenges for General Sale classification was acknowledged by the Australian Advisory Committee on Medicines Scheduling with their decision to list flurbiprofen lozenges (when in packs containing ≤ 16 dose units and for the use by adults and children 12 years or over) as an Unscheduled medicine. In reaching this decision the Committee indicated that the net benefits of broadening the availability 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. That flurbiprofen lozenges have the potential to improve the self-management of sore throats. That the low bioavailability of the lozenge preparation will minimise the known drug interactions and contraindications. That flurbiprofen lozenges are able to be supplied at the general sales level, with reasonable safety, without any access to health professional advice.(26) Excluding the issue of the risk of acute rheumatic fever in Māori and Pacific peoples in specific impoverished regions of New Zealand we believe that the findings of the Advisory Committee on Medicines Scheduling are applicable to the general New Zealand population.

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 lower risk of harm compared to the use of systemic analgesics.

- Flurbiprofen lozenges are an alternative to oral analgesics that are also used to manage sore throats. Oral analgesics are used at higher doses, deliver higher systemic exposures to the active ingredients and are available in larger pack sizes than that proposed for flurbiprofen lozenges.

The proposed reclassification reduces the risk of harm compared to the use of benzydamine lozenges in Māori and Pacific children at risk of rheumatic fever.

- Flurbiprofen lozenges are an alternative to benzydamine lozenges, with the main difference being that flurbiprofen lozenges can be used by fewer children at risk of developing acute rheumatic fever than benzydamine lozenges due to differences in the age posology (12 years and older versus 6 years and older, respectively). Hence, the risk posed by the reclassification of flurbiprofen lozenges is lower than the current risk which can be assumed to be an acceptable level of risk associated with General Sale benzydamine.

The label for Strepfen lozenges has been redesigned and complies 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.

- New Zealand label discernment research demonstrated that consumers could differentiate Strepfen lozenges for Strepsils lozenges confirming that the vast majority understood that Strepfen lozenges were anti-inflammatory and for the relief of severe sore throats. They also understood maximum daily doses and avoiding use with other anti-inflammatory medicines.(10)

As the risk of harm associated with this reclassification is negligible, Reckitt believes that no additional post-marketing surveillance studies are required.

However, if after considering all the evidence outlined specifically regarding the risk of rheumatic fever as addressed in Part A, Section 11, the Committee believes that the risk associated with the proposed General Sale classification for flurbiprofen lozenges is greater than that posed General Sale benzydamine lozenges, Reckitt proposes that this risk can be effectively mitigated by adjusting the proposed classification for use by adults aged 18 years or older, thus eliminating use in children.

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 such 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.(29)

New Zealand market research has confirmed that consumers can differentiate Strepfen lozenges from Strepsils lozenges and understand key differences in usage, including use in children and with other anti-inflammatory medications.(10)

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.

The availability of flurbiprofen lozenges does not carry a significant risk of masking or delaying the treatment of serious medical conditions such as Streptococcal A throat infections in at risk Māori and Pacific Island people. Research has confirmed that these cohorts have a high awareness of rheumatic fever and would seek medical advice in a manner that is consistent with current National Heart Foundation guidelines.(9, 10)

Most importantly, the potential risk of delaying the treatment of Streptococcal A throat infections in at risk Māori and Pacific Island people is effectively managed with labelling. Strepfen label discernment research found that after reading the label for Strepfen lozenges, 9 in 10 people would seek medical advice if their sore throat persisted for more than 2 days and only 1% of consumers would continue to use Strepfen lozenges and not seek medical advice.(10)

In addition, any risk posed by the proposed General Sale availability of flurbiprofen lozenges would be less than the current risk posed by the General Sale availability of benzydamine lozenges, which have comparable efficacy but can be used by children from 6 years of age compared to 12 years for flurbiprofen and comes in much larger pack sizes. Given that the risks associated with General Sale benzydamine lozenges is considered to be acceptable, the potential risk associated with flurbiprofen lozenges as a General Sales medicine must also be considered acceptable.

However, if the Committee after considering this application still has some concerns about the use in adolescents and the risk of rheumatic fever, Reckitt proposes that the General Sales classification of flurbiprofen lozenges be restricted to adults (aged 18 years or older) thereby effectively eliminating any risk regarding streptococcal A sore throat and acute rheumatic fever. In this situation the proposed wording for the reclassification would be; 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 and when labelled only for the treatment of adults aged 18 years or over.

References

1. de Looze F, Russo M, Bloch M, Montgomery B, Shephard A, Smith G, et al. Efficacy of flurbiprofen 8.75 mg spray in patients with sore throat due to an upper respiratory tract infection: A randomised controlled trial. Eur J Gen Pract. 2016;22(2):111-8.
2. Gonzalez-Younes I, Wagner JG, Gaines DA, Ferry JJ, Hageman JM. Absorption of flurbiprofen through human buccal mucosa. J Pharm Sci. 1991;80(9):820-3.
3. Medsafe. Minutes for the 65th meeting of the Medicines Classification Committee. 2020.
4. Ministry of Health. Reducing rheumatic fever. 2020.
5. Gurney JK, Chong A, Culliford-Semmens N, Tilton E, Wilson NJ, Sarfati D. High levels of rheumatic fever and sore throat awareness among a high-risk population screened for rheumatic heart disease. N Z Med J. 2017;130(1450):107-10.
6. Reckitt Benckiser. CONFIDENTIAL Data on file, Study TH0504 A single centre, randomised, single (patient) blind, single dose, parallel group exploratory study to compare the efficacy and duration of action of an 8.75 mg flurbiprofen lozenge (Strepfen®) with a 3 mg benzydamine hydrochloride lozenge (Difflam®) following administration in 200 subjects with sore throat 2006.
7. The Institute of Environmental Science and Research Ltd. Notifiable Diseases in New Zealand: Annual Report 2018. Porirua, New Zealand. 2020.
8. The Institute of Environmental Science and Research Ltd. Notifiable Diseases in New Zealand: Annual Report 2019. . Porirua, New Zealand 2021.
9. National Heart Foundation of New Zealand. Group A Streptococcal Sore Throat Management Guideline. 2019 Update. Auckland, National Heart Foundation of New Zealand. 2019;
10. One Picture. CONFIDENTIAL Data on file, Strepfen lozenge sore throat market research 2022.
11. Medsafe. Minutes of the 43rd meeting of the Medicines Classification Committee - 13 April 2010. 2010.
12. Neilsen. Reckitt Benckiser Cold and flu omnibus. 2019.
13. Therapeutic Guidelines. eTherapeutic Guidelines March 2021 edition. 2021.
14. Eccles R. Mechanisms of symptoms of the common cold and influenza. Br J Hosp Med (Lond). 2007;68(2):71-5.
15. Aspley S, Shephard A, Schachtel E, Sanner K, Savino L, Schachtel B. Efficacy of flurbiprofen 8.75 mg lozenge in patients with a swollen and inflamed sore throat. Curr Med Res Opin. 2016;32(9):1529-38.
16. Schachtel B, Aspley S, Shephard A, Shea T, Smith G, Sanner K, et al. Onset of action of a lozenge containing flurbiprofen 8.75 mg: a randomized, double-blind, placebo-controlled trial with a new method for measuring onset of analgesic activity. Pain. 2014;155(2):422-8.
17. McNally D, Simpson M, Morris C, Shephard A, Goulder M. Rapid relief of acute sore throat with AMC/DCBA throat lozenges: randomised controlled trial. Int J Clin Pract. 2010;64(2):194-207.
18. van Driel ML DSA, Deveugele M, Peersman W, Butler CC, De Meyere M, De Maeseneer J, et al. Are Sore Throat Patients Who Hope for Antibiotics Actually Asking for Pain Relief? . Ann Fam Med. 2007;4:494-9.
19. Shephard A. A Questionnaire-Based Study in 12 Countries to investigate the Drivers of Antibiotic-Seeking Behavior for Sore Throat. J Family Med Community Health. 2014;1(3):1014.
20. Mehta N, Schilder A, Fragaszy E, H ERE, Dukes O, Manikam L, et al. Antibiotic prescribing in patients with self-reported sore throat. J Antimicrob Chemother. 2017;72(3):914-22.

21. Lee CHJ, Norris P, Duck IM, Sibley CG. Demographic and Psychological Factors Associated with Feelings of Antibiotic Entitlement in New Zealand. Antibiotics (Basel). 2018;7(3).
22. Williamson DA, Roos R, Verrall A, Smith A, Thomas MG. Trends, demographics and disparities in outpatient antibiotic consumption in New Zealand: a national study. J Antimicrob Chemother. 2016;71(12):3593-8.
23. Ministry of Health and Ministry for Primary Industries. Antimicrobial Resistance: New Zealand's current situation and identified areas for action. Wellington: Ministry of Health and Ministry for Primary Industries.; 2017.
24. Colmar Brunton. Sore throat omnibus research. 2019.
25. Neilsen. Australian Lozenge Market. 2019.
26. Therapeutic Goods Administration. Interim decisions by delegates of the Secretary to the Department of Health - ACMS and ACCS meetings - March 2020. 2020.
27. Therapeutic Goods Administration. Database of Adverse Event Notifications - medicines. 2022.
28. Therapeutic Goods Administration. Australian Register of Therapeutic Goods Strepfen Intensive Sugar Free Orange flurbiprofen 8.75mg lozenge blister pack (reformulation). Australian Register of Therapeutic Goods. 2019.
29. Reckitt Benckiser. Periodic Safety Update Report, flurbiprofen. 2022.
30. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. 2020.
31. Health Canada. The Drug and Health Product Register. 2019.
32. Gurney JK, Stanley J, Baker MG, Wilson NJ, Sarfati D. Estimating the risk of acute rheumatic fever in New Zealand by age, ethnicity and deprivation. Epidemiol Infect. 2016;144(14):3058-67.
33. Cannon JW, Zhung J, Bennett J, Moreland NJ, Baker MG, Geelhoed E, et al. The economic and health burdens of diseases caused by group A Streptococcus in New Zealand. Int J Infect Dis. 2021;103:176-81.
34. Dobson SR. Group A streptococci revisited. Arch Dis Child. 1989;64(7):977-80.
35. Ebell MH, Smith MA, Barry HC, Ives K, Carey M. The rational clinical examination. Does this patient have strep throat? JAMA. 2000;284(22):2912-8.
36. Shephard A, Smith G, Aspley S, Schachtel BP. Randomised, double-blind, placebo-controlled studies on flurbiprofen 8.75 mg lozenges in patients with/without group A or C streptococcal throat infection, with an assessment of clinicians' prediction of 'strep throat'. Int J Clin Pract. 2015;69(1):59-71.
37. Heart Foundation of New Zealand. New Zealand Guidelines for Rheumatic Fever: Diagnosis, Management and Secondary Prevention of Acute Rheumatic Fever and Rheumatic Heart Disease: 2014 Update. 2014.
38. Gurney J, Stanley J, Sarfati D. The incidence of acute rheumatic fever in New Zealand, 2010-2013. Wellington: University of Otago. 2015.
39. Lennon D. Rheumatic fever as an indicator of child health. N Z Med J. 2017;130(1460):6-9.
40. Lennon D, Anderson P, Kerdemilidis M, Farrell E, Crengle Mahi S, Percival T, et al. First Presentation Acute Rheumatic Fever is Preventable in a Community Setting: A School-based Intervention. Pediatr Infect Dis J. 2017;36(12):1113-8.
41. National Center for Biotechnology Information. PubChem Compound Summary for CID 65464, Benzydamine hydrochloride. . Retrieved December 28, 2020 from https://pubchemncbinlmnihgov/compound/Benzydamine-hydrochloride. 2020.
42. New Zealand Guidelines Group. Management of Group A Streptococcal Sore Throat. . Wellington: New Zealand Guidelines Group. 2011.
43. Kljakovic M, Crampton P. Sore throat management in New Zealand general practice. N Z Med J. 2005;118(1220):U1609.
44. Ministry of Health. Sore throat. https://wwwhealthgovtnz/your-health/conditions-and-treatments/diseases-and-illnesses/sore-throat. 2018.
45. Medsafe. Suspected Medicine Adverse Reaction Search - Flurbiprofen, Benzdamine. 2022.
46. Martindale 35th Edition. 2006.

47. Schachtel B, Aspley S, Shephard A, Shea T, Smith G, Schachtel E. Utility of the sore throat pain model in a multiple-dose assessment of the acute analgesic flurbiprofen: a randomized controlled study. Trials. 2014;15:263.
48. Schachtel BP, Shephard A, Shea T, Sanner K, Savino L, Rezuke J, et al. Flurbiprofen 8.75 mg lozenges for treating sore throat symptoms: a randomized, double-blind, placebo-controlled study. Pain Manag. 2016;6(6):519-29.
49. National Institute for Health Care and Excellence. NICE Guideline, Sore throat (acute): antimicrobial prescribing. 2018.
50. Blagden M, Christian J, Miller K, Charlesworth A. Multidose flurbiprofen 8.75 mg lozenges in the treatment of sore throat: a randomised, double-blind, placebo-controlled study in UK general practice centres. Int J Clin Pract. 2002;56(2):95-100.
51. Farrer F. Sprays and lozenges for sore throats S Afr Fam Pract. 2012;54:120-2.
52. Australian Medicines Handbook (online). 2021.
53. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med. 1996;27(4):485-9.
54. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J. 2001;18(3):205-7.
55. Britt H MG, Henderson J, Bayram C, Harrison C, Valenti L, Wong C, et al. General practice activity in Australia 2014–15. General practice series no 38 Sydney: Sydney University Press. 2015.
56. Butler CC, Rollnick S, Pill R, Maggs-Rapport F, Stott N. Understanding the culture of prescribing: qualitative study of general practitioners' and patients' perceptions of antibiotics for sore throats. BMJ. 1998;317(7159):637-42.
57. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. Cochrane Database Syst Rev. 2013(11):CD000023.
58. Moore RA, Derry S, Aldington D, Wiffen PJ. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2015(10):CD011407.
59. Moore N VGE, Le Parc JM, Wall R, Schneid H, Farhan M, Verrière F, Pelen F. The PAIN Study: Paracetamol, Aspirin and Ibuprofen new tolerability study a large-scale, randomised clinical trial comparing the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. Clin Drug Invest. 1999;18(2):89-98.
60. Moore A CA, Ng B, Phillips LD, Sancak Ö, Rainsford KD. Use of multi-criteria decision analysis (MCDA) for assessing the benefit and risk of OTC analgesics. . J Pharm and Pharmacol. 2017(ISSN 2042-7158.).
61. Southey ER, Soares-Weiser K, Kleijnen J. Systematic review and meta-analysis of the clinical safety and tolerability of ibuprofen compared with paracetamol in paediatric pain and fever. Curr Med Res Opin. 2009;25(9):2207-22.