Reclassification of a Medicine for consideration by the Medicine Classification Committee

Application for the reclassification of ibuprofen 400 mg from Restricted Medicine to Pharmacy Only Medicine

23 August 2022

Submitted by:

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Table of Contents

Executive summary

This application seeks the reclassification of ibuprofen 400 mg, in packs containing not more than 12 dose units when sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age, from a Restricted Medicine to a Pharmacy Only Medicine. Larger pack sizes containing 13 to 50 dose units are to remain as a Restricted Medicine and are not the subject of this application.

This application will harmonise the scheduling the double strength ibuprofen 400 mg tablets, between Australia and New Zealand.

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). It works by inhibiting the enzyme cyclooxygenase (COX), to reduce inflammation, relieve pain and reduce fever. Ibuprofen is used in the management of mild to moderate pain and inflammation. It is also used to reduce fever.

There are multiple health benefits of having increased access to ibuprofen 400 mg tablets as a Pharmacy Only medicine including:

- Providing the most effective OTC ibuprofen dose(1, 2) in a single tablet format.
- Providing the most commonly used dosage of ibuprofen(3, 4) in a single tablet format.
- Providing a more effective treatment for strong pain, with a better risk/benefit profile than most OTC alternatives.(5)
- Satisfying a common (1 in 4) consumer preference for taking fewer tablets.(3)
- Providing consumers with difficulties swallowing tablets an easier to use treatment option.

The benefits of increased access to ibuprofen 400 mg tablets were acknowledged by the Australian Advisory Committee on Medicines Scheduling (ACMS) with their decision to reschedule immediate release 400 mg of ibuprofen in a primary pack containing not more than 12 dose units from Schedule 3 to Schedule 2 (Pharmacy Only medicine) at the 31st meeting in 2020.(6) At this meeting the Delegate stated that the benefits included, the relief of pain and fever, ibuprofen is well tolerated with an excellent safety profile at these doses [≤ 1200 mg/day] and only a single tablet is required to be taken. The Delegate also stated that the small pack size of 12 tablets is consistent with short-term use and mitigates any risk if excessive use was to occur. Any risk associated with dose confusion is mitigated by labelling and the small pack size being proposed for Pharmacy Only medicine. It was also recognised that the safety risks of 400mg ibuprofen are consistent with other already unscheduled and Schedule 2 ibuprofen products, and they acknowledged that the risk profile of ibuprofen is superior to that of other NSAIDs and comparable to paracetamol plus ibuprofen combinations in Schedule 2.

At the 65th meeting of the Medicines Classification Committee an application to reclassify ibuprofen 400 mg, in packs containing not more than 12 dose units when sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age, from a Restricted Medicine to a Pharmacy Only Medicine was considered. At this meeting the decision was to maintain the current classification as a Restricted Medicine. The Committee raised several concerns which are specifically addressed in this current application.(7)

Issue raised at the 65th meeting	Key evidence addressing this issue
• Safety of ibuprofen in the elderly, due to potential increased use amongst those	• The risk of use in elderly is no greater than the current risk which exists for

consumers who previously managed their pain with codeine-based analgesics, thus increasing the risk of upper gastrointestinal bleeding and acute kidney injury with wider availability.	other NSAIDs available as a Pharmacy Only medicine. • The label for both regular Nurofen and Nurofen 400 DOUBLE STRENGTH warn elderly people not to use ibuprofen except on the advice of their doctor and there is no evidence that this advice is not followed. • The labels also advise not to use ibuprofen for people with stomach ulcers, or other stomach disorders or kidney problems. • New Zealand research indicates that elderly people are unlikely to self-manage pain and are unlikely to manage their pain with OTC ibuprofen, but that they will speak with their doctor to manage pain when they believe it needs to be relieved.(8) • The reclassification of codeine-based analgesics in New Zealand has been in effect since 2020 and consumers who previously used OTC codeine-based analgesics would have already discussed alternative options with their doctor or pharmacist and already be using these alternatives as part of their pain management. Hence, the proposed reclassification of ibuprofen 400 mg will not substantially alter the relative use of NSAIDs amongst these consumers. • In addition, consumer research from a comparable market, Australia, indicates that following the reclassification codeine-based analgesics to prescription medicines that paracetamol was the most commonly used OTC analgesic to manage pain, irrespective of pain severity. That OTC ibuprofen use was less common and not excessive.(9) • Ibuprofen has an excellent safety profile in elderly patients, as demonstrated in meta-analysis(10) and New Zealand post-marketing adverse event reporting where the proportion of adverse events in elderly correlates with the proportion of elderly people (noting that this adverse event data does not distinguish between OTC and prescription ibuprofen use).(11, 12) • OTC doses of ibuprofen are not associated with an increased risk of

	gastrointestinal adverse events in people without GI issues.(13, 14) • Serious renal pathology has rarely been observed with ibuprofen. The evidence from literature surveys and clinical trials suggests OTC use of ibuprofen does not cause significant renal injury.(15)
• Limited consumer familiarity with the double strength 400 mg single tablet, due to limited in-market availability	• Although New Zealand experience with the double strength format is less than with regular strength, clinical research of the pharmacy self-selection use of ibuprofen 400 mg double strength tablets amongst users previously not aware of this dosage format showed that 95.2% of consumers exhibited correct or acceptable use of the 400 mg tablets, in terms of adhering to total daily dosing instructions (≤ 1200 mg/day).(16) • In-market evidence from Australia following the availability of Nurofen 400 DOUBLE STRENGTH as a Pharmacy Only medicine indicates that consumers can safely and appropriately use this medication. There have been no reports of adverse events with the double strength formulation and there has been no change in the rate of adverse events reported in the Database of Adverse Event Notifications for Nurofen/ibuprofen since this reclassification.(17) • Front of pack labelling clearly distinguishes the DOUBLE STRENGTH formulation from regular Nurofen.
• Consumer benefit being minimal compared to the potential for harm associated with accidently taking twice the recommended OTC dose due to dosage confusion.	• There are multiple benefits for self-selection access to ibuprofen 400 mg (outlined above). These benefits are also reflected in consumer research that found that Nurofen 400 DOUBLE STRENGTH was the third most popular purchase consideration (at 33%) amongst the Pharmacy Only Nurofen product range.(18) • The risk of accidently taking twice the recommended dose is low, as was demonstrated in the clinical research of the pharmacy self-selection use of ibuprofen 400 mg double strength tablets amongst users previously not aware of this dosage format. The use of 2400 mg/day only occurred in 0.6% of users and when it did occur it was an intentional decision to use a higher dose.(16)

	• Taking ibuprofen 2400 mg/day does not represent taking an overdose but is taking a commonly used therapeutic dose that is well tolerated. • The short-term use of ibuprofen at 2400 mg/day has a similar safety profile to ibuprofen 1200 mg/day.(19-21). • A Medsafe report concluded that the cardiovascular risks associated with ibuprofen 2400 mg/day are small.(22) • The short-term use of ibuprofen at 1600 to 2400 mg/day taken for up to 3 days results in little or no injury to the gastric mucosa.(13) • If a patient was to inadvertently take this higher therapeutic dose, the pack size limitation of 12 dose units means that the exposure is limited to a maximum of two days.

At the 66th meeting of the Medicines Classification Committee an appeal to the 2020 decision was considered. At this meeting the Committee also commented that requiring healthcare professional (pharmacist) input for the sale of the higher strength ibuprofen tablets is consistent with other NSAIDs available in the market.(23) Although this is correct at face value, there is a clear difference between double strength ibuprofen 400 mg tablets and double strength diclofenac 25 mg tablets. For ibuprofen both regular and double strength tablets have the same maximum daily dose (≤ 1200 mg/day) and therefore the safety profile is essentially the same. For diclofenac the maximum daily dose of the Pharmacy Only 12.5 mg formulations are 75 mg/day,(24) and the Restricted Medicine double strength 25 mg formulations are higher at 150 mg/day.(25) Hence, the higher (double) maximum daily dose translates into a significantly different safety profile that warrants pharmacist oversight for double strength diclofenac, but not for double strength ibuprofen where there is no difference in the maximum daily dose.

The evidence enclosed in this submission demonstrates that ibuprofen 400 mg in primary packs limited to 12 dose units or less is suitable for reclassification to a Pharmacy Only medicine:

- The approved indications for ibuprofen 400 mg are the same as that for regular ibuprofen 200 mg which are available as Unscheduled and Pharmacy Only medicines. It is accepted that these ailments are easily recognised, are unlikely to be confused with more serious conditions and are appropriate for self-selection by a consumer within pharmacy.
- Ibuprofen 400 mg with a maximum daily dose of 1200 mg (and limited to 12 tablets) has the same excellent safety profile as 200 mg ibuprofen.
- The safety profile associated with the short-term use of ibuprofen 400 mg and 200 mg is essentially the same and is equivalent to placebo.(2, 26)
- Ibuprofen has a wide therapeutic index and risk of harm from overdose (intentional or accidental) is minimal. More than 400 mg/kg of ibuprofen needs to be consumed to cause moderate to severe adverse effects.(27) This is significantly more than the 4800 mg contained in a 12 tablet pack of Nurofen 400 DOUBLE STRENGTH.

- Safety in at risk populations is effectively addressed by product labelling, and the proposed changes to the Pharmacy Only label for Nurofen 400 DOUBLE STRENGTH mitigate the risk of dosing confusion.
- The most commonly used dose of ibuprofen is 400 mg (two tablets of 200 mg Nurofen product),(3, 4) hence availability of the 400 mg dose for self-selection matches consumer use and needs, and is unlikely to alter medication usage.

Part A

1. International Non-proprietary Name of the medicine.

Ibuprofen

2. Proprietary name(s).

NUROFEN 400 DOUBLE STRENGTH

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

[redacted]

Reckitt Benckiser (New Zealand) Pty Limited

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

Phone: [redacted]

Email: [redacted]

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

Ibuprofen 400 mg oral tablets or capsules

5. Pack size, storage conditions and other qualifications.

Pack size: Up to 12 dose units to be reclassified as Pharmacy Only Medicine

Qualifications: for oral use in tablets or capsules containing up to 400 milligrams per dose with a recommended daily dose of not more than 1200mg and in packs containing not more than 12 dose units when sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age.

Note, this application is not proposing any change to the classification of ibuprofen 400 mg in larger pack sizes 13 to 50 dose units. These medicines are to remain unchanged as Restricted Medicines.

Store below 25^{o}C.

6. Indications for which change is sought.

The approved indications for ibuprofen 400 mg are the same as that for regular ibuprofen 200 mg which are available as General Sale and Pharmacy Only medicines.

Nurofen 400 DOUBLE STRENGTH is indicated for the temporary relief of pain and /or inflammation associated with headache, migraine headache, tension headache, sinus pain, dental pain, backache, muscular aches and pains, period pain, sore throat, arthritic pain and the symptoms of colds and flu. Reduces fever.

7. Present classification of the medicine.

The current classification of ibuprofen is summarised in Table 1. The classification of oral ibuprofen 400 mg tablets or capsules is a Restricted medicine.

Table 1: Current classification of ibuprofen

Ingredient	Conditions (if any)	Classification
Ibuprofen	**except** when specified elsewhere in this schedule	Prescription
Ibuprofen	for oral use in tablets or capsules containing up to 400 milligrams per dose form and in packs containing not more than 50 dose units and that have received the consent of the Minister or the Director-General to their distribution as restricted medicines and that are sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age	Restricted
Ibuprofen	for oral use in liquid form with a recommended daily dose of not more than 1.2 grams for the relief of pain and reduction of fever or inflammation when sold in the manufacturer's original pack containing not more than 8 grams; for oral use in solid dose form containing not more than 200 milligrams per dose form and with a recommended daily dose of not more than 1.2 grams when sold in the manufacturer's original pack containing not more than 100 dose units; **except** in divided solid dosage forms for oral use containing 200 milligrams or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units	Pharmacy Only
Ibuprofen	for external use; in divided solid dosage forms for oral use containing 200 milligrams or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units per pack	General sale

8. Classification sought.

The classification sought is Pharmacy Only medicine, for oral use in tablets or capsules containing up to 400 milligrams per dose with a recommended daily dose of not more than 1.2 grams and in packs containing not more than 12 dose units when sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age.

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

Table 2: Proposed classification of ibuprofen

Ingredient	Conditions (if any)	Classification
Ibuprofen	**except** when specified elsewhere in this schedule	Prescription
Ibuprofen	for oral use in tablets or capsules containing up to 400 milligrams per dose form and in packs containing not more than 50 dose units and that have received the consent of the Minister or the Director-General to their distribution as restricted medicines and that are sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age **except** for oral use in tablets or capsules containing up to 400 milligrams per dose form with a recommended daily dose of not more than 1.2 grams and in packs containing not more than 12 dose units when sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age	Restricted
Ibuprofen	for oral use in liquid form with a recommended daily dose of not more than 1.2 grams for the relief of pain and reduction of fever or inflammation when sold in the manufacturer's original pack containing not more than 8 grams; for oral use in tablets or capsules containing up to 400 milligrams per dose form with a recommended daily dose of not more than 1.2 grams and in packs containing not more than 12 dose units when sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age for oral use in solid dose form containing not more than 200 milligrams per dose form and with a recommended daily dose of not more than 1.2 grams when sold in the manufacturer's original pack containing not more than 100 dose units; **except** in divided solid dosage forms for oral use containing 200 milligrams or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units	Pharmacy Only
Ibuprofen	for external use; in divided solid dosage forms for oral use containing 200 milligrams or less per dose form with a recommended daily dose of not more than 1.2 grams and when sold in the manufacturer's original pack containing not more than 25 dose units per pack	General sale

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

Globally Reckitt Benckiser holds the marketing authorisation of ibuprofen in 82 countries.(28) The 400 mg dosage format is available as 400 mg tablets in 43 countries and as 400 mg liquid capsules in 27 countries. The number of countries where the 400 mg dosage form is available for self-selection has increased in recent years, with it available for general sale in Hungry and self-selection within pharmacy in 9 countries including Australia and the United Kingdom. (See Table 3)

Table 3: Scheduling status of ibuprofen 400 mg in comparable markets

Country	Status	Switch date	Registration date
Australia	OTC Pharmacy Only (≤12 dosage units) Pharmacist Only (13-50 dosage units)	February 2021	11/07/2007
Belgium	OTC Pharmacy Behind Counter		5/11/1998
Czech Republic	OTC Pharmacy Behind Counter		19/5/1999
Estonia	OTC Pharmacy Behind Counter		13/8/2004
Germany	OTC Pharmacy Behind Counter	1989	16/6/1998
Hungary	General sale		12/3/1999
Israel	OTC Pharmacy Front of Counter	1999	13/6/1997
Latvia	OTC Pharmacy Front of Counter		24/10/2003
Luxembourg	OTC Pharmacy Behind Counter		30/9/1998
Netherlands	OTC Pharmacy and Drug Stores Front of Counter		30/9/1998
Poland	OTC Pharmacy Front of Counter		14/4/2000
Romania	OTC Pharmacy Front of Counter		11/8/1998
Russian Federation	OTC Pharmacy Front of Counter		25/11/2004
Slovakia	OTC Pharmacy Front of Counter		1/11/1992
South Africa	OTC Pharmacy Behind Counter		27/9/1998
Spain	OTC Pharmacy Behind Counter	1986	23/10/1989
Switzerland	OTC Pharmacy and Drug Stores Front of Counter		
Thailand	OTC Pharmacy Behind Counter		15/12/1997
Ukraine	OTC Pharmacy Behind Counter		23/3/2004
United Kingdom	OTC Pharmacy Front of Counter	1983	25/3/1985

In Australia, 400 mg of ibuprofen immediate release tablets in a primary pack containing not more than 12 dosage units, when labelled with a recommended daily dose of 1200 mg or less of ibuprofen is Schedule 2 (Pharmacy Only Medicine). The scheduling change was made at the 31st meeting of the Australian Advisory Committee on Medicines Scheduling (ACMS). In reaching this decision the Delegate stated that the benefits associated with Pharmacy Only listing included:(6)

- the relief of pain and fever,
- ibuprofen is well tolerated with an excellent safety profile at these doses [≤ 1200 mg/day], and
- only a single tablet is required to be taken.

The Delegate also stated that the small size of pack at 12 tablets is consistent with short-term use and is a significant mitigation for concern around excessive doses. That the risk around dose confusion is mitigated by labelling and the small pack size proposed. That the safety risks are consistent with other already unscheduled and Schedule 2 ibuprofen products and they acknowledged that the risk profile of ibuprofen is superior to that of other NSAIDs and comparable to paracetamol plus ibuprofen combinations in Schedule 2.(6)

Health Canada regulates ibuprofen in strengths of 200 mg, 300 mg and 400 mg as over-the-counter medicines.

In the United States of America, ibuprofen 400 mg products are prescription only medicines, noting that there is no “Pharmacy Only” equivalent schedule.

In the United Kingdom, ibuprofen 400 mg products are available for self-selection within pharmacy.

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

Ibuprofen was first available in New Zealand in 1975 and in Australia in 1979 as a prescription medicine under the brand name BRUFEN. It was available in both 400 mg and 200 mg strengths.

As a prescription medicine, the recommended initial dosage of ibuprofen 400 mg is 1200 mg to 1800 mg daily in divided doses. In severe or acute conditions, the total daily dose can be increased to 2400 mg (800 mg three times a day) until the acute phase is brought under control.

In 1985, ibuprofen 200 mg was reclassified to Pharmacy Only Medicine and was available in New Zealand as the OTC brand, Nurofen.

In 2004, the New Zealand Medicines Classification Committee approved the reclassification of ibuprofen 200 mg to be available for General Sale when sold in packs of 25 dose units or less. In Australia, the availability of ibuprofen 200 mg as an unscheduled medicine occurred a year earlier in 2003.

In 2006, following the 35th meeting, the NZ Medicines Classification Committee, ibuprofen 400 mg in packs containing not more than 50 dose units that are sold in the manufacturer's original pack labelled for use by adults and children over 12 years of age was reclassified as a Restricted Medicine in alignment with an equivalent rescheduling to Pharmacist Only medicine in Australia in the same year.

Nurofen 400 DOUBLE STRENGTH tablets was launched in New Zealand in June 2019. Since the launch [redacted] days’ supply of the 400 mg DOUBLE STRENGTH tablets have been purchased in New Zealand. This product has been temporarily discontinued in the New Zealand market due to loss of harmonisation with Australia with the last sales being reported in February 2022.

In Australia the non-prescription sale of Nurofen 400 DOUBLE STRENGTH has been available for longer than that in New Zealand. Since its launch in 2016 patient exposures to the 400 mg DOUBLE STRENGTH tablets are estimated to be over [redacted]. In addition, Nurofen 400 DOUBLE STRENGTH has been sold in Australia as a self-selection Pharmacy Only medicine since February 2021, with patient exposures since this time being in excess of [redacted]

In the UK and Europe, ibuprofen 200 mg and 400 mg in various pack sizes have been available as Pharmacy products since 1984 with a maximum daily dose of 1200 mg. Globally the use of Nurofen 400 DOUBLE STRENGTH is extensive. For example, for the 12 month period of November 2018 to September 2019, the sales of Nurofen 400 mg DOUBLE STRENGTH were in excess of [redacted] units. There have been no signals to suggest that the increasing use of Nurofen 400 DOUBLE STRENGTH tablets has changed the excellent safety profile of OTC ibuprofen.(28)

Globally, the non-prescription availability of ibuprofen (400 mg or 200 mg strengths) is a testament to the fact that consumers, healthcare professionals and regulators regard ibuprofen as an effective pain reliever with a well-established safety profile that is suitable for general sale use at a maximum dose of 1200 mg/day.

As a non-prescription medicine, ibuprofen 400 mg double strength has the same maximum daily dose of 1200 mg/day as current General Sale and Pharmacy Only ibuprofen 200 mg products. The smaller pack size of 12 dose units or less, represents equivalent days treatment as ibuprofen 200 mg when sold as a General Sale medicine (4 days' supply). It is expected that the Pharmacy Only availability of this medication under the proposed conditions will provide the same efficacy and safety profile as regular ibuprofen 200 mg products but in a single tablet format.

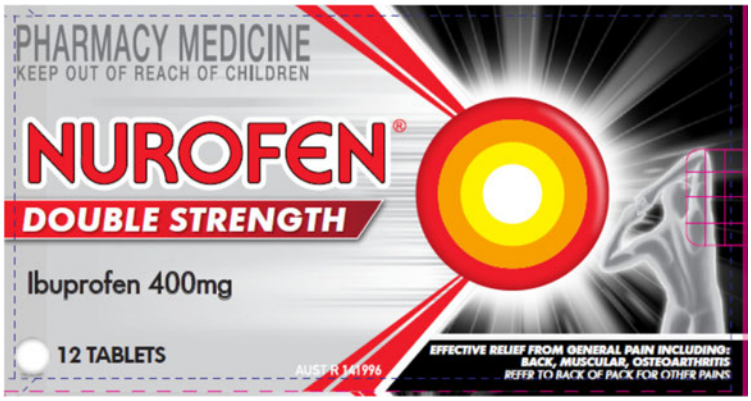
11. Local data or special considerations relating to New Zealand (if applicable).

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

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

If this application is successful, it is proposed to harmonise the New Zealand label with the new Australian Pharmacy Only (Schedule 2) packaging (See Figure 1 below). This packaging has multiple design elements that clearly distinguish it from regular Nurofen 200 mg tablets (See Figure 2 below). In addition, this new Pharmacy Only label is distinctly different to the label for this product when it was first launched in New Zealand (See Figure 3) with an altered colour scheme that more clearly distinguishes the DOUBLE STRENGTH product from regular Nurofen.

Figure 1: Nurofen 400 DOUBLE STRENGTH proposed harmonised Pharmacy Only label



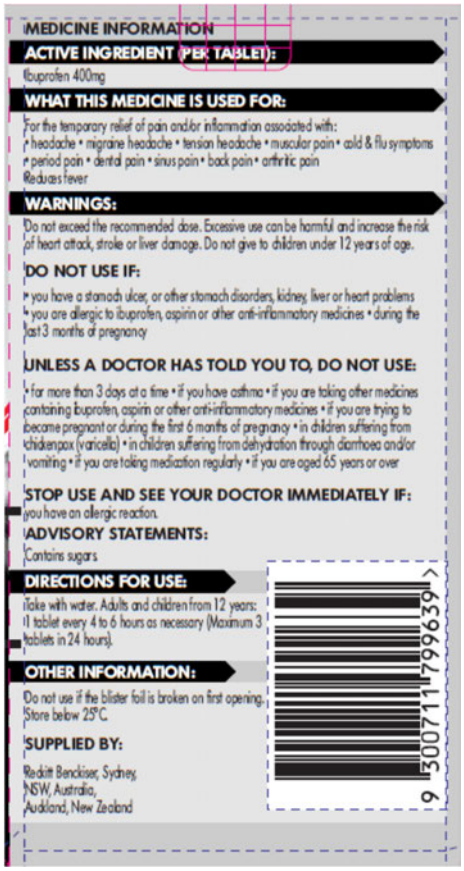


Figure 2: Nurofen 200 mg Pharmacy Only label

MEDICINE INFORMATION

ACTIVE INGREDIENT (PER TABLET):

Ibuprofen 200mg

WHAT THIS MEDICINE IS USED FOR:

For the temporary relief of pain and/or inflammation associated with:
• headache • migraine headache • tension headache • back pain
• muscular pain • cold & flu symptoms • period pain • dental pain
• sinus pain • arthritic pain
Reduces fever

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 IF:

• you have a stomach ulcer, or other stomach disorders, kidney, liver or heart problems • you are allergic to ibuprofen, aspirin or other anti-inflammatory medicines • during the last 3 months of pregnancy

UNLESS A DOCTOR HAS TOLD YOU TO, DO NOT USE:

• for more than 3 days at a time • if you have asthma • if you are taking other medicines containing ibuprofen, aspirin or other anti-inflammatory medicines • if you are trying to become pregnant or during the first 6 months of pregnancy • in children suffering from chickenpox (varicella) • in children suffering from dehydration through diarrhoea and/or vomiting • if you are taking medication regularly • if you are aged 65 years or over • in children under 7 years of age.

STOP USE AND SEE YOUR DOCTOR IMMEDIATELY IF: you have an allergic reaction.

ADVISORY STATEMENTS:

Contains sucrose.

DIRECTIONS FOR USE:

Take with water. Adults and children from 12 years: 2 tablets, then 1 or 2 tablets every 4 to 6 hours as necessary (maximum 6 tablets in 24 hours). Children (7 to 12 years): 1 tablet every 6 to 8 hours as necessary (maximum 4 tablets in 24 hours).

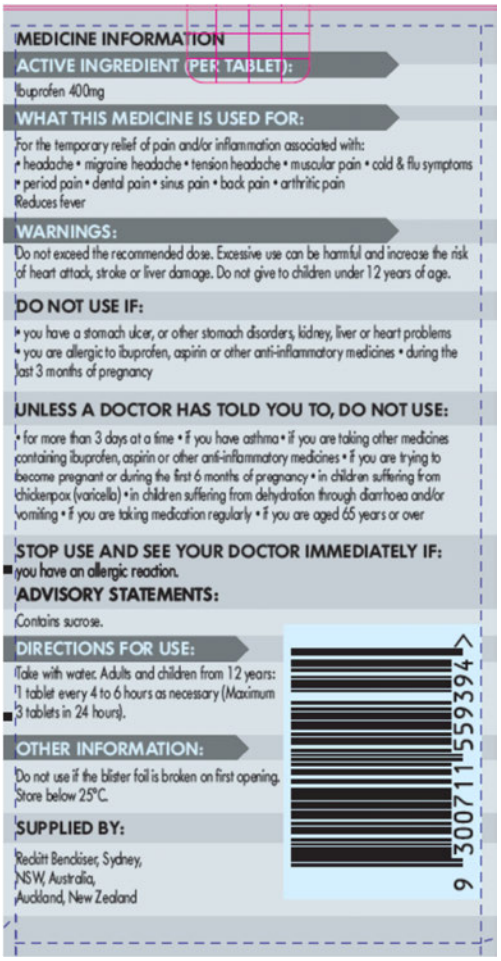
OTHER INFORMATION:

Do not use if the blister foil is broken on first opening.
Store below 25°C.

SUPPLIED BY:

Reckitt Benckiser,
Sydney, NSW, Australia,
Auckland, New Zealand

Figure 3: Nurofen 400 DOUBLE STRENGTH Current Restricted medicines label



The Nurofen DOUBLE STRENGTH label is clearly differentiated from the regular strength Nurofen (200 mg) tablets. The difference in tablet strength and one tablet dosage is effectively communicated with:

- Colours on label are black/dark grey and red, while the colours for regular Nurofen do not include the black/dark grey.
- DOUBLE STRENGTH in a red call out box immediately underneath the brand name.
- The ibuprofen content of 400 mg being communicated on front and back of pack.
- The one tablet dose being visually illustrated on front of pack, noting that regular Nurofen depicts two tablets on front of pack.
- The dosage directions provided on back of pack.

It is important to note, that the Advisory Committee on Medicines Scheduling (ACMS) with their decision to reschedule 400 mg of ibuprofen from Schedule 3 to Schedule 2 (Pharmacy Only medicine) determined that the risk around dosing confusion was mitigated by comparable labelling.(6)

In addition to the above labelling elements that distinguish Nurofen 400 DOUBLE STRENGTH from regular strength Nurofen (200 mg) tablets, it is important to understand that double strength product also is different regular Nurofen in terms of pack size

dimensions. The dimensions of the front of pack for Nurofen 400 DOUBLE STRENGTH is 116 x 61 mm, which is taller and longer than regular Nurofen at 107 x 46 mm. This different facing dimensions are only used for formulations that are different to the base (regular) Nurofen range and help consumers recognise that this is a different formulation.

13. Proposed warning statements (if applicable).

Nurofen 400 DOUBLE STRENGTH has the same warning statements as that required for regular ibuprofen 200 mg. The warning statements applied to the proposed, harmonised Pharmacy Only product label is the same as the current approved label for this product as a Restricted Medicine. (See Figures 1 to 3).

Except for clearly communicated differences in tablet strength and one tablet dosing directions, the back of pack medicines information panel for Nurofen 400 DOUBLE STRENGTH is essentially the same as that for regular Nurofen 200 mg.

The medicines information panel clearly stipulates how to use the product and highlights the contraindications, warnings and precautions (including that it is not to be used if you are aged 65 years or older except under a doctor's advice) as per the requirements of Medsafe and Australia's Therapeutic Goods Administration. Therefore, given this is an approved label which meets the Medsafe labelling requirements as well as those of the TGA's TGO92 (aimed at improving consumer understanding of medicine labels) it is reasonable to conclude that the packaging and labelling for regular Nurofen and Nurofen 400 DOUBLE STRENGTH effectively supports the quality use of ibuprofen for self-selection within pharmacy.

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 ibuprofen 400 mg in packs of 12 dose units or less. Other products that could potentially be affected by this change are listed in Table 4. None of these three brands are currently available for consumer purchase in New Zealand.

Table 4: Other products affected by the proposed change

Brand name (Sponsor)	Number of tablets per pack	Current classification
Brufen One (Viatris Limited)	10 tablets	Restricted
Ibuprofen Liquid Capsules (Neo Health NZ Limited)	6, 10 and 12 capsules	Restricted
AdiraMedica Ibuprofen Capsules 400 mg Soft gelatin capsule, 400 mg (AdiraMedica Pty Ltd)	10 capsules	Restricted

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?

Ibuprofen 400 mg is indicated for the temporary relief of acute pain (and discomfort) associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, period pain, sore throat, tennis elbow, arthritis, rheumatic pain and the aches and pains associated with colds and flu. Reduces fever.

These are the same indications as regular ibuprofen 200 mg formulations which are available as General Sale and Pharmacy Only medicines (pack size dependent). Therefore, it has been previously established and accepted that these ailments are easily recognised by consumers and are unlikely to be confused with more serious conditions and are appropriate for self-selection within a grocery and pharmacy environment.

The treatment population for these indications are adults (less than 65 years) and children aged 12 years or older.

The dosing instructions for Nurofen 400 DOUBLE STRENGTH are: take with water. Adults and children from 12 years. 1 tablet every 4 to 6 hours as necessary. Maximum 3 tablets per 24 hours.

The maximum dose of 1200 mg per day is the same as regular Nurofen 200 mg which is available for self-selection in packs of 25 or less for General Sale and as a Pharmacy Only medicine in packs up to 100 dose units.

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 400 mg tablets. This is the same dosage form and strength for all indications.

In terms of disposal consideration, the usual process for disposal of medicines would be followed as the proposed Pharmacy Only pack size of 12 dose units, is unlikely to require any special disposal considerations.

In terms of how practical and easy it is to use the proposed formulation; it is very easy for consumers to use one tablet per dose presentation associated with Nurofen 400 DOUBLE STRENGTH. The one tablet dosing posology is the core consumer benefit of this reclassification application.

A single dose of ibuprofen 400 mg is clinically proven to be more effective analgesic than a 200 mg dose. This has been confirmed by two Cochrane reviews amongst patients with acute pain (e.g., following dental surgery).(1, 2) Therefore, use of the double strength formulation will provide consumers with the most efficacious OTC ibuprofen dose via a single tablet.

Another benefit of the double strength 400 mg tablet is that consumers can take the most commonly used dose of ibuprofen (400mg) in a single tablet. Two consumer research studies, one conducted in Australia(3) and one conducted in the United Kingdom(4) found that the majority of Nurofen users normally take the 400 mg dose to relieve their pain (77% in Australia and 78.4% in the UK).

Consumers are accustomed to seeing double/extra strength products on shelfs alongside their regular strength (less concentrated) alternatives and know that dosing of the two would be different. The most relevant example to this application is for aspirin, where Aspro Clear Regular Strength (300 mg) and Aspro Clear Extra Strength (500 mg) are both available for self-selection as a General Sales medicines. These two formulations have different tablet strengths and different dosage regimens:

- Aspro Clear Extra Strength (500mg): 1-2 tablets to be dissolved in water
- Aspro Clear Regular Strength (300mg): 2-3 tablets to be dissolved in water.

It is also noteworthy, that aspirin has a poorer safety profile relative to ibuprofen,(5, 14) therefore the potential risk associated with medication errors due to dosing confusion is greater for aspirin which is available for self-selection outside the pharmacy setting. This indicates that both strengths of ibuprofen (200 and 400 mg) with its superior safety profile is also suitable for self-selection within pharmacy as a Pharmacy Only medicine.

In addition, a one tablet posology is not unusual amongst OTC medicines with products such as Somac (pantoprazole), Zyrtec (cetirizine) and Claratyne (loratadine) all requiring only one tablet per dose.

The proposed harmonised Nurofen 400 DOUBLE STRENGTH pack label clearly calls out that this formulation is twice the strength and that only one tablet is required per dose, therefore, the presentation of ibuprofen 400 mg DOUBLE STRENGTH is suitable for self-selection in pharmacy as a Pharmacy Only medicine. In addition, Nurofen label comprehension research conducted in Australia in 2022, found that 87% of consumers followed the dosage instructions on the label (every time, most of the time or when buying the product for the first time) with a similar proportion (85%) indicating that they followed the instructions for use on the label. This same study also found that the majority of consumers when using a new product/formulation for the first time, would seek advice from pharmacy staff prior to the purchase.(18) This indicates that a Pharmacy Only classification has the appropriate balance between increased access and pharmacist oversight when required.

3. Consumer benefits

− What is the history of this medicine's use for the proposed indication(s) ie, number of; 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?

Ibuprofen 200 mg oral preparations are currently exempt from classification (unclassified), Pharmacy Only Medicine, Restricted Medicine or Prescription Medicine classification, depending on the total daily dose, and the pack size. Ibuprofen 400 mg oral preparations are currently Restricted Medicine or Prescription Medicine classification, depending on the total daily dose, indication and the pack size. It is well established that a total daily dose up to 1200 mg per day of ibuprofen is suitable for non-prescription use for pain and fever, whereas at higher doses (typically up to 1600-2400 mg per day) are used as an anti-inflammatory for chronic arthropathies and other conditions under the care of a doctor. The currently available

non-prescription ibuprofen products are presented as oral solid dosage forms of 200 mg (with or without additional active ingredients), 400 mg as well as oral liquid preparations and topical formulations.

As summarised in Part A, Section 10, the non-prescription availability of ibuprofen (400 mg or 200 mg strengths) is a testament to the fact that consumers, healthcare professionals and regulators regard ibuprofen as an effective pain reliever with a well-established safety profile that is suitable for general sale use at a maximum dose of 1200 mg/day.

Globally Reckitt Benckiser holds the marketing authorisation of ibuprofen in 82 countries.(28) The 400 mg dosage is available in 48 countries. It is available as an unscheduled medicine in one country and is available for self-selection within pharmacy in 9 countries including Australia and the United Kingdom. (See Part A, Section 9, Table 3)

There has been extensive global use of Nurofen 400 DOUBLE STRENGTH. For example, for the 12 month period of November 2018 to September 2019, the sales of Nurofen 400 mg formulations were in excess of [redacted] units. Since the non-prescription availability of the 400 mg strength there have been no safety signals to suggest that the increasing use of the DOUBLE STRENGTH tablets has changed the excellent safety profile of OTC ibuprofen.(28)

It is estimated that the patient exposure to Nurofen 400 DOUBLE STRENGTH in New Zealand is [redacted] days' supply.

Since February 2021, Nurofen 400 DOUBLE STRENGTH has been available in Australia as a Pharmacy Only medicine. Patient exposures in Australia as a Pharmacy Only medicine are substantial at over 333,000 and there is no evidence of safety issues with its availability as a self-selection medication within pharmacy. This is evident by the fact that there have been no reports of adverse events with Nurofen 400 DOUBLE STRENGTH in the DAENs database since its availability as both a Schedule 3 and Schedule 2 medicine in Australia. In addition, the number of adverse events for Nurofen or ibuprofen (tradename not specified reported in the 17 months (1st February to 30tth July 2022) when Nurofen 400 DOUBLE STRENGTH has been available as a Pharmacy Only medicine is lower than the preceding 17 months (1st September 2019 to 31st January 2021) at 85 and 95 respectively.(17) This indicates that consumers can safely and appropriately use ibuprofen 400 mg double strength tablets as a Pharmacy Only medicine.

The ability of new consumers to appropriately use the ibuprofen 400 mg double strength tablets has been assessed in a single-arm, open-label clinical study that simulated its OTC use in the United States. At the time of the study the 400 mg strength was not available for OTC use and this allowed the researchers to investigate the use amongst consumers who were unfamiliar with the product and were previously only aware of the regular 200 mg strength. In this study eligible participants went to a pharmacy study site, where they were shown the OTC ibuprofen 400 mg tablet packaging and were given time to review the on-pack information and to make a purchase decision. Purchasers used the 400 mg tablets as needed over the next 30 days, recording all use during this time. In this study 1,315 people presented to a pharmacy and 738 purchased ibuprofen 400 mg tablets. 736 of these took at least one dose (safety population) and 685 were included in the actual use population.(16)

In this simulation of self-selection OTC use, participants took an average daily dose of 644.8 mg (SD 255.66 mg) equivalent to 1.6 tablets/day, and the average maximum daily dose was 972.3 mg (SD 476.33 mg) equivalent to 2.4 tablets/day. Consumer use of the 400 mg strength tablets was overall consistent with the dosing instructions. 95.2% of consumers exhibited correct or acceptable use of the 400 mg tablets, in terms of adhering to total daily dosing instructions (≤ 1200 mg/day). The main reason for exceeding the recommended daily

dose was the desire for pain relief and it was not related to dosage confusion. Importantly consumers with low literacy had a slightly higher level of correct use than those with normal literacy (96.9, 95% CI: 93.8-99.9%, vs. 94.8%, 95% CI: 92.9-96.6%). Excessive use was infrequent, observed in only four (0.6%) participants. In this study excessive use was defined as those who used the product for > 10 days during the study and had an average daily dose > 1,600 mg, or who used the product for ≤ 10 days, took more than 30 tablets, and had an average daily dose > 1,600 mg. (Note, the first criteria for excessive use does not apply to the New Zealand situation as the proposed Pharmacy Only pack size is limited to 4 days' supply). Reasons for excessive use were that they "always take ibuprofen and other pain relievers in this manner" or they "had severe pain not relieved with 1 pill" (2 participants each). Hence, this study provides evidence that amongst consumers who are unfamiliar with the ibuprofen 400 mg double strength tablets, that almost all use following self-selection of the double strength formulation was in a manner consistent with directions on the label.(16)

Ibuprofen 400 mg double strength tablets are indicated for the temporary relief of acute pain (and discomfort) associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, period pain, sore throat, tennis elbow, arthritis, rheumatic pain and the aches and pains associated with colds and flu. Reduces fever. These are the same indications as regular ibuprofen 200 mg formulations which are available as General Sale and Pharmacy Only medicines (pack size dependent).

The duration of use is limited to short-term use. This is clearly communicated on pack with instructions that unless advised by your doctor not to use this medication for more than 3 days at a time. Short-term use is further reinforced by limiting the proposed Pharmacy Only pack size to 12 or less dose units, representing 4 days' supply. The effectiveness of this risk mitigation strategy was acknowledged by the Australian Advisory Committee on Medicines Scheduling when reaching their decision to list this product within Schedule 2 with the Delegate stating that "The small size of the pack at 12 tablets is consistent with short-term use and is a significant mitigation for concern around excessive doses."(6)

There are multiple consumer benefits of self-selection access to ibuprofen 400 mg, and these are primarily due to being able to take the most effective OTC dose of ibuprofen in a single tablet.

A single dose of ibuprofen 400 mg is clinically proven to provide more effective pain relief than a 200 mg single dose. This has been confirmed by two Cochrane reviews amongst patients with acute pain (acute post-operative pain, e.g., following dental surgery).(1, 2)

The Cochrane review by Moore et al (2015a) assessed the relative efficacy and safety of non-prescription (OTC) analgesics in the management of acute pain. The number needed to treat (NNT) for at least 50% pain relief was lower for ibuprofen 400 mg (NNT = 2.5; 95% CI: 2.4-2.6) than for ibuprofen 200 mg (NNT = 2.9; 95% CI: 2.7-3.2) indicating superior analgesia for the 400 mg dose.(2)

Equivalent findings were demonstrated in the Cochrane review by Derry et al. (2009) that investigated the use of ibuprofen for acute postoperative pain. The 400 mg dose provided better pain relief as well as longer lasting pain relief than the 200 mg dose. The number needed to treat for at least 50% pain relief compared with placebo was lower for the 400 mg dose (NNT = 2.5; 95% CI: 2.4-2.6) than for 200 mg (NNT = 2.7; 95% CI: 2.5-3.0). Similarly, the need for re-medication within 6 hours was lower for the 400 mg dose compared to the 200 mg dose (42% vs. 48%).(1)

In addition, these same reviews as well as one other that focused only on tolerability have confirmed that a single doses of ibuprofen 400 mg are as well tolerated as single doses of

ibuprofen 200 mg and that the rate of adverse events with both ibuprofen doses were comparable to placebo.(1, 2, 26) For example, Moore et al (2015a) found that the relative risk of an adverse event was numerically lower for single doses of ibuprofen 400 mg (RR = 0.9; 95% CI: 0.7-1.02) than single doses of 200 mg (RR = 1.2; 95% CI: 0.7-2.1).(2)

Consumer research (n = 1186) regarding the use of Nurofen 400 DOUBLE STRENGTH found that 61% of people surveyed would use the 400 mg tablets in preference to regular Nurofen 200 mg to relieve strong pain. This research also investigated the consumer benefits of having Nurofen 400 DOUBLE STRENGTH formulation available for self-selection within pharmacy. The most common consumer benefits were:(3)

- The convenience of only needing to take a single tablet (40%)
- It works better to relieve strong pain (35%)
- The dislike for taking tablets and therefore using a product that requires fewer tablets to be taken (23%)
- Being as effective as regular Nurofen (17%).

The consumer need for expanded access to Nurofen 400 DOUBLE STRENGTH is further highlighted by consumer research conducted in 2022 in Australia where this product had been available as a Pharmacy Only medicine for more than a year. When consumers were shown the Pharmacy Only Nurofen range, Nurofen 400 DOUBLE STRENGTH was the third most popular product for purchase consideration at [redacted], behind regular Nurofen 200 mg [redacted] and Nurofen Zavance [redacted].(18) This clearly indicates that there is a consumer benefit and need for a single tablet format of ibuprofen 400 mg.

The Pharmacy Only availability ibuprofen 400 mg double strength tablets will give consumers improved access to the most effective single active dose of OTC ibuprofen available in a single tablet, a benefit that was acknowledged at the 31st meeting of the Australian Advisory Committee on Medicines Scheduling (ACMS) with their decision to reschedule ibuprofen 400 mg from Schedule 3 to Schedule 2 (Pharmacy Only medicine) in 2020.(6)

Ibuprofen 400 mg is the most commonly taken OTC ibuprofen dose

Consumers experiencing pain want to take effective doses of analgesics to relieve their pain and discomfort promptly. As the experience of pain is subjective and highly individualised, the person experiencing pain is best able to determine how much pain relief they need. For many consumers the 200 mg dose is inadequate to manage their pain and they choose to manage pain with the 400 mg OTC dose.

The consumer need to take ibuprofen 400 mg dose has been confirmed by two consumer research studies, one conducted in Australia, and one conducted in the United Kingdom. Both studies found that the most common single ibuprofen dose taken to relieve pain was 400 mg and this was used by almost 8 in 10 consumers, 77% in the Australian study(3) and 78.4% in the UK study.(4)

The Pharmacy Only availability ibuprofen 400 mg double strength (≤ 12 dose units) will give consumers improved access to the most effective single active OTC ibuprofen dose and the most commonly used OTC ibuprofen dose in a single tablet format.

Consumers will benefit from the availability of a double strength (400mg) ibuprofen product to manage strong pain as it has a more favourable risk-benefit profile vs current alternatives.

The reclassification of all codeine-based analgesics to prescription medicines in New Zealand has created a consumer need for alternative easily accessible analgesics to manage stronger pain. Current Pharmacy Only treatment options to manage acute strong pain include paracetamol/ibuprofen combinations, ibuprofen, diclofenac, paracetamol and naproxen. Of the single agent options, ibuprofen has the most favourable risk-benefit profile.(5)

Consumer research conducted in Australia following the rescheduling of all codeine-based analgesics to prescription medicine found that paracetamol was the most commonly used OTC analgesic to manage pain and that close to one-quarter of consumers reported that they do not believe that their analgesic medicines are providing adequate pain relief. Ibuprofen was the second most commonly used OTC analgesic and its use was more frequent as the severity of pain increased.(9) Hence, this indicates that there is a need for more analgesic options to manage pain. The self-selection availability of ibuprofen 400 mg tablets would help meet this consumer need as consumer research indicates that in the majority of cases Nurofen 400 DOUBLE STRENGTH would be considered for the relief of strong pain.(3)

There is a clear dose-relationship for ibuprofen in the management of pain, with a 400 mg dose being more effective and providing longer lasting pain relief than a 200 mg dose. This dose-response has been demonstrated by the Cochrane review of non-prescription (OTC) analgesics for acute pain by Moore (2015a) which found a lower (which equates to better efficacy) number needed to treat (NNT) for at least 50% pain relief for ibuprofen 400 mg (NNT = 2.5; 95% CI: 2.4-2.6) than for ibuprofen 200 mg (NNT = 2.9; 95% CI: 2.7-3.2). In addition, the NNTs for other single ingredient analgesic options are generally higher than that for ibuprofen 400 mg further supporting the consumer benefits of the Pharmacy Only availability of double strength product. For example, the NNTs for paracetamol, naproxen and aspirin are all higher than for ibuprofen 400 mg which was comparable to diclofenac 25 mg (paracetamol 1000 mg NNT = 3.6; 95% CI: 3.2-4.1: diclofenac potassium 25 mg NNT = 2.4; 95% CI: 2.0-2.9 [noting that there was no NNT calculated for the 12.5 mg dose]: naproxen 500/550 mg NNT = 2.7; 95% CI: 2.3-3.3: aspirin 1000 mg NNT = 4.2; 95% CI: 3.8-4.6). Importantly, this same analysis demonstrated that both ibuprofen doses were well tolerated, with adverse events occurring at comparable rates to placebo. The relative risk of an adverse event was numerically lower for the 400 mg dose (RR = 0.9; 95% CI: 0.7-1.02) than the 200 mg dose (RR = 1.2; 95% CI: 0.7-2.1).(2)

The Cochrane review by Moore (2015a) indicated that ibuprofen 400 mg is less efficacious than the combination of paracetamol/ibuprofen (1000 mg/400 mg).(2) However, data from head-to-head comparisons such as the study by Mehlisch (2010) has shown that 400 mg ibuprofen is just as effective as one tablet of paracetamol/ibuprofen (500 mg/200 mg) combination and is modestly less efficacious than two tablets (1000 mg/400 mg).(29) A study by Thybo (2019) in the post-operative pain setting, found that ibuprofen 400 mg provided similar opioid sparing effects than one or two tablets of paracetamol/ibuprofen (500 mg/200 mg or 1000 mg/400 mg). In this study, although two tablets of paracetamol/ibuprofen (1000 mg/400 mg) provided the greatest morphine sparing effect, this difference was not clinically meaningful compared to ibuprofen (400 mg) alone.(30)

Given concerns about paracetamol overdose (intentional or accidental) as well as the risk of inadvertently taking multiple paracetamol-based products, ibuprofen 400 mg is an appropriate self-selection alternative to help consumers manage acute strong pain. Limiting the Pharmacy Only pack size is to 4 days' supply (12 dose units) and the well-established safety profile associated with the short-term use of ibuprofen, there is minimal risk that this Pharmacy Only availability will increase the incidence of harm or misadventure.

The Pharmacy Only availability ibuprofen 400 mg double strength (≤ 12 dose units) will give consumers improved access to an alternative analgesic to help manage acute strong pain which is more effective and as well tolerated as ibuprofen 200 mg,(1, 2, 26), and has a favourable risk-benefit profile that is superior to paracetamol, diclofenac and aspirin.(5) There this reclassification would result in a net positive public health benefit.

Many consumers dislike taking tablets and approximately 1 in 6 adults have difficulties swallowing tablets and both groups would benefit from taking fewer tablets

Many consumers dislike taking tablets and desire strategies and treatment options to reduce their use of tablets. This was confirmed by the consumer research regarding the use of Nurofen 400 DOUBLE STRENGTH. In this research the third most common benefit associated with the use of Nurofen 400 DOUBLE STRENGTH was the preference to take fewer tablets secondary to a general dislike for taking tablets. This benefit was stated by 23% of consumers.(3)

In addition to a dislike for taking tablets many people experience significant difficulty in swallowing solid dosage forms such as tablets and capsules.

Swallowing medicines without chewing is not a natural process but is a learnt skill. Humans are wired to chew even the smallest of foods (e.g. sultanas) before swallowing them.(31) Difficulties swallowing tablets is not always secondary to a medical condition and is not limited to people with dysphagia.

Research conducted amongst customers of community pharmacies found that 15.1% (56/369) or approximately 1 in 6 adults had difficulties taking oral medications. This difficulty is not limited to older people but occurred at similar prevalence across all adult age groups.(31) (see Table 5)

Table 5: Prevalence of swallowing difficulties amongst community pharmacy customers, by age(31)

Age group (years)	Prevalence of swallowing difficulty
18-29	12/81 (14.8%)
30-39	8/61 (13.1%)
40-49	13/72 (18.1%)
50-59	18/87 (20.6%)
60+	10/68 (14.7%)

Another pharmacy study found that 9% of customers had ongoing difficulty swallowing medications and 13.4% had a past history of difficulty swallowing medications. For the vast majority (83.7%) difficulties swallowing tablets occurred when taking every single dose.(32)

Limiting ibuprofen 400 mg double strength tablets to a Restricted Medicine is not beneficial to consumers with medication swallowing difficulties as research indicates that the majority of consumers do not raise this issue with their pharmacists, even amongst those who have resorted to modifying their medication (e.g. crushing or chewing it) to make it easier to swallow.(31, 32) Similarly, pharmacist research indicates that 43% of pharmacists rarely or never ask their customers about swallowing difficulties and only 14% often or always ask about this issue.(33) This indicates that, pharmacist oversight is not beneficial as conversations about swallowing issues are not occurring as commonly as they should. However, if the double strength tablet with its one tablet dosing regimen was available as a Pharmacy Only medicine, consumers with swallowing difficulties could self-select this

treatment and/or discuss it with pharmacist staff as commonly occurs when consumers first use a new medication.(18)

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 Nurofen 400 DOUBLE STRENGTH are:(34)

- Known hypersensitivity to ibuprofen or any of the inactive ingredients
- Hypersensitivity (e.g., asthma, rhinitis or urticaria) to aspirin or other nonsteroidal anti-inflammatory drugs.
- History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.
- History of ulcerative colitis, Crohn's disease, recurrent peptic ulceration or gastrointestinal haemorrhage (defined as two or more distinct episodes of proven ulceration or bleeding).
- Severe heart failure (NYHA IV).
- Severe liver failure.
- Severe renal failure (glomerular filtration below 30 mL/min).
- Conditions involving an increased tendency or active bleeding.
- During the third trimester of pregnancy.
- Adults over 65 years of age

These contraindications are the same as those for regular Nurofen 200 mg which is available for general sale (in packs up to 4 days' supply) and as a Pharmacy Only medicine (in packs up to 16 days' supply). As these pack sizes are available for self-selection within and outside the pharmacy setting, it is clear that previous scheduling reviews have concluded that the contraindications are easily identified and understood by consumers and inappropriate use/misuse is mitigated by current approved labelling. Please note that the warning statements on the proposed Pharmacy Only packaging for Nurofen 400 DOUBLE STRENGTH are the same as those for regular Nurofen 200 mg tablets and that the medicines information panel on the back of the pack will also be the same except for the posology.

Precautions

The precautions associated with the use of Nurofen 400 DOUBLE STRENGTH include:(34)

- Cardiovascular thrombotic events
- Hypertension
- Heart failure
- Gastrointestinal events
- Severe skin reactions
- Impaired liver function or a history of liver disease

- Impaired renal function.

Many of these precautions arise from clinical use of ibuprofen and other NSAIDs in the prescription setting, where use is at higher daily doses (> 1200 mg/day) and for prolonged periods of time to manage chronic pain.

It is well accepted that the short-term use of ibuprofen in lower doses used in the OTC setting has an excellent safety profile.(5, 14, 26)

The precautions for ibuprofen 400 mg double strength tablets are identical to those for regular Nurofen 200 mg which is available for self-selection as general sale and Pharmacy Only medicines. It is therefore clear that previous reclassification reviews have concluded that these precautions are readily identified and understood by consumers and that the short-term use of ibuprofen with a maximum daily dose of 1200 mg/day is safe and appropriate for self-selection.

Wide therapeutic index

Ibuprofen has a wide therapeutic index due to its excellent safety profile. There is no evidence to suggest that the toxicity or safety profile of ibuprofen has changed over time. This is supported by safety data from the latest Reckitt Benckiser Periodic Safety Update Report (PSUR) for ibuprofen, which has information about the safety of ibuprofen from 19 February 1969 to 31 October 2021. This report confirms that no new safety concerns or potential risks have emerged, and that ibuprofen's risk-benefit profile remains positive.(28)

As the most commonly used single dose of regular Nurofen is 400 mg(3, 4) and the maximum daily dose is 1200 mg/day, both of which are applicable to Nurofen 400 DOUBLE STRENGTH, the therapeutic index of this double strength formulation is expected to be equivalent to the regular strength which is available for self-selection. In addition, research has established that OTC ibuprofen has a superior risk-benefit profile than paracetamol and aspirin which are both available for self-selection.(5)

As ibuprofen has a wide therapeutic index, toxicity would only occur in situations of excessive overdoses. With ibuprofen overdoses, mild adverse effects are observed at doses of 100 to 400 mg/kg, while moderate to severe effects may occur at doses greater than 400 mg/kg.(27) If a person was to take the entire proposed Pharmacy Only pack of 12 ibuprofen 400 mg tablets as a single dose, the total dose would be 4800 mg and the 400 mg/kg dose would only be experienced by a person weighing 12 kg or less. An adult weighing 70 kg would be exposed to a non-toxic, asymptomatic dose of 68 mg/kg.(27) Therefore, a consumer would need to deliberately ingest multiple (six) packets of the proposed Pharmacy Only ibuprofen 400 mg double strength at one time to achieve a 400 mg/kg ibuprofen dose for moderate to severe toxicity to occur. If a person was to try and purchase multiple packs of 400 mg double strength tablets at one time, standard quality care pharmacy protocols would take effect, and the customer would be referred to the pharmacist. Therefore, classification as a Pharmacy Only medicine provides the appropriate balance between the benefits of self-selection access and pharmacist intervention when required.

Class effect – cardiorenal safety

One of the main class effects of NSAIDs of potential concern relates to the cardiorenal safety, especially amongst elderly patients with heart failure or renal dysfunction. This risk is effectively addressed with labelling that clearly states not to use this product if you have kidney or heart problems and not to use without doctors' advice if you are aged 65 years or older. The effectiveness of product labelling to manage this risk is established as ibuprofen at OTC doses (≤ 1200 mg/day) are available for self-selection as both General Sales and

Pharmacy Only medicines. In addition, recent label comprehension research found that the majority of consumers regularly read the label of analgesics before use and would consult pharmacy staff about the medication if they were using it for the first time.(18)

The cardiovascular and renal safety risks for ibuprofen 400 mg double strength tablets is no different to that of the regular 200mg ibuprofen products as consumer research confirms that consumers mainly use 2 x 200mg of regular ibuprofen tablets per dosing occasion.(3, 4) However, at the previous consideration of the reclassification of ibuprofen 400 mg double strength tablets in 2020, there were comments regarding potential safety issue if consumers incorrectly took the double strength tablets with the 200 mg tablet dosing regimen and inadvertently took a higher daily dose (2400 mg/day).(7)

It is important to recognise if this dosing error was to occur, it results in a person taking a standard and well tolerated therapeutic dose of ibuprofen (6 x 400 mg/day or 2400 mg/day) and not a supratherapeutic or overdose of ibuprofen. If this was to occur, the exposure to this standard prescription dose is limited to a maximum of 2 days as the proposed Pharmacy Only pack contains 12 dosage units.

In 2015, Medsafe published the findings of a Medsafe and the Medicines Adverse Reactions Committee (MARC) evaluation of the risk of cardiovascular events with the use of ibuprofen. This report concluded that OTC doses of ibuprofen (≤ 1200 mg/day) were not associated with an increased risk of cardiovascular thrombotic events. The available evidence indicates that that there is a small increased risk of cardiovascular thrombotic events when ibuprofen is used at high doses (2400 mg/day). Overall, the benefit to risk of harm balance for ibuprofen remains positive.(22) Hence, this small increased risk associated with inadvertently taking a 2400 mg for 2 days is unlikely to be substantively clinically relevant.

There is no evidence to suggest that the cardiorenal safety profile of ibuprofen has changed since this 2015 Medsafe review. The current PSUR for Nurofen confirms that the risk of arterial thrombotic events (MI or stroke) with ibuprofen are rare with an adverse event rate of 0.000000121% and that renal impairment and use in patients with renal failure or those who are dehydrated are also rare, with an event rate of 0.000000719%.(28)

The cardiorenal safety of OTC analgesics, including ibuprofen, has been reviewed by White (2018). This review assessed the use of ibuprofen in normotensive patients, patients with hypertension, cardiovascular events from clinical trials and from observational databases. The authors defined OTC ibuprofen use being up to 10 days continuous use. The relevant findings of this extensive review were that the available data suggest that there is little cardiovascular risk when OTC ibuprofen is used as directed.(35)

An UK retrospective cohort study using data from 1987 to 2006 investigated the risk of myocardial infarction (MI) with prescription NSAID use in participants aged > 40 years. In those with a first prescription for ibuprofen (8.2% of whom were prescribed doses > 1200 mg/day), the relative rate of MI during ibuprofen use overall versus controls was 1.04 (95% CI: 0.98-1.09), indicating no increased risk. With ibuprofen dosing of 1200 mg/day the risk of MI was equivalent to the control at 1.02 (95% CI: 0.94-1.11). At doses higher than the OTC dose 1201 to 2399 mg/day and doses ≥ 2400 mg/day, the relative risk of a MI was 1.22 (95% CI: 1.03-1.44), and 1.96 (95% CI: 1.05-3.65), respectively. It is also important to note that in this study use of NSAIDs was generally long-term use and not short-term OTC use. However, patients with intermittent NSAID use or frequent short-term use had lower risk of MI, whilst patients with long-term frequent use had higher risks of MI.(36) Although the risk of MI is higher with prescription doses of ibuprofen than OTC doses, this risk is reduced with short-term use as would occur in situations if a person inadvertently took a 2400 mg/day dose with ibuprofen 400 mg double strength tablets for two days.

A systemic review of community-based controlled observational studies assessed cardiovascular risks amongst widely used NSAIDs. This review included 21 case controlled studies and 17 cohort studies assessing the cardiovascular safety of ibuprofen. Note this analysis was based on prescription use of NSAIDs, with a sub-analysis performed on the use of OTC doses (ibuprofen ≤ 1200 mg/day). The researchers concluded that OTC doses of ibuprofen appear to be free from cardiovascular risk and that low-dose ibuprofen, alongside naproxen are the NSAIDs least likely to increase cardiovascular risk, while low dose diclofenac was associated with increased cardiovascular risk.(37)

A systematic review of 18 observational studies assessed the risk of acute myocardial infarction (AMI) with use of individual NSAIDs including ibuprofen. The relative risk for AMI was lowest for naproxen (RR: 1.06, 95% CI 0.94–1.20), celecoxib (RR: 1.12, 95% CI1.00–1.24), and ibuprofen (RR: 1.14, 95% CI 0.98–1.31). When the influence of dose was assessed, low dose ibuprofen was not associated with increased risk (RR: 0.97, 95% CI 0.76–1.22) and although there was a trend for a small increased risk with high dose ibuprofen, this risk was not statistically significant (RR: 1.20, 95% CI 0.99–1.46).(38)

Regarding renal safety, a review by Rainsford 2009 indicated that serious renal pathology has been rarely observed with ibuprofen, and these reactions have not been observed in trials with OTC ibuprofen. The evidence from literature surveys and clinical trials suggests OTC use of ibuprofen does not cause significant renal injury. Overall, evidence from the published literature suggest that OTC ibuprofen is a low risk factor for developing acute or chronic renal conditions, but that as with other NSAIDs there is increasing risk particularly in elderly individuals or those with compromised renal function.(15) These risks are effectively mitigated with the current warnings provided on label that direct those aged 65 years and older and those with kidney disease not to use OTC ibuprofen.

Griffin 1998(39) performed a nested case-control study amongst Tennessee Medicaid patients aged 65 years or older (n = 11,698) to assess the association between community acquired acute renal failure and NSAID use. In this study, ibuprofen accounted for 35% of all NSAID use, with 31% of ibuprofen use being at OTC doses (≤ 1,200 mg). This study confirmed the good renal safety of OTC doses of ibuprofen as this use was not associated with any increased risk of acute renal failure; adjusted odds ratio 0.98 (95% CI: 0.58-1.51). In this study, the risk of was dose dependent, with odds ratios of 0.94 (95% CI: 0.58-1.51), 1.89 (95% CI: 1.34-2.67), and 2.32 (95% CI: 1.45-3.71), respectively for ibuprofen doses of ≤ 1200 mg/day, > 1200 to ≤ 2400 mg/day and ≥ 2400 mg/day. However, it is important to note that the patient cohort in this study is not reflective of the OTC ibuprofen user but represents a population at high risk of renal complications for whom OTC ibuprofen use is contraindicated. For example, all patients were aged 65 years or older, 39% were aged 75 to 84 years and 40% were aged 85 years or older. Compared to the control cohort, patients that experienced acute renal failure were the very old and frail, with a higher proportion of patients aged ≥ 85 years (40% vs 21%) and a higher proportion living in residential aged-care facilities (46% vs 20%). Hence, despite this evaluation being performed in a patient cohort that is not representative of healthier OTC analgesic users, OTC doses of ibuprofen did not elevate the risk of acute kidney injury.

Data from the New Zealand Suspected Medicine Adverse Reaction Search (SMARS) database for the period of 1st January 2000 to 1st June 2022 also supports the good renal and cardiac safety of ibuprofen, noting that it is not possible to assess this data based on OTC versus prescription use or dose taken.(11) (See Table 6). It is also noteworthy that in many of the adverse events, ibuprofen was not the sole suspected medication. For example, in 10 of the 14 cases of acute kidney injury other medications were also suspected and in 8 of these cases the other medications were prescription medicines, suggesting that the use of ibuprofen was with medical advice.

Table 6: Renal and cardiovascular adverse events reported on the Suspected Medicine Adverse Reaction Search database(11)

System	MedDRA reaction term	Number of reports for ibuprofen	Number of reports with more than one suspected medicine
Cardiac disorders	Atrial fibrillation	2	-
	Bradycardia	1	1
	Cardiac failure	1	1
	Cardiomyopathy	1	1
	Chest pain	7	3
	Myocardial infarction	2	1
	Palpitations	2	-
	Tachycardia	4	-
Renal disorders	Acute kidney injury	14	10
	Nephropathy	1	
	Renal failure	4	3
	Renal impairment	8	2
	Renal tubular disorder	1	
	Renal tubular necrosis	4	2
	Tubulointerstitial nephritis	6	3

Data from the Australian Database of Adverse Event Notifications (DAENs) for the period of 1st January 1971 to 25th July 2022 also supports the good renal and cardiac safety of OTC and prescription ibuprofen (See Table 7). Although it is difficult to interpret this data due to differences in the total exposure, it is reassuring that this data for the prescription use of ibuprofen (2400 mg/day) has a very small number of reports of serious renal and cardiac adverse events. This low event rate is also mirrored with OTC ibuprofen use.(17)

Table 7: Selected renal and cardiovascular adverse events reported on the Database of Adverse Event Notifications(17)

Adverse event	OTC ibuprofen			Prescription ibuprofen		
	Number of cases	Number of cases with a single suspected medicine	Number of cases where death was a reported outcome	Number of cases	Number of cases with a single suspected medicine	Number of cases where death was a reported outcome
Renal impairment	20	9	0	4	0	0
Renal failure	9	1	1	0	0	0
Acute kidney injury	61	27	2	3	2	0
Myocardial infarction	2	1	0	1	0	0
Cardiac failure	0	0	0	1	1	0
Cardiac failure congestive	1	1	0	1	1	0

Cardiac failure acute	1	0	0	0	0	0
Cardiac arrest	2	1	1	0	0	0
Tachycardia	13	6	1	2	1	0

Therefore, the risk of clinically relevant cardiovascular or renal adverse events in patients taking a 400 mg of ibuprofen per dose for a short duration (up to 4 days) is likely to be minimal even in older people. In addition, this risk is addressed by the warning statements on the packaging, which previously evaluated research demonstrated will be read, especially amongst people with existing health issues.

Class effect – gastrointestinal safety
NSAID use is associated with gastrointestinal side effects, but this risk is predominantly associated with prolonged (prescription) NSAID use and is dose-related.(40). However, it is well established that these risks are lowest with ibuprofen and negligible with OTC ibuprofen use. Clinical data has established that OTC ibuprofen (≤ 1200 mg/day) has a gastrointestinal safety profile comparable to placebo, at least equivalent to paracetamol and better than other NSAIDs including aspirin.(14, 41, 42)

For example, a 2020 review reconfirmed that ibuprofen has the lowest risk of GI side effects compared to other NSAIDs and that a meta-analysis of ibuprofen safety found that the frequency of digestive system adverse events with ibuprofen was comparable to placebo (12.1% vs. 11.0%, p = 0.420).(42)

The PAIN study by Moore 1999,(14) compared up to 7 days use of aspirin, paracetamol (both up to 3000 mg daily) or ibuprofen (up to 1200 mg daily) for the management of pain in 8,633 evaluable patients. This trial confirmed the good safety profile of OTC ibuprofen with:

- Rates of significant adverse events being equivalent for ibuprofen and paracetamol and lower than that for aspirin (ibuprofen 13.7%, paracetamol 14.5%, aspirin 18.7%)
- Total gastrointestinal events (including dyspepsia) and abdominal pain were less frequent with ibuprofen (4 and 2.8%, respectively) than with paracetamol (5.3 and 3.9%) or aspirin (7.1 and 6.8%) [all $p < 0.035$].
- There were no cases of gastrointestinal bleeding or ulcers with ibuprofen use. Noting that there were 4 cases of non-serious gastrointestinal bleeding with paracetamol and 2 with aspirin, and 1 case of peptic ulcer with aspirin.

Similarly, a randomised placebo controlled trial by Doyle 1999(43) compared the safety of maximal OTC dose of ibuprofen 1,200 mg (400 mg three times daily) for 10 consecutive days in 1,246 healthy adults. Note, patients with a positive gastrointestinal history were not excluded from this study. This trial confirmed the good safety profile of OTC ibuprofen with:

- Ibuprofen having an overall lower adverse event rate than placebo (OR = 0.71, 95% CI: 0.55-0.90, P = 0.005)
- Ibuprofen having a comparable rate of gastrointestinal adverse events to placebo (OR = 1.24, 95% CI: 0.90-1.72, P = 0.187, not statistically significant)
- The frequency of positive stool occult blood tests was comparable between ibuprofen and placebo. Of the 17 of 1,216 subjects that had positive tests, 5 (all in the ibuprofen group) had an underlying non-drug related gastrointestinal condition (e.g., haemorrhoids). 9 of the 12 remaining subjects agreed to further investigations and all patients had no gastrointestinal pathology, including GI ulcers.

In terms of the influence of dose, the risk of GI complications with ibuprofen is increased with the use of higher anti-inflammatory doses. However, ibuprofen at higher doses (up to 2400 mg/day) has a lower incidence of ulcers and bleeding than most other NSAIDs.(41, 44)

The relative impact of different doses of ibuprofen has been assessed in a review of endoscopic studies by Lanza 1984. This review analysed the results of multiple endoscopic studies that assessed the degree of gastric mucosal injury and haemorrhage in healthy volunteers taking a range of NSAIDs for short time periods. Studies with ibuprofen found that the OTC dose 1200 mg/day was associated with the lowest degree of gastric mucosal injury 0.48. The degree of mucosal injury was increased with higher ibuprofen doses, 1.24 for 1600 mg/day and 1.75 for the prescription dose (2400 mg/day). Duodenal injury was assessed in some of the studies and there was essentially no mucosal injury with ibuprofen at 1600 or 2400 mg/day. However, short-term use of the ibuprofen at 1600 to 2400 mg/day taken for up to 3 days produced little or no injury to the gastric mucosa.(13) Therefore, if a consumer inadvertently took a twice the recommended dose of Nurofen 400 DOUBLE STRENGTH tablets for 2 days (which represents the use of all the tablets in the proposed Pharmacy Only pack) there is a negligible risk that this would result in a clinically meaningful gastrointestinal adverse event.

Risks of the medicine used in the OTC setting

For the vast majority of consumers there is minimal risk associated with use of 400 mg tablets of ibuprofen (maximum daily dose of 1200mg and in small pack sizes of 12 or less dose units). This is supported by the facts that:

- The 400 mg dose is the single dose most commonly used by consumers to manage acute pain.(3, 4)
- The maximum daily dose (1200 mg/day) is the same as currently available for regular ibuprofen 200 mg which are available for self-selection as General Sales and Pharmacy Only medicines.
- Ibuprofen at OTC doses has a favourable risk-benefit profile which is superior to paracetamol and aspirin.(5)
- Pack size is limited to 4 days' supply, which is consistent with short-term use and effectively mitigates the risk of excessive use.
- Ibuprofen has a wide therapeutic index and for an adult weighing 70 kg, six packets of the proposed Pharmacy Only ibuprofen 400 mg tablets would need to be taken as a single dose to result in an moderate to severe overdose.(27)

Potential issues associated with double strength 400 mg ibuprofen tablets are;

- Some individuals may take a higher dose than they may need, that is take a 400 mg dose when a 200 mg dose may have been adequate.
- There is a perceived risk (raised by MCC) of increased use amongst older people with the reclassification of codeine-based analgesics to prescription medicines.
- There could be dosing confusion resulting in some individuals taking two 400 mg tablets three times a day, rather than one tablet three times per day. (This issue is addressed in detail in Part B Section 7). This is mitigated through labelling and small pack size.

<u>Consideration of taking a higher ibuprofen dose than needed</u>

We acknowledge that 200 mg ibuprofen is an effective analgesic dose and as directed on packs of regular strength ibuprofen can be taken after an initial 400 mg dose is used to manage mild to moderate acute pain. However, consumer research indicates that

consumers do not commonly use the 200 mg dose to manage pain and that 400 mg is the most commonly used dose.(3, 4)

Australian consumer research, reported that people choosing to use ibuprofen 400 mg to manage their pain are likely to be selecting the “DOUBLE STRENGTH” product for its longer duration of action and/or to help manage strong acute pain.(3)

The short-term use of ibuprofen 400 mg overall has an equivalent safety profile to ibuprofen 200 mg, paracetamol and placebo. This has been established by several Cochrane reviews.(1, 2, 26) Hence, the evidence indicates that the dose-related risk (200 mg versus 400 mg) of adverse events with short term use is negligible.

When the risks of adverse events are considered from the perspective of the total daily exposure, the maximum daily dose for Nurofen 400 DOUBLE STRENGTH is the same as regular Nurofen (1200 mg/day). Hence, there is no change in the safety profile with the double strength tablets.

There does not appear to be evidence that intentional or accidental overdose with ibuprofen is an issue and given recent concerns with increasing rates of paracetamol overdose and hospitalisation(45) offering an alternative treatment for acute pain which has a wide therapeutic index and much less likely to be used in overdose or to cause significant harm is a positive step.(5) In fact, if a consumer did accidentally or intentionally take a higher dose than recommended on pack e.g. 2 x 400 mg three times a day (maximum 6 tablets in 24 hours) as per the current 200 mg product posology, they would be taking a standard prescription dose for a maximum of 2 days. This does not represent an overdose nor increase risk of any GI or CV issues. In order for ibuprofen overdoses to have a harmful effect one would need to take 100-400 mg/kg for mild effects, and greater than 400 mg/kg for moderate to severe effects.(27) For example, if a person was to take the entire pack of 12 ibuprofen 400 mg tablets as a single dose, the total dose would be 4800 mg and an adult weighing 70 kg would be exposed to asymptomatic dose of 68 mg/kg.(27)

As the experience of pain is a subjective and highly individualised, only the person experiencing pain will be able to make the judgment as to how much pain relief they need. For many the 200 mg dose is unlikely to be considered adequate to manage their pain. Australian omnibus research has shown that 77% of Nurofen users use 2 x 200mg tablets per dose.(3) This is further supported by UK consumer research that found that 78.4% used the 2 x 200 mg dose.(4) In addition, consumer research indicates that in the majority of cases Nurofen 400 DOUBLE STRENGTH would be considered for the relief of strong pain.(3) Hence, this research suggests that the overall pattern of medication usage will not be changed by the Pharmacy Only availability of ibuprofen 400 mg in primary packs limited to no more than 12 dose units. The incidence of people taking the 400 mg dose, when a 200 mg dose would have been sufficient is likely to be low or infrequent.

In Australia, Nurofen 400 DOUBLE STRENGTH has been available as a Pharmacy Only medicine since February 2021 and there are no safety signals to indicate increased risk in this setting. For example, there has not been a single report of an adverse event in the Australian DAENs database associated with the use of Nurofen 400 DOUBLE STRENGTH.(17)

<u>Consideration of safety risk in the elderly</u>

At the 65th meeting of the Medicines Classification Committee, the Committee raised the concerns that consumers who would have otherwise used a codeine containing analgesic would replace these with a NSAID and there were concerns regarding the safety in particular amongst the elderly.(7)

This concern is less relevant in 2022 as all codeine-based analgesics have been prescription medicines since November 2020 and users of these analgesics would have discussed alternative methods to manage their pain with their doctor or pharmacist and be using these alternatives for pain management. Hence, the proposed reclassification of ibuprofen 400 mg would not substantially influence the relative use of NSAIDs amongst these consumers.

The “elderly” is commonly defined as people aged 65 years and older. The non-prescription use of ibuprofen has a clear prominent warning statement that prohibit its OTC use in this patient population except on doctor’s advice.

- DO NOT USE UNLESS A DOCTOR HAS ADVISED YOU if you are 65 years and older.

This warning statement is common to both regular strength 200 mg ibuprofen and Nurofen 400 DOUBLE STRENGTH.

There is no evidence to suggest that older people do not follow this instruction.

New Zealand research amongst elderly people investigated their attitudes about medication usage. This research found that older peoples’ attitudes to pain and non-prescription medicines meant that they were unlikely to self-manage their pain, nor were they likely to use OTC ibuprofen. This indicates that the concerns raised by the MCC are unwarranted. Relevant findings from this New Zealand research include:(8)

- Many older people were reluctant to take analgesics when they were prescribed on an as-needed basis.
- Many older people believed that certain types of pain were a natural part of ageing and not something that should or could be treated with medications.
- Older people grew up in a time when the current range of medicines to relieve pain were not available. When they were young, they continued working despite experiencing pain and would not complain about pain or seek to treat pain.
- They were already taking multiple prescription medicines and were not keen to take additional non-prescription medicines.
- Most older people talked to their doctor about the use of medicines, in preference to their pharmacist.
- Most older people aimed to limit the use of analgesics and non-prescription medicines which they perceived as unnecessary.

This research is consistent with another New Zealand study that assessed medication usage amongst the elderly. This study found that older people predominantly managed their health conditions with prescription medications, taking a median of 7 prescribed medications and a median of 1 non-prescription medication. In this study the most commonly used prescription medicines were aspirin (60%), paracetamol (41%), simvastatin (35%), metoprolol (31%) and cilazapril ± hydrochlorothiazide (31%) and the most commonly used non-prescription medicines were paracetamol (17%), glucosamine ± chondroitin (14%), fish oils (11%), multivitamins ± minerals (7%) and aspirin (5%). Ibuprofen use was not common.(46)

In addition, consumer research in Australia, following the rescheduling of all codeine-based analgesics to prescription medicines assessed consumer knowledge and practices regarding pain management and their views of community pharmacy pain management services. 15.8% of consumers who completed the research were aged 65 years or older and 32.5% were aged 56 years or older and 86.7% had chronic pain (that was present for 3 or more months). Although this is not representative of the typical user of OTC analgesics, this

research is relevant to the issue at hand as it investigated how these consumers managed their pain in the period after codeine-based analgesics were no longer available without a prescription. This research showed that amongst OTC analgesics, paracetamol was the most commonly used analgesic in the post-codeine rescheduling environment irrespective of the severity of pain. Ibuprofen was the next most common followed by other options such as paracetamol/ibuprofen combination, diclofenac and other oral anti-inflammatories.(9) Although this data does not indicate if there has been a change in use, it does indicate that the use of ibuprofen is not excessive. (See Table 8).

Table 8: Treatment options selected to treat pain symptoms of different severities in the post-codeine rescheduling era (n = 120)(9)

Treatment	Mild pain	Moderate pain	Severe pain
Unsure	9.2%	3.3%	6.7%
Nil	56.7%	11.7%	0.8%
Paracetamol	30.8%	51.7%	39.2%
Ibuprofen	16.7%	28.3%	30.0%
Paracetamol + Ibuprofen combination	5.8%	10.8%	13.3%
Aspirin	3.3%	7.5%	7.5%
Diclofenac	1.7%	8.3%	9.2%
Other Oral Anti-Inflammatories	9.2%	16.7%	12.5%
Topical Anti-Inflammatories	9.2%	20.0%	27.5%
Other Topical Analgesics	6.7%	15.8%	17.5%
Visit Pharmacy/Pharmacist for help	4.2%	7.5%	12.5%
Visit GP for help	8.3%	19.2%	42.5%
Visit Hospital	1.7%	4.2%	22.5%
Other (e.g., prescription analgesics, non-pharmacotherapies)	15.0%	31.7%	40.8%

An analysis on New Zealand unit pharmacy sales data for the 12 months before and after the reclassification of codeine-based analgesics to Prescription medicines indicates that the increase in OTC analgesics was similar for ibuprofen [redacted] and paracetamol [redacted] with the largest proportional change observed for the combination of ibuprofen/paracetamol [redacted]. Note, this was expected as people using codeine-based analgesics are treating more severe pain than would be effectively managed by paracetamol alone.

Given that the elderly overwhelming seek doctor advice about their medications and in particular analgesic use,(8) and that the codeine reclassification event has transpired, concerns about the elderly being put at risk by replacing codeine-based analgesics with ibuprofen 400 mg is not supported by the available evidence, and the risk is mitigated by existing labelling.

An analysis of the New Zealand Suspected Medicine Adverse Reaction Search (SMARS) database for the period of 1st January 2000 to 1st June 2022 for adverse events reported with oral ibuprofen, identified 55 patients aged 65 years or older who had a suspected adverse event.(11) This represented 13.3% of all patients that had an adverse event over this period and this correlates to the proportion of the elderly population in New Zealand at 14.9% (in 2018).(12) Hence, this data does not signal any excessive risk associated with the real-world use of ibuprofen amongst the elderly in New Zealand (noting that this data does not distinguish between OTC and prescription use). It also indicates that the current risk management strategies that surround the OTC use of ibuprofen including its availability as a

general sale medicine (at the same maximum dose of 1200 mg/day as it pertains to the 400 mg double strength tablets) are appropriate and effective.

Published clinical evidence also supports the excellent safety profile of ibuprofen in the elderly. A meta-analysis assessed the incidence of adverse events amongst elderly people, aged 65 years or older (range 65 - 92 years) taking multiple doses of OTC ibuprofen (400 mg three times daily for up to 10 days) for osteoarthritis pain, compared with placebo. This meta-analysis found no statistically significant difference in the overall incidence of adverse events between ibuprofen and placebo (OR 1.02, 95% CI: 0.66-1.56, P = 0.943). The difference was also not statistically significant for 'body as a whole' events (P=0.315), digestive system events (P = 0.712), or any individual digestive system event.(10)

Similarly, a randomised placebo-controlled clinical trial of maximal OTC doses of ibuprofen 1200 mg/day for 10 days found no difference in the adverse event rate between ibuprofen and placebo amongst patients who were aged 65 years or older.(43)

It is also important to note that the use of ibuprofen to manage pain is appropriate and has a favourable benefit/risk profile to alternative NSAIDs (e.g. diclofenac and aspirin)(5) and fixed dose combination of paracetamol/ibuprofen, such as Maxigesic® which is available as General Sales medicines in New Zealand. With Maxigesic®, elderly consumers will be exposed to a full OTC dose of both paracetamol (4000 mg/day) and ibuprofen (1200 mg/day). This comes with added risk relative to just taking a single ingredient.

Hence, in previous classification deliberations the conclusion must be that this risk to the elderly is mitigated by appropriate warnings on product labels and are outweighed by the benefit of wider access for the majority of the New Zealand population aged 13 to 64 years. We believe the same conclusion should extend to ibuprofen 400 mg allowing its reclassification to a Pharmacy Only medicine.

Drug interactions – ibuprofen and low-dose aspirin

As previously stated, the 2015 Medsafe and MARC evaluation of the risk of cardiovascular events with the use of ibuprofen concluded that lower doses of ibuprofen of 1200 mg per day or less (the dose used for over-the-counter [OTC] preparations) were not associated with an increased risk of cardiovascular thrombotic events.(22)

The review by White (2018) also addressed the issue of the co-administration of ibuprofen with low-dose aspirin and potential impact on aspirin's cardioprotective effects. Studies of greatest relevance summarised in this review included:(35)

- A post-hoc analysis of the Physicians' Health Study, a 5-year randomised double-blind, placebo-controlled trial of the administration of 325 mg aspirin every other day with observational data on NSAID use. The investigators found that the risk of MI was not increased with intermittent NSAID use (1-59 days/year) either when taken alone (i.e., by the placebo group) or concomitantly with aspirin.
- A prospective, double-blind, randomised, placebo-controlled study in which 51 participants received aspirin (81 mg once daily) for 8 days and were then randomised to receive aspirin followed at 1, 7, and 13 hours by either ibuprofen 400 mg 3 times a day or placebo for 10 days. This study showed no evidence of loss of the cardioprotective effect of aspirin with ibuprofen with thromboxane B2 inhibition being > 90% on all days tested in all participants in the ibuprofen group.

Overall, this evidence supports the low risk of adverse outcomes associated with short-term exposure of OTC ibuprofen. This position is further supported by the FDA that indicated that

the risk of decreasing the antiplatelet effect of low-dose aspirin is likely to be minimal with the occasional use of ibuprofen.(35)

Food/drink interactions

There are no relevant food or drink interactions. Ibuprofen can be taken with or without food and pharmacokinetic studies have demonstrated that food does not markedly affect total bioavailability of ibuprofen.(34)

Other restrictions

There are no additional restrictions regarding the use of ibuprofen 400 mg.(34)

Special populations where exposure to the medicine needs to be restricted

Patient groups that should not take Nurofen 400 DOUBLE STRENGTH are the same groups that cannot take regular Nurofen 200 mg which is available for self-selection as a General Sale and Pharmacy Only medicine. These groups are listed on the product packaging and are as follows, patients with:

- Stomach ulcers, or other stomach disorders
- Heart problems
- Kidney problems
- Liver problems
- Allergies to ibuprofen, aspirin or other anti-inflammatory medicines
- During the last 3 months of pregnancy, and
- Adults 65 years and over

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 ibuprofen in OTC doses of 1200 mg/day have been presented and evaluated in the previous classification applications for ibuprofen. These evaluations have accepted that ibuprofen has an excellent safety profile and that regular ibuprofen (200 mg) taken in daily doses of up to 1200 mg/day is available as General Sale and Pharmacy Only medicines (pack size dependent). In addition, clinical data confirms that OTC ibuprofen (1200 mg/day) has a gastrointestinal safety profile at least equivalent to paracetamol and better than other NSAIDs including aspirin.(5, 14) Ibuprofen has a lower risk of adverse events and serious effects after overdose compared to paracetamol. It is noted that the numbers of hospital admissions and cases of liver injury attributed to paracetamol overdose have increased in Australia since 2004 as have the number and reported size of overdoses reported to the NSW Poisons Information Centre.(45)

The safety data of 400 mg ibuprofen has been examined by several Cochrane reviews of non-prescription (OTC) analgesics for acute pain. The first by Moore (2015a) found that both ibuprofen doses (200 and 400 mg) were well tolerated, with adverse events occurring at comparable rates to placebo. The relative risk of an adverse event was numerically lower for the 400 mg dose (RR = 0.9; 95% CI: 0.7-1.02) than the 200 mg dose (RR = 1.2; 95% CI: 0.7-2.1).(2)

Equivalent findings were demonstrated in the Cochrane review by Derry (2009) that investigated the use of ibuprofen for acute postoperative pain. In this review the rate of adverse events for both ibuprofen doses (200 and 400 mg) were equivalent to placebo.(1)

Another Cochrane review by Moore (2015b) investigated the adverse events associated with the use of OTC analgesics for the management of acute pain. This review demonstrated that the incidence of adverse events with both ibuprofen doses was equivalent to placebo, with no differences in relative risks (400 mg RR = 0.9; 95% CI: 0.8-1.04, 200 mg RR = 0.9; 95% CI: 0.7-1.02).(26)

There is no evidence to suggest that the toxicity or safety profile of ibuprofen has changed. This is supported by safety data from the latest Reckitt Benckiser PSUR for the 19 February 1969 to 31 October 2021. This report confirms that no new safety concerns or potential risks have emerged, and that ibuprofen's risk-benefit profile remains positive.(28)

In addition, a comprehensive assessment of the cardiovascular, renal and gastrointestinal safety has been provided in the previous section (4. Contraindications and precautions). This evidence indicates that individual doses of ibuprofen 400 mg have comparable safety to ibuprofen 200 mg and placebo. That there is minimal risk of serious cardiovascular or renal adverse events even amongst older people.(35) The favourable risk-benefit profile of OTC ibuprofen has been acknowledged by Medsafe in their 2015 review of the cardiovascular safety of ibuprofen. In addition, this review indicated that the higher 2400 mg/day dose was only associated with a small risk of cardiovascular events.(22)

Data from the New Zealand Suspected Medicine Adverse Reaction Search (SMARS) database for the period of 1st January 2000 to 1st June 2022 also supports the good overall safety profile of ibuprofen. Although it is difficult to interpret this data due to differences in the exposures for the different medicines, amongst the three analgesics summarised (ibuprofen, paracetamol and aspirin), the number of adverse events reported for ibuprofen is less than paracetamol. Noting that this data will include OTC and prescription ibuprofen use.(11) (See Table 9)

Table 9: Summary of SMARS reports for ibuprofen, paracetamol and aspirin(11)

Adverse event	Ibuprofen	Paracetamol	Aspirin
Number of reports (cases)	413	526	320
Number of reactions	791	906	574
Number of cases where death was a reported outcome	3	3	30

Equivalent data from the Database of Adverse Event Notifications (DAENs) for the period of 1st January 1971 to 25th July 2022 also supports the good overall safety profile of OTC and prescription ibuprofen in Australia (see Table 10). It is also important to note that there have been no reports of adverse events directly attributed to Nurofen 400 DOUBLE STRENGTH tablets during this period, including the time it has been available for self-selection as a Pharmacy Only medicine.(17) Although it is difficult to interpret this data due to differences in

the exposures for the different medicines, amongst the three OTC analgesics the number of case reports is lowest for OTC ibuprofen including a significantly lower number of adverse events where death was a reported outcome. Given the previous raised concerns about the potential safety implications of the inadvertent use of a higher 2400 mg/day dose, it is reassuring to see that the number of reports of adverse events with prescription ibuprofen (commonly prescribed at this dose) is not excessive despite this use expected to be for prolonged treatment periods, much longer than the short term use associated with OTC ibuprofen use.

Table 10: Summary of DAEN reports for ibuprofen, paracetamol and aspirin(17)

Adverse event	OTC ibuprofen	Prescription ibuprofen	OTC paracetamol	OTC aspirin
Number of reports (cases)	1212	497	2885	3097
Number of cases with a single suspected medicine	763	325	1228	609
Number of cases where death was a reported outcome	53	9	212	208

Ibuprofen has not been withdrawn from any market due to safety concerns related to the active ingredient.(28)

There are no withdrawal effects following the cessation of ibuprofen therapy.

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?

The potential for harm with ibuprofen is low given its wide therapeutic index and its negligible potential for misuse and abuse. In addition, research has shown that OTC ibuprofen has a superior risk-benefit profile than paracetamol. This same research found that ibuprofen had the lowest potential for overdose toxicity compared to paracetamol, aspirin, naproxen and diclofenac.(5)

Extensive use of ibuprofen locally and internationally has confirmed that ibuprofen has a wide margin of safety and low toxicity following overdose. There is no defined toxic dose on a mg/kg basis due to its wide therapeutic index. There have been some documented reports of overdose, with survival after supportive measures with no lasting negative effects. Doses of less than 100mg/kg do not routinely require intervention, only supportive care.(27)

Additional evidence to the wide therapeutic index of ibuprofen comes from the review of the long-term misuse of codeine/ibuprofen combination products. For example, Frei (2010) evaluated the morbidity related to misuse of OTC codeine/ibuprofen combination analgesics in Victoria. Between May 2005 and December 2008, 27 people presented or were inpatients referred for treatment of opioid dependence. Twenty six of the 27 cases involved prolonged

use (greater than 6 months, mean duration 3.6 years) of supratherapeutic doses (mean dose range 6,800 to 9,400 mg of ibuprofen). This long-term misuse of codeine-ibuprofen analgesics resulted in significant NSAID toxicity, however there were no deaths with all patients recovering following supportive measures.(47) Note, ibuprofen (alone) has no abuse potential and this issue of misuse or abuse is not applicable to the use of single ingredient OTC ibuprofen and was due to opioid dependence.

A search of the Suspected Medicine Adverse Reaction Search (SMARS) database for the period of 1st January 2000 to 1st June 2022 identified no reports of accidental overdoses with ibuprofen and a single report of an intentional overdose with ibuprofen in New Zealand. In this case ibuprofen and fluoxetine were the suspected medicines. The patient survived and reported the following symptoms headache, ataxia, muscle twitching and trismus.(11)

Unlike aspirin and paracetamol, no additional pathophysiological findings have been demonstrated with ibuprofen overdose. The toxic effects relate to its known pharmacological actions, through the inhibition of prostaglandin synthesis. Gastrointestinal symptoms observed in severe overdose include nausea, vomiting and abdominal discomfort. Impairment of renal function is possible in overdose, however in clinical practice renal effects are infrequent and are more likely to occur at blood concentrations greater than 280 mg/L. Metabolic acidosis is uncommon but may occur blood concentrations of 600-1000 mg/L. Central nervous system depression may occur, but it typically manifests as mild drowsiness or light coma. Severe coma is usually associated with acidosis. People may also experience blurred vision, nystagmus, tinnitus, dizziness or headache. In most cases, ibuprofen overdose results in no symptoms or only mild symptoms. In terms of dose/response relationship, doses up to 100 mg/kg generally are asymptomatic. Doses between 100 to 400 mg/kg result in mild to moderate symptoms and doses greater than 400 mg/kg may result in moderate to severe symptoms.(27)

In terms of toxicity which would only occur in situations of overdose, ibuprofen has a wide therapeutic index. For example, if a person was to take the entire pack of 12 ibuprofen 400 mg tablets as a single dose, the total dose would be 4800 mg and the 400 mg/kg dose would only be experienced by a patient weighing 12 kg or less. An adult weighing 70 kg would be exposed to non-toxic asymptomatic dose of 68 mg/kg. Hence for a consumer to experience a toxic dose (≥ 400 mg/kg ibuprofen) they would need to consume multiple packets of the proposed Pharmacy Only ibuprofen 400 mg double strength (12 tablets) at one time.(27) In addition, even if the complete packet (12 tablets, 4800 mg) of ibuprofen were taken all at once this is still less than what could be taken if a whole pack of any Pharmacy Only NSAID or paracetamol were taken all at once, due to the small pack size (12 tablets). In fact, paracetamol is the analgesic of greatest concerns as it relates to toxicity in overdose. It is the number one reason for overdose reported to Australian poisons centre(45) and the highest pack quantity available as a Pharmacy Only medicine equates to 5 times the toxic dose.

As such improving the availability of ibuprofen 400 mg by making it a Pharmacy Only medicine, when total daily dose remains the same as regular ibuprofen (1200 mg/day) does not contribute to an increased risk of toxicity. In addition, limiting pack size to 12 tablets further negates any potential risk.

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

Reclassification will not affect the risk of unnecessary use. In part B, Section 4, the potential for patients to take a higher dose than that may be required, that is 400 mg instead of 200 mg was addressed and it was demonstrated that this would be an infrequent event.

Consumer research has shown that the most commonly used dose of ibuprofen is 400 mg and in the majority of cases Nurofen 400 DOUBLE STRENGTH would be considered for the relief of strong pain.(3) This research suggests that the overall pattern of medication usage will not be changed by the Pharmacy Only availability of ibuprofen 400 mg in primary packs limited to no more than 12 dose units.

Even if people did take the higher dose, there is no safety implications as the short term use of ibuprofen 400 mg overall has an equivalent safety profile to ibuprofen 200 mg, paracetamol and placebo. This has been established by several Cochrane reviews.(1, 2, 26) In addition, when the risks of adverse events are considered from the perspective of the total daily exposure, the amount of ibuprofen per tablet (i.e. 200mg vs 400mg) is not relevant as the total daily dose is the same at 1200 mg/day.

Potential for medication errors

At the 65th meeting of the Medicines Classification Committee an application to reclassify ibuprofen 400 mg from a Restricted Medicine to a Pharmacy Only Medicine was considered and declined. One of the reasons for this decision was potential confusion leading to safety concerns if consumers accidently takes twice the recommended dose by applying the dosage regimen for regular 200 mg ibuprofen to the double strength 400 mg tablets.(7)

Reckitt respectfully disagrees that this risk is significant and does not warrant limiting access to this medicine to a Restricted Medicine based on the following:

- Taking two ibuprofen 400 mg tablets three times per day, is not an overdose generally as it is taking a commonly used therapeutic prescription dose that is well tolerated.
- If a patient was to inadvertently take this higher dose, the small Pharmacy Only pack size of 12 dose units or less means that the potential exposure to this higher dose is limited to a maximum of two days.
- The short-term use of ibuprofen 2400 mg/day has a similar safety profile to ibuprofen 1200 mg/day.
- The short-term use of ibuprofen 2400 mg/day has a better safety profile than other NSAIDs that are available as OTC medications.
- Evidence indicates that this type of dosing error is uncommon.(16)
- The risk of dosing confusion is effectively mitigated by product labelling, as acknowledged by the Australian Advisory Committee on Medicines Scheduling (ACMS) when it rescheduled 400 mg of ibuprofen from Schedule 3 to Schedule 2 (Pharmacy Only medicine).(6)

To address the issue of the relative safety of ibuprofen at daily doses of 1200 mg/day and 2400 mg/day, we have conducted a literature review for published randomised clinical trials that compared the two doses and reported the tolerability of the two doses. Three studies were identified, and the relevant safety data are summarised below.

Bierma-Zeinstra et al, conducted a multicentre, randomised, double-blind trial to investigate short-term efficacy and safety of a lipid ibuprofen formulation (1200 mg/day) compared with standard ibuprofen (1200 mg/day) and (2400 mg/day) for episodic knee arthralgia/flaring pain in adults aged 18–70 years with a history of at least one knee flare episode within 12 months. Patients were recruited within 24 hours of new flare with pain severity ≥ 5 on a 0–10 numerical rating scale (n = 462). Ibuprofen was taken three times daily with water on an empty stomach for 5 days with an optional further 5 days of treatment.(19) Note only the results for the two standard ibuprofen formulations are summarised below.

Overall, both doses of ibuprofen were well-tolerated. Most adverse events were mild or moderate in severity, with two patients in each group experiencing severe adverse events. The most frequent drug-related adverse events were gastrointestinal disorders, with no significant difference between 1200 mg/day (22.6%) compared to 2400 mg/day (28.3%). (See Table 11). The Gastrointestinal Symptom Rating Scale also showed no significant differences between the 1200 mg/day and 2400 mg/day dosage regimens (adjusted mean changes from baseline being: 0.05 and 0.13, respectively). Hence, this study demonstrated that the short-term use of 1200 mg/day and 2400 mg/day had comparable tolerability.(19)

Table 11: Adverse events reported for > 1% of patients in any treatment group(19)

Adverse event (AE)	Ibuprofen 1200 mg/day n = 155 (%)	Ibuprofen 2400 mg/day n = 159 (%)
Number of patients with at least one drug-related AE	37 (23.9)	50 (31.4)
Gastrointestinal disorders	35 (22.6)	45 (28.3)
Diarrhoea	8 (5.2)	8 (5.0)
Nausea	7 (4.5)	8 (5.0)
Abdominal distension	4 (2.6)	12 (7.5)
Abdominal discomfort	3 (1.9)	9 (5.7)
Dyspepsia	7 (4.5)	11 (6.9)
Constipation	2 (1.3)	6 (3.8)
Flatulence	5 (3.2)	5 (3.1)
Abdominal pain upper	8 (5.2)	5 (3.1)
Gastro-oesophageal reflux disease	5 (3.2)	7 (4.4)
Eructation	4 (2.6)	5 (3.1)
Gastrointestinal motility disorder	3 (1.9)	2 (1.3)
Abdominal pain	3 (1.9)	6 (3.8)
Gastrointestinal sounds abnormal	4 (2.6)	4 (2.5)
Defaecation urgency	1 (0.6)	2 (1.3)
Faeces hard	1 (0.6)	3 (1.9)
Abdominal tenderness	0 (0.0)	2 (1.3)
General disorders and administration site conditions	1 (0.6)	4 (2.5)
Nervous system disorders	2 (1.3)	1 (0.6)
Headache	2 (1.3)	0 (0.0)

Bradley et al, conducted a randomised, double-blind trial comparing the efficacy and safety of ibuprofen 1200 or 2400 mg/day, with that of paracetamol (4000 mg/day), in adults (≥ 30 years old) with chronic knee pain due to osteoarthritis (n = 184) for four weeks.(20) Note, this duration of use is longer than that associated with short-term OTC use which is limited to 3 days before seeking medical advice.

All side effects were minor in severity and occurred at similar rates across all three groups. (See Table 12). There was a non-significant trend toward increased incidence of nausea and dyspepsia with 2400 mg/day ibuprofen compared to 1200 mg/day. Patient withdrawal from the study due to adverse events occurred at comparable rates, 4 cases for ibuprofen 1200 mg/day, 6 cases for ibuprofen 2400 mg/day and 5 cases for paracetamol 4000 mg/day.(20)

Table 12: Adverse events reported during the 4-week treatment period(20)

Adverse event	Number of patients		
	Paracetamol 4000 mg/day (n = 61)	Ibuprofen 1200 mg/day (n = 62)	Ibuprofen 2400 mg/day (n = 61)
Gastrointestinal	10	7	14
Nervous system	4	7	4
Rash	1	0	2
Oedema	1	2	3
Mucous membrane	0	0	1
Haematologic	1	0	0
Genitourinary	1	0	0
Renal	1	0	0

Godfrey et al, conducted a randomised double-blind trial in patients with rheumatoid arthritis to compare the tolerability and efficacy of ibuprofen 1200 mg/day and 2400 mg/day for 4 weeks (n = 41),(21) again significantly longer than OTC use.

The incidence of adverse events did not differ significantly between the two dosage groups and most events were mild in severity. (See Table 13 for gastrointestinal adverse events). Clinical laboratory screening studies at weeks 0, 2 and 4, for liver and renal function, blood cell and platelet counts, urinalyses, and weekly tests for occult blood in stools showed no significant differences individually nor between the 1200 mg/day and 2400 mg/day dosage groups. 4 weeks' treatment of either ibuprofen 1200 or 2400 mg/day were well tolerated and there was no evidence suggesting substantial toxicity.(21)

Table 13. Gastrointestinal adverse events related to ibuprofen therapy(21)

Adverse events	1200 mg/day		2400 mg/day	
	Definitely or probably related	Possibly related	Definitely or probably related	Possibly related
Gastrointestinal	3	0	4	2
Epigastric pain	1	0	0	0
Nausea	0	0	1	0
Abdominal distress	1	0	0	0
Flatulence or feeling of fullness	1	0	1	0
Diarrhoea or frequent bowel movements	0	0	2	2

As can been seen from these results of these three clinical studies, if there was dosing confusion and 6 tablets of Nurofen 400 DOUBLE STRENGTH tablets were taken per day, the risk of experiencing an adverse event is comparable to taking the recommended maximum dose of 1200 mg/day.

The safety risks associated with taking the 2400 mg/day dose has also been address in Part B Section 4, under class-related effects.

From a cardiovascular safety perspective, Medsafe's own report on the risk of cardiovascular events with the use of ibuprofen concluded that OTC doses of ibuprofen (≤ 1200 mg/day) were not associated with an increased risk of cardiovascular thrombotic events and that there is a small increased risk of cardiovascular thrombotic events when ibuprofen is used at high doses (2400 mg per day). Overall, the benefit to risk of harm balance for ibuprofen remains positive.(22) Hence, this small increased risk when limited to 2 days' exposure is unlikely to be substantively relevant.

In terms of the risk of GI complications with ibuprofen, the risk is dose dependent and is increased with the use of 2400 mg/day dose. However, much of this data comes from clinical studies that don't reflect short-term OTC use. Analysis of endoscopic studies that assessed gastrointestinal safety of the short-term use of ibuprofen at 1200, 1600 and 2400 mg/day found that "dosage levels of ibuprofen at 1,600 or 2,400 mg daily, given for three days or less, produced little or no injury to the gastric mucosa."(13)

Nurofen label comprehension research indicates that 87% of consumers followed the dosage instructions on the label (every time, most of the time or when buying the product for the first time) with a similar proportion (85%) indicating that they followed the instructions for use on the label.(18) Hence it is unlikely that dosage confusion and taking 2400 mg/day dose would be a common occurrence. In addition, the ability of consumers to correctly use ibuprofen double strength 400 mg in a self-selection environment has been demonstrated in a simulated pharmacy self-selection study conducted in the USA. At the time of the study the 400 mg strength was not available for OTC use and this allowed the researchers to investigate the use amongst consumers who were only previously exposed to the 200 mg strength. In this study only 4 (0.6%) of the 736 consumers took the ibuprofen double strength tablets at a dose of 2400 mg/day. In addition, all four consumers indicated that this use was intentional, e.g., as a single tablet was not providing sufficient pain relief (2 cases) and not due to dosage confusion.(16)

This potential for dosage confusion is effectively mitigated by the product label. As previously discussed, if the reclassification application is successful, Reckitt proposes to relaunch Nurofen 400 DOUBLE STRENGTH using an Australian harmonised label (see Part A, Section 12, Figure 1).

The proposed Nurofen 400 DOUBLE STRENGTH label is clearly differentiated from the regular strength Nurofen (200 mg) tablets. The difference in tablet strength and one tablet dosage is effectively communicated with:

- DOUBLE STRENGTH in a red call out box immediately underneath the brand name.
- The ibuprofen content of 400 mg being communicated on front and back of pack.
- .
- The one tablet dose being visually illustrated on front of pack, noting that regular Nurofen depicts two tablets on front of pack.
- The dosage directions provided on back of pack.

In addition, Nurofen 400 DOUBLE STRENGTH are further distinguished from regular strength Nurofen (200 mg) tablets as the dimensions of front facing differ. Nurofen 400 DOUBLE STRENGTH is 116 x 61 mm, which is a taller and longer than regular Nurofen (107 x 46 mm). This different facing dimensions are only used for formulations that are different to the base Nurofen range and help consumers recognise that this is a different formulation.

Addiction, misuse, abuse, accidental overdose

There is no evidence that ibuprofen would produce dependency at either therapeutic or supratherapeutic doses. Ibuprofen has no abuse potential and is not a candidate for illicit or recreational use.

The potential for misuse is also negligible. Even if Nurofen 400 DOUBLE STRENGTH was misused, the wide therapeutic index and the limited pack size (12 tablets) reduces any likelihood of harm. In addition, research has shown that OTC ibuprofen has a superior risk-benefit profile than paracetamol. This same research found that ibuprofen had the lowest potential for overdose toxicity compared to paracetamol, aspirin, naproxen and diclofenac.(5)

The safety of ibuprofen in overdose has been addressed in Part B, Section 6. The rate of accidental overdose with single ingredient ibuprofen is extremely low, with no reports of accidental overdose in New Zealand, in the Suspected Medicine Adverse Reaction Search (SMARS) database, for the period of 1st January 2000 to 1st June 2022.(11) In addition, data from the Reckitt Benckiser PSUR for the period from 19 February 1969 to 31 October 2021 reported 190 cases of accidental overdose from over [redacted] billion patient exposures.(28)

Import considerations

Nurofen 400 DOUBLE STRENGTH has been temporarily discontinued in the New Zealand market due to lack of harmonisation with Australia with the last sales to pharmacy occurring in February 2022.

Reclassification to Pharmacy Only which would allow harmonisation with Australia would see a return of this product to New Zealand consumers.

There are no other import considerations.

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 ibuprofen 400 mg with a maximum daily dose of 1200 mg in a primary pack containing no more than 12 dose units is a safe and well-tolerated medication, providing short-term relief from acute pain and fever.

There are multiple health benefits of having increased access to ibuprofen 400 mg tablets as a Pharmacy Only and these include:

- Providing the most efficacious OTC ibuprofen analgesic dose(1, 2) in a single tablet format
- Providing the most commonly used dosage of ibuprofen in a single tablet format(3)
- Provide an effective treatment for strong pain with a better risk/benefit profile than most OTC alternatives.(5)
- Satisfying consumer preference for taking fewer tablets, noting that consumer research indicates that approximately 1 in 4 consumers dislike taking tablets and have a preference for treatments that require fewer tablets to be taken(3)
- Providing consumers with difficulties swallowing tablets an easier to use treatment option, noting that 1 in 6 pharmacy customers have difficulty swallowing medications.(31)

The benefits of increased access to ibuprofen 400 mg tablets were acknowledged by the Australian Advisory Committee on Medicines Scheduling (ACMS) with their decision to reschedule immediate release 400 mg of ibuprofen from Schedule 3 to Schedule 2 (Pharmacy Only medicine) at the 31st meeting in 2020.(6) At this meeting the Committee stated that the benefits included, the relief or pain and fever, ibuprofen is well tolerated with an excellent safety profile at these doses [≤ 1200 mg/day] and only a single tablet is required to be taken. In addition, the Delegate also stated that the small size of pack at 12 tablets is consistent with short-term use and is a significant mitigation for concern around excessive doses. That the risk around dose confusion is mitigated by labelling and the small pack size. That the safety risks are consistent with other already unscheduled and Schedule 2 ibuprofen products, and they acknowledged that the risk profile of ibuprofen is superior to that of other NSAIDs and comparable to paracetamol plus ibuprofen combinations in Schedule 2.

There is a need for more self-select OTC treatments to manage pain, with the reclassification of all codeine-based analgesics to Prescription medicines.(48) Although experience from Australia indicates that paracetamol is the most commonly used OTC analgesic in this environment, ibuprofen use was more frequently used when the consumers' pain was more severe. As ibuprofen 400 mg represents a more effective analgesic option than ibuprofen 200 mg(1, 2) with equivalent tolerability(2, 26) self-selection access to this medicine will help satisfy this consumer need. This need has also been confirmed in consumer research that indicates that Nurofen 400 DOUBLE STRENGTH would be used to manager stronger pain.(3) In addition, ibuprofen 400 mg is a viable alternative to paracetamol/ibuprofen (1000 mg/400 mg) as data from head-to-head clinical trials suggest that the modest differences in efficacy are not necessarily clinically meaningful differences.(29, 30)

The short-term OTC use of ibuprofen 400 mg is well tolerated. The incidence of adverse events is equivalent to ibuprofen 200 mg and placebo.(2, 26) The maximum recommended daily dose for Nurofen 400 DOUBLE STRENGTH (1200 mg/day) is the same as that for regular ibuprofen 200 mg. The safety of this daily dose is well established and considered appropriate for use as both an Unscheduled medicine and a Pharmacy Only medicine in various pack sizes.

The cardiovascular and renal safety of OTC ibuprofen has been shown to be similar to control (placebo) and this includes assessments in older people with risk factors. Epidemiologic studies of prolonged use of OTC doses of ibuprofen overall reinforce a favourable cardiorenal safety profile.(35) In addition, the 2015 Medsafe review of the cardiovascular safety of ibuprofen concluded that OTC doses of ibuprofen (≤ 1200 mg/day) were not associated with an increased risk and that the benefit to risk of harm balance for ibuprofen remains positive.(22) OTC doses of ibuprofen are well tolerated and have a

gastrointestinal safety profile equivalent to paracetamol and superior to aspirin. Ibuprofen's safety in overdose is superior to paracetamol.(14)

The labelling proposed makes it clear that Nurofen 400 DOUBLE STRENGTH contains twice the quantity of ibuprofen versus regular Nurofen and that the dosage is a 1 tablet dose. Consumers are accustomed to seeing double strength and regular strength OTC medicines sold alongside each other and understand that dosing of the two is different.

Since ibuprofen 400 mg was rescheduled to a Pharmacy Only medicine in Australia in February 2021 there has been no safety signal to indicate that favourable benefit/risk profile has been diminished, noting that there to date there have been no reports of adverse events in the DAENs database up to 25 h July 2022.(17)

The risk associated with a person taking a higher dose by inadvertently taking the 400 mg tablets using the dosing regimen for regular ibuprofen is small for multiple reasons. First this is a commonly used, well tolerated therapeutic dose,(3, 4) it is not a supratherapeutic or toxic dose.(27) Several head to head clinical trials have demonstrated that ibuprofen 1200 mg/day and 2400 mg/day have similar tolerability.(19-21) From a cardiorenal safety perspective a Medsafe review concluded that OTC doses of ibuprofen (≤ 1200 mg/day) is not associated with increased risk and that there was a small increased risk of cardiovascular thrombotic events at 2400 mg/day.(22) From a gastrointestinal safety perspective the short-term use of the ibuprofen at 1600 to 2400 mg/day taken for up to 3 days produced little or no injury to the gastric mucosa.(13) In addition, if a consumer inadvertently took a twice the recommended dose of Nurofen 400 DOUBLE STRENGTH tablets, this is exposure is limited to a maximum of two days and there is minimal additional risk that this would result in a significant adverse event.

Nurofen 400 DOUBLE STRENGTH will be advertised within the same advertisements as regular Nurofen (200 mg). As such consumers will be made aware that there are two strengths of Nurofen available.

The proposed reclassification would make ibuprofen 400 mg available for self-selection in pharmacy in packs of up to 12 dose units. This represents fewer days' exposure than other Pharmacy Only NSAIDs and paracetamol and equivalent patient exposure to Unscheduled ibuprofen. (See Table 14). Given that that OTC ibuprofen has a favourable risk-benefit profile compared to these other analgesic options.(5) The proposed reclassification is appropriate and poses negligible change in safety risk.

Table 14: Relative exposure to self-selection analgesics

Analgesic	Classification	Maximum pack size	Patient exposure (days' therapy at maximum daily dose)
Ibuprofen 400 mg	Proposed Pharmacy Only	12	4 days
Ibuprofen 200 mg	Unscheduled	25	4.2 days
Ibuprofen 200 mg	Pharmacy Only	100	16.7 days
Naproxen 250 mg	Pharmacy Only	30	5 days
Diclofenac 12.5 mg	Pharmacy Only	30	5 days
Paracetamol 500 mg	Pharmacy Only	100	12.5 days

In summary, there are clear and substantial health benefits associated with Pharmacy Only availability and a negligible change in safety risk with the proposed change in the classification of ibuprofen 400 mg.

10. Risk mitigating strategies

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

The proposed reclassification poses negligible change in risk as the total daily dose of ibuprofen available for self-selection within pharmacy remains unchanged at 1200 mg/day. In addition, as the pack size proposed for self-selection limited to 12 dose units, which represents 4 days' supply, the risk of harm from any potential incorrect use is negligible. Even if all 12 tablets were taken as a single dose, this use does not represent a toxic dose. For example, an adult weighing 70 kg would be exposed to non-toxic dose of 68 mg/kg and would be unlikely to experience even mild symptoms.(27)

At the 66th meeting of the Medicines Classification Committee an appeal against the decision not reclassify ibuprofen 400 mg tablets was considered and in upholding its original decision, the Committee noted that reserving the health professional input for the higher strength is consistent with other NSAIDs available in the market.(23) Although this is correct at face value, there are differences in maximum daily dose between ibuprofen and diclofenac which substantially alters the risk/benefit considerations, therefore making this comparison less relevant. For diclofenac 12.5 mg dosage forms are available as a Pharmacy Only medicine when in pack sizes limited to 30 or less dosage units and at a maximum daily dose of 75 mg/day,(24) and the double strength 25 mg formulations are Restricted Medicines, however the maximum daily dose for the double strength 25 mg formulation is higher at 150 mg/day.(25) As the double strength diclofenac formulation can be taken at a higher daily dose there are dose-related safety issues that warrant pharmacist oversight to manage the increased risk of side effects. However, this situation does not exist for ibuprofen. For ibuprofen the maximum OTC daily dose for both regular (200 mg) ibuprofen and the double strength formulation is the same at 1200 mg/day. Therefore, the safety of both tablet strengths is the same(1, 2, 26) and small pack sizes (limited to 4 days' supply) is suitable for use as a Pharmacy Only medicine.

To minimise the risk of taking the incorrect dose, the Australian harmonised Pharmacy Only label is proposed to be used in New Zealand. This has multiple design features that clearly distinguishes the 400 mg product from regular Nurofen and clearly communicates the one tablet dosing. (See Part A Section 12). In addition, Nurofen 400 DOUBLE STRENGTH has been available for self-selection within pharmacies in Australia since February 2021 and there is no evidence of a change in the safety profile.(17) Similarly, global use of the double strength formulations has not resulted in any signals of a change in the risk-benefit profile of ibuprofen.(28)

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

Conclusion

From the information provided, it is clear that ibuprofen 400 mg with a maximum daily dose of 1200 mg in a primary pack containing no more than 12 dose units is a safe and well-tolerated medication, providing short-term relief from acute pain and fever.

The public health benefits of having ibuprofen 400 mg as a Pharmacy Only medicine includes providing consumers with the most efficacious OTC ibuprofen analgesic dose in a single tablet format.(1, 2) This one tablet dosing matches consumer use of ibuprofen, as the most commonly used dose is 400 mg.(3) The one tablet posology also satisfies consumer preference for taking fewer tablets, noting that consumer research indicates that approximately 1 in 4 consumers dislike taking tablets and have a preference for treatments that require fewer tablets to be taken.(20) Also the one tablet posology is more suitable for the 1 in 6 people who have difficulty swallowing oral medicines.(31) This reclassification will also provide consumers with an effective treatment for strong pain with a better risk/benefit profile than most Pharmacy Only alternatives (e.g. paracetamol, aspirin, and diclofenac.(5)

These benefits are delivered without a change in the excellent safety of OTC ibuprofen. This is supported by the facts that single doses of ibuprofen 400 mg have a comparable safety profile to single doses of ibuprofen 200 mg.(1, 26) The total daily dosage of Nurofen 400 DOUBLE STRENGTH tablets is the same as regular Nurofen 200 mg, therefore there is no change in tolerability. Ibuprofen has a wide therapeutic index and a favourable risk-benefit profile, which is better than other OTC NSAIDs and paracetamol which are available for self-selection.(5) In-market evidence from Australia following the availability of Nurofen 400 DOUBLE STRENGTH as a Pharmacy Only medicine indicates that consumers can safely and appropriately use this medication. There have been no reports of adverse events with the double strength formulation and there has been no change in the rate of adverse events reported in the DAENs database for Nurofen/ibuprofen since this reclassification.(17)

The proposed labelling makes it clear that Nurofen 400 DOUBLE STRENGTH contains twice the amount of ibuprofen versus regular Nurofen and that the dosage is a 1 tablet dose. Consumers are accustomed to seeing double strength and regular strength OTC medicines sold alongside each other and understand that dosing of the two is different.

The label of Nurofen 400 DOUBLE STRENGTH tablets carries clear directions to avoid the use in specific subsets of patients at increased risk of adverse events, including the elderly. These warning statements are the same as for regular ibuprofen 200 mg that is available both as General Sale and Pharmacy Only medicines. Previously submitted and reviewed consumer research associated with down-scheduling of 200 mg ibuprofen to a General Sale medicine established that patients with pre-existing medical conditions do read the labels before taking OTC medicines. Hence, the risk of harm is low and essentially equivalent to Pharmacy Only and General Sale ibuprofen products and is adequately addressed by the product label.

The risks associated with potential dosage confusion, resulting in a person inadvertently taking two 400 mg tablets three times daily is not substantive. This type of medication error is uncommon as demonstrated by a consumer usage study, where the use of ibuprofen at 2400 mg/day was uncommon occurring in only 0.6% of users and when it occurred it was a deliberate decision and not due to dosage confusion.(16) Taking 2400 mg/day does not represent taking an overdose generally as it is taking a commonly used therapeutic prescription dose that is well tolerated. The short-term use of ibuprofen at 2400 mg/day has a similar safety profile to ibuprofen 1200 mg/day as established in multiple head-to-head clinical trials.(19-21). Even though NSAID adverse events are dose related, the cardiovascular risks associated with 2400 mg/day are small(22) as are the risk of gastrointestinal mucosal injury.(13) Importantly, if a patient was to inadvertently take this higher therapeutic dose, the pack size limitation of 12 dose units means that the exposure is limited to a maximum of two days. Therefore, the risk of adverse outcomes is low and is effectively mitigated by product labelling that clearly calls out the higher strength tablet and the one tablet dosing on front and back of pack as well as appropriate pack size limitations.

The availability of Nurofen 400 DOUBLE STRENGTH in limited pack sizes (≤ 12 dose units) as a Pharmacy Only medicine will benefit the self-management of pain without altering overall medication usage patterns or the well-established safety profile of OTC ibuprofen.

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