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

30 June 2020

Submitted by:

Reckitt Benckiser (New Zealand) Pty Limited

Level 47 / 680 George Street Sydney NSW 2000, Australia

Table of Contents

Executive summary 4
Part A 6
1. International Non-proprietary Name of the medicine. 6
2. Proprietary name(s). 6
3. Name and contact details of the company / organisation / individual requesting a reclassification. 6
4. Dose form(s) and strength(s) for which a change is sought. 6
5. Pack size, storage conditions and other qualifications. 6
6. Indications for which change is sought. 6
7. Present classification of the medicine. 7
8. Classification sought. 7
9. Classification status in other countries (especially Australia, UK, USA, Canada). 9
10. Extent of usage in New Zealand and elsewhere (eg, sales volumes) and dates of original consent to distribute. 10
11. Local data or special considerations relating to New Zealand (if applicable). 11
12. Labelling or draft labelling for the proposed new presentation(s). 11
13. Proposed warning statements (if applicable). 11
Part B 12
1. Indications and dose 12
2. Presentation 12
3. Consumer benefits 13
4. Contraindications and precautions 17
5. Undesirable effects 26
6. Overdose 28
7. Medication errors and abuse/misuse potential 29
8. Communal harm and / or benefit 32
9. Integrated benefit-risk statement 32
10. Risk mitigating strategies 34
References 36

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.

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.

The public health benefits of having a small pack (limited to no more than 12 dose units) of ibuprofen 400 mg in Pharmacy Only is broader than the convenience of and preference for taking fewer tablets.

The upcoming implementation of the reclassification of all codeine-based analgesics to prescription medicines will create a consumer need for alternative easily accessible analgesics to manage strong pain. The 400 mg DOUBLE STRENGTH ibuprofen tablets are likely to be used by people seeking relief of strong pain. Cochrane reviews have confirmed that the 400 mg dose of ibuprofen is more efficacious than the 200 mg dose with equivalent tolerability(1-3), and is less efficacious than the fixed combination of paracetamol/ibuprofen (1000 mg/400 mg) one of the main self-selection options for the relief of acute strong pain.(1) However in head-to-head clinical trials, a single dose of ibuprofen 400 mg has been clinically demonstrated to be as efficacious as the fixed combination of paracetamol/ibuprofen (500 mg/200 mg, one tablet) and modestly less efficacious than two tablets (1000 mg/400 mg)(4). In addition, another head-to-head trial suggests that this difference in efficacy is not always clinically meaningful, demonstrating that ibuprofen 400 mg provided similar morphine sparing effects than one or two tablets of paracetamol/ibuprofen (500 mg/200mg or 1000 mg/400 mg) in the post-operative setting.(5) Ibuprofen 400 mg is appropriate for inclusion as a Pharmacy Only medicine as it has a superior risk-benefit profile to that of paracetamol, aspirin and diclofenac, as single agents(6) and it is a viable alternative to paracetamol/ibuprofen combination. Consequently, improving the availability of 400 mg ibuprofen by permitting self-selection as a Pharmacy Only medicine will provide consumers with an effective option which also has a very good benefit risk profile to relieve strong pain.

Approximately 1 in 6 customers of retail pharmacies have difficulty swallowing oral medications.(7) For the vast majority, this difficulty is not due to an underlying medical condition but is due to the fact that swallowing medications whole is not a natural process. For these people, the benefit of taking fewer tablets is meaningful and is not adequately addressed by the current scheduling as swallowing difficulties are not commonly discussed. Please note, the Nurofen 400 DOUBLE STRENGTH tablet is a small easy to swallow tablet.

OTC ibuprofen (doses ≤ 1200 mg/day) is well tolerated and when taken as directed has a gastrointestinal safety profile equivalent to paracetamol and superior to aspirin. Ibuprofen’s safety in overdose is superior to paracetamol.(8)

The maximum daily dose for Pharmacy Only 400 mg ibuprofen (Nurofen 400 DOUBLE STRENGTH) will remain at 1200 mg per day the same as regular 200 mg ibuprofen and the pack size will be limited to 4 day’s supply (12 tablets), hence the Pharmacy Only availability does not pose additional safety risk to the consumer. In addition, a risk-benefit assessment

of OTC analgesics concluded that ibuprofen (both as the acid and faster dissolving salts) has a superior risk-benefit profile than paracetamol and aspirin.(6)

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.(1, 3) As such the use of 400 mg ibuprofen (Nurofen 400 DOUBLE STRENGTH) instead of the regular 200 mg is unlikely to pose any additional safety risk.

A 2015 Medsafe review of the cardiovascular safety of ibuprofen concluded that OTC doses of ibuprofen at maximum of 1200 mg per day or less were not associated with an increased risk of cardiovascular events and that overall the benefit to risk of harm balance for ibuprofen remains positive.(9) This finding is further supported by a systematic review of the cardiorenal safety of OTC ibuprofen (White 2018). This review demonstrated that there is little risk of cardiovascular adverse events when used as per the product label. The risk is essentially equivalent to that of placebo or no-use in people with (e.g. older people with pre-existing risk factors) and without contraindications as defined on the label.(10)

A systematic review of community-based controlled observational studies indicated that amongst widely used NSAIDs, low-dose ibuprofen (i.e. OTC dose) appears to be free of cardiovascular risk and is one of the NSAIDs least likely to increase cardiovascular risk.(11)

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 .
- 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.(12) 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),(13, 14) 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 87 countries.(15) The 400 mg dosage form is available in 48 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 8 countries including 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 Behind Counter Pharmacist Only Medicine		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 in a primary pack containing not more than 50 dosage units, when labelled with a recommended daily dose of 1200 mg or less of ibuprofen is Schedule 3 (Pharmacist Only Medicine). A similar application has been submitted to the Advisory Committee on Medicines Scheduling (ACMS) to reschedule 400 mg of ibuprofen in a primary pack containing not more than 12 dose units from Schedule 3 to Schedule 2 (Pharmacy Only medicine). This application will be considered at the June 2020 meeting.

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.

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, following the 30th meeting, the NZ Medicines Classification Committee also 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. In the 9 months since launch over 8,300 day's supply of the 400 mg DOUBLE STRENGTH tablets have been purchased in New Zealand.

In Australia the non-prescription sale of Nurofen 400 DOUBLE STRENGTH has been available for longer than that in New Zealand. Over the past three years (January 2017 to January 2020) over [redacted] day's supply of the 400 mg DOUBLE STRENGTH tablets have been purchased in Australia.

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 sales of Nurofen 400 mg DOUBLE STRENGTH for the 12 month period of November 2018 to September 2019 was in excess of [redacted] million units. There have been no signals to suggest that the increasing use of the DOUBLE STRENGTH tablets has changed the excellent safety profile of OTC ibuprofen.(15)

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 non-prescription ibuprofen 400 mg (DOUBLE STRENGTH) has the same maximum daily dose of 1200 mg/day as current unscheduled and pharmacy only ibuprofen 200mg 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 day's supply-maximum daily dose 1200mg). It is expected that the Pharmacy Only availability of this medication under the

proposed conditions will provide the same efficacy and safety profile as general sale ibuprofen 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).

Nurofen 400 DOUBLE STRENGTH is marketed in New Zealand in pack sizes of 12 and 24 tablets as a Restricted Medicine. A copy of the proposed Pharmacy Only label is included in Appendix 1 as well as copy of the current Pharmacy Only label for regular Nurofen 200 mg tablets (for the purpose of comparison).

The label is clearly differentiated from the regular strength Nurofen (200 mg) and makes it clear that Nurofen 400 DOUBLE STRENGTH is a 'double strength' formulation, hence containing twice the amount of active ingredient vs regular Nurofen.

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 Pharmacy Only product label is the same as the current approved label for this product as a Restricted Medicine. (See Appendix 1)

Except for differences in dose strength and dosing directions, the back of pack medicines information panel for ibuprofen 400 mg is essentially the same as that for regular ibuprofen 200 mg. The medicines information panel clearly stipulates how to use the product and highlights the contraindications, warnings and precautions as per the requirements of Medsafe and Australia's Therapeutic Goods Administration. Therefore, given this is an approved label which meets the Medsafe labelling requirements as well as those of TGO92 (aimed at improving consumer understanding of medicine labels) it is reasonable to conclude that the current 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 would potentially affected by this change are listed in Table 4. Of these three brands only Brufen One is 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 (Mylan New Zealand Ltd)	10 tablets	Restricted
Ibuprofen Liquid Capsules (Neo Health NZ Limited)	6, 10 and 12 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.

One of the benefits of the ibuprofen 400 mg is that consumers can take the most commonly used dose of ibuprofen (400mg) in a single tablet. Australian omnibus research (conducted in February 2020) reported that 77% of Nurofen users normally take two x 200 mg tablets (400 mg dose) to relieve their pain.(13) This finding is essentially the same as the findings of a UK omnibus research (conducted in 2009) that found that 78.4% of consumers surveyed take two x 200 mg tablets (400 mg dose) to relieve their acute pain.(14)

Consumers are accustomed to seeing double strength products on shelfs alongside their original regular strength (less concentrated) alternatives and know that dosing of the two would be different on the basis of concentration e.g. Gaviscon Original and Gaviscon Double

Strength, Zantac (150mg) and Zantac Double Strength (300mg) and Aspro Clear Regular Strength (300 mg) and Aspro Clear Extra Strength (500 mg).

In addition, there are other OTC medicines in which the double strength or forte option requires fewer tablets per dose (versus the regular strength option) such as Zantac 150mg ranitidine (up to two tablets) and Zantac Double Strength 300mg ranitidine (one tablet per dose) and Aspro Clear Extra Strength (500mg) stating that 1-2 tablets to be dissolved in water while Aspro Clear Regular Strength (300mg) requiring 2-3 tablets to be dissolved in water.

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 Nurofen 400m DOUBLE STENGTH front of pack label calls out the that it 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 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.

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 87 countries.(15) The 400 mg dosage is available in 48 countries. It is available as an unscheduled medicine in one country and available for self-selection within pharmacy in 8 countries including the United Kingdom. (See Part A, Section 9, Table 3)

Globally the sales of Nurofen 400 mg DOUBLE STRENGTH for the 12 month period of November 2018 to September 2019 was in excess of [redacted] million 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.(15)

A single-arm, open-label clinical study simulated the OTC use of ibuprofen 400 mg 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 only previously exposed to the 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 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. 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 the vast majority of consumers used ibuprofen 400 mg tablets in a manner consistent with directions on the label. Overall misuse was uncommon, and the levels and patterns of misuse were small and unlikely to generate an excess risk of clinically important adverse events.(16)

There are multiple consumer benefits of self-selection access to ibuprofen 400 mg, including convenience, the desire to take fewer tablets and seeking relief of strong pain.

Pain is a subjective and individual experience. It is accepted that consumers have the ability to decide for themselves on treatment options to manage acute strong pain without the need for pharmacist intervention, as this currently occurs with the Pharmacy Only availability of ibuprofen/paracetamol combinations, diclofenac and naproxen. The Pharmacy Only availability of ibuprofen 400 mg will give consumers an option to help manage strong pain that has a better risk-benefit profile than currently available Pharmacy Only options.(5, 6)

Research amongst Australian consumers (n = 1186) about 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 benefits of this formulation. The most common consumer benefits were convenience (40%), relief of strong pain (35%), the desire to take fewer tablets (23%) and it was as effective as regular Nurofen (17%).(13)

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,(1-3), and has a favourable risk-benefit profile that is superior to paracetamol, diclofenac and aspirin.(6)

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 upcoming implementation of the reclassification of all codeine-based analgesics to prescription medicines will create a consumer need for alternative easily accessible analgesics to manage strong pain.

Australia has already implemented this reclassification and research amongst Australian pharmacists reported that not all consumers have been able to easily access the strong pain relief they need. Consumers had both an economic and access burden placed upon them to access medications that were previously managed in pharmacy.(17)

The current options available in pharmacy to manage acute strong pain include paracetamol/ibuprofen combinations, ibuprofen, diclofenac, paracetamol and naproxen. Of these single agent options, ibuprofen has the more favourable risk-benefit profile.(6)

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 (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).(1)

Equivalent findings were demonstrated in the Cochrane review by Derry (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%). In this review the rate of adverse events for both ibuprofen doses were equivalent to placebo.(2)

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).(3)

The Cochrane review by Moore (2015a) indicates that ibuprofen 400 mg is less efficacious than the combination of paracetamol/ibuprofen (1000 mg/400 mg).(1) 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 modestly less efficacious than two tablets (1000 mg/400 mg).(4) 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.(5) Another study (Daniels 2011) demonstrated that one tablet of paracetamol ibuprofen (500 mg/200 mg) combination was more effective than paracetamol plus codeine (1000 mg/30 mg).(18) Given concerns about paracetamol overdose (intentional or accidental) as well as the risk of inadvertently taking multiple paracetamol-based products, ibuprofen 400 mg offers a reasonable self-selection alternative to help manage acute strong pain. Limiting the Pharmacy Only pack size is to 4 day's supply (12 dose units) and the well-established safety profile associated with the short-term use of ibuprofen 400 mg (at a maximum daily dose of 1200 mg), there is minimal risk that this Pharmacy Only availability will increase the incidence of harm or misadventure and there is a clear clinical benefit. Therefore, this represents a net positive public health benefit.

Many patients have difficulties swallowing medicines and could benefit from taking fewer tablets

Many people experience difficulty swallowing solid dosage forms such as tablets and capsules. Swallowing medicines without chewing is not a natural process but is a learnt skill. The gag reflex aims to eject items that are too large to be safely swallowed and humans are wired to chew even the smallest of foods (e.g. sultanas) before swallowing them. Swallowing even the smallest of tablets is in opposition to human's natural reflexes.(7) Difficulties swallowing tablets is not necessarily secondary to a medical condition and is not limited to people with dysphagia.

Research amongst customers of Australian community pharmacies Lau (2015) found that 14.1% (52/369) of customers had difficulties taking oral medications. A further 3.5% had difficulty swallowing food and/or drink, with 4 of these customers having an issue with swallowing medications. Overall, 15.1% (56/369) or approximately 1 in 6 people have difficulties taking oral medications. This research also found that this difficulty was not skewed towards older customers but occurred at similar prevalence across all age groups.(7) (see Table 5) A similar prevalence was reported by Marquis (2013) in another pharmacy study conducted in Switzerland, with 9% of customers having current difficulty swallowing medications and 13.4% having difficulty in the past. In this study, swallowing difficulties was most commonly reported with the taking of analgesics (e.g. paracetamol) and for the majority of people difficulties swallowing tablets occurred when taking every single dose.(19)

Table 5: Prevalence of swallowing difficulties amongst Australian community pharmacy customers, by age(7)

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%)

In addition, research amongst Australian consumers (n = 1186) reported that 23% did not like taking tablets and saw the benefit of taking fewer tablets associated with the use of Nurofen 400 DOUBLE STRENGTH tablets.(13)

In most cases this issue goes unnoticed as the majority of customers do not raise this issue with their healthcare professionals, pharmacist or doctor, even amongst those who resorted to modifying their medication (e.g. crushing or chewing it) to make it easier to swallow.(7, 19) The reasons for this include they perceive this difficulty as being normal, while others felt embarrassed or did not think they could be helped.(7) This resistance by customers to voluntarily raise swallowing difficulties was validated by another Australian study, Nguyen (2014). In this study only 7% of pharmacists indicated that their customers would 'often' or 'always' volunteer information about difficulties swallowing medicines, while 51% of pharmacists indicated that their customers 'rarely' or 'never' raised this issue with them.(20)

Research shows that the majority of people who use Nurofen 200 mg tablets in Australia and globally take two tablets to help relieve their pain.(13, 14) Hence, if ibuprofen 400 mg (12 units) was available for self-selection as Pharmacy Only medicine, consumers with difficulties swallowing medications who generally take a 400 mg dose (two tablets of regular ibuprofen 200mg) will be able to choose to purchase a potentially more suitable product, ibuprofen 400mg. For these people taking just one small tablet to achieve effective pain relief represents a positive health benefit.

In summary, the Pharmacy Only availability of ibuprofen 400 mg double strength (≤ 12 dose units) will give consumers improved access to an effective analgesic to help manage acute strong pain which is more effective and as well tolerated as ibuprofen 200 mg(1-3),and is a viable alternative to paracetamol/ibuprofen (1000/400 mg) combination(5) and has a favourable risk-benefit profile that is superior to paracetamol, diclofenac and aspirin.(6)

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:(21)

- 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 hemorrhage (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 day's supply) and as a Pharmacy Only medicine (in packs up to 16 day's 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:(21)

- 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 doses for prolonged periods of time. It is well accepted that the short-term use of ibuprofen in lower doses used in the OTC setting has an excellent safety profile.(3, 6, 8) The precautions for ibuprofen 400 mg 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 scheduling reviews have concluded that these precautions can be easily 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 2019. This report confirms that no new safety concerns or potential risks have emerged, and that ibuprofen's risk-benefit profile remains positive.(15)

As the most commonly used single dose of regular Nurofen is 400 mg (2 x 200 mg)(13, 14) 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.(6)

As ibuprofen has a wide therapeutic index, toxicity would only occur in situations of intentional overdose. 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.(12) 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 dose of 68 mg/kg.(12) Therefore, a consumer would need to deliberately ingest multiple (six) packets of the proposed Pharmacy Only ibuprofen 400 mg double strength (12 tablets) at one time to achieve a 400 mg/kg ibuprofen dose for toxicity to occur.

Class effect – cardiorenal safety

The main class effects of NSAIDs of potential concern relates to the cardiorenal safety, especially amongst elderly patients with heart failure or renal dysfunction. The risk of cardiovascular and renal safety in the elderly 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.(13, 14) However, much of this potential concern relates to elevated risks associated with prescription doses of NSAIDs and not evidence associated with the use of lower OTC doses for short durations.

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 the available data suggested that a dose response relationship exists. That there is a small increased risk of cardiovascular thrombotic events when ibuprofen is used at high doses (2400 mg per day). Lower doses of ibuprofen of 1200 mg per day or less (the dose used for over-the-counter preparations) were not associated with this increased risk. Overall, the benefit to risk of harm balance for ibuprofen remains positive.(9)

There is no evidence to suggest that this risk profile has changed since this 2015 Medsafe review as established by the current PSUR for Nurofen.(15) This safety report establishes that the risk of arterial thrombotic events (MI or stroke) with ibuprofen is rare with an adverse event rate of 0.000002329% and that renal impairment and use in patients with renal failure or those who are dehydrated are also rare an event rate of 0.000013959%.

The cardiorenal safety of OTC analgesics, including ibuprofen, has been recently 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 findings of this extensive review were that the available data suggest that there is little cardiovascular risk when OTC NSAIDs including ibuprofen are used as directed.(10)

<u>Normotensive patients</u>

In normotensive patients the OTC use of ibuprofen 200 and 400 mg was comparable to placebo and paracetamol. Studies of greatest relevance summarised in this review included:(10)

- A meta-analysis of 15 single-dose randomised, double-blind trials evaluating the safety of OTC ibuprofen (200 or 400 mg; n = 878) and paracetamol (650 or 1000 mg; n = 849) versus placebo (n = 852) in healthy participants with acute pain conditions. The frequency of adverse events did not differ significantly between the groups (2.4% with ibuprofen, 3.2% with paracetamol, and 2.1% with placebo), and no renal adverse events were reported.
- Another analysis evaluated the safety of OTC ibuprofen and paracetamol use for less than 7 days. Data from 96 randomised, double-blind studies found no differences between ibuprofen and paracetamol in adverse event rates for any organ system.
- A meta-analysis of 8 randomised, double-blind, placebo-controlled trials compared OTC ibuprofen (800-1200 mg/d; n = 1094) with placebo (n = 1093), found that

significantly fewer (P = 0.018) participants receiving ibuprofen (27.4%) experienced an adverse event compared with those receiving placebo (31.7%).

Hypertensive patients

The renal safety of ibuprofen 400 mg three times daily (maximum daily dose 1200 mg) amongst patients aged > 60 years with hydrochlorothiazide-treated stage 1 hypertension and mild renal insufficiency (serum creatinine 1.3-3.0 mg/dL) was assessed in a randomised clinical trial. In this trial, the safety of OTC ibuprofen use was compared to paracetamol 650 mg three times a day and aspirin 650 mg three times a day for 7 days. No significant changes from baseline in supine diastolic or systolic blood pressure occurred with ibuprofen or paracetamol. Small, but not clinically significant, decreases in supine diastolic blood pressure were observed for aspirin use. In addition, no significant changes from baseline occurred for creatinine clearance, serum creatinine, potassium, blood urea nitrogen, or sodium for any treatment.(10) This study amongst a subgroup of older patients with risk factors provides evidence that the cardiovascular and renal safety risks with ibuprofen 400 mg three times daily (maximum daily dose 1200mg) was minimal, equivalent to paracetamol and less than that observed with aspirin which is available as a Pharmacy Only medicine at these doses.

Safety data from epidemiological studies

The cardiovascular risk of OTC doses of ibuprofen has also been assessed from several epidemiological studies. It should be noted that these studies involve ibuprofen use for generally a much longer duration than that associated with OTC use and specifically the 4 day's supply represented by the current scheduling application. The majority of these studies demonstrate that the use of OTC doses (≤ 1200 mg/day) of ibuprofen is not associated with increased cardiovascular risk. Relevant studies are summarised below:(10)

- A nested case–control study in a cohort of 486,378 participants aged > 40 years registered in the UK General Practice Research Database who had at least 1 prescription for a NSAID between June 1, 2000, and October 31, 2004. They matched 3,643 cases of myocardial infarction (MI) from this group with 13,918 controls. The mean follow-up duration was 542 days in both cohorts. At ibuprofen doses ≤ 1200 mg/day, the risk of MI was no different to controls at 0.99 (95% CI: 0.81-1.21).
- A UK population-based retrospective cohort study in participants aged 50 to 84 years between January 2000 and October 2005 with a nested case-control analysis (n = 8,852 cases; n = 20,000 controls) examined the effect of dose on the risk of non-fatal MI associated with current NSAID use. The relative risk of MI with OTC ibuprofen doses up to 1200 mg/day was not increased over that with non-use (RR = 1.00; 95% CI: 0.80-1.25).
- An UK retrospective cohort study using data from 1987 to 2006 investigated the risk of MI with NSAID use in participants aged > 40 years. In those with a first prescription for ibuprofen (8.2% of whom were prescribed doses > 1200 mg/d), 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). Doses higher than the OTC dose 1201 to 2399 mg/day and doses ≥ 2400 mg/day, the relative risk of an MI were 1.22 (95% CI: 1.03-1.44), and 1.96 (95% CI: 1.05-3.65), respectively.
- A nested case-control study from the Netherlands examined the risk of first hospitalisation for MI or other cardiovascular events (unstable angina, cerebrovascular accident, transient ischemic attack [TIA]) in COX-2 and traditional NSAID users between January 2001, and December 2004. The adjusted odds ratio for MI risk with current low-dose (≤ 1200 mg/d) ibuprofen use versus remote use

(defined as whose drug supply ended > 60 days prior to the event date) was 1.51(95% CI: 1.06-2.14).

- A Danish epidemiological study assessed the risk of death and MI with NSAID use in 1,028,437 apparently healthy individuals aged ≥ 10 years. The hazard ratio for death with OTC ibuprofen doses ≤ 1200 mg/day was lower than controls at 0.78 (95% CI: 0.73-0.84; P < 0.01), similarly the hazard ratio for the MI and death composite end point was 0.92 (95% CI: 0.86-0.97; P < 0.01). Additional analysis of this database found that at ibuprofen doses ≤ 1200 mg/day, the risk of coronary death or nonfatal MI was increased (OR = 1.45; 95% CI: 1.19-1.77; P < 0.01), but the risk of fatal or nonfatal stroke was not different to controls (OR = 1.21; 95% CI: 0.95-1.53).
- A systematic review and meta-analysis compared the risk of serious CV events among participants using COX-2-selective NSAIDs or nonselective NSAIDs from 30 case–control and 21 cohort studies. The lowest overall relative risks were observed for ibuprofen and naproxen. In studies that assessed the risk with low-dose ibuprofen (variably defined as ≤ 1200 mg/day, ≤ 1600 mg/day, or <1800 mg/day), ibuprofen use was not was associated with an increased risk of CV events (RR = 1.05; 95% CI: 0.96-1.15).
- An individual patient data meta-analysis of studies derived from healthcare databases examined the time course for the risk of MI, as well as the effects of dose and use duration for commonly used NSAIDs. The cohort of 446,763 individuals included 61,460 cases of MI and 385,303 controls. When ibuprofen was taken at a daily OTC dose of ≤ 1200 mg/day for 8 to 30 days the adjusted odds ratio for the risk of MI was equivalent to controls (OR: 1.04; 95% CI 0.72-1.35).

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.(11)

The label of Nurofen 400 mg DOUBLE STRENGTH tablets carries clear directions to avoid the use in this specific subset of patients. “DO NOT USE IF: you have a stomach ulcer, or other stomach disorders, kidney, liver or heart problems”. This warning statement also appears on the label for regular ibuprofen 200 mg that is available both as Unscheduled and Pharmacy Only medicines. Previously submitted and reviewed consumer research associated with down-scheduling of 200 mg ibuprofen to an Unscheduled 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 Unscheduled ibuprofen products and is adequately addressed by the product label. In addition, there is no evidence that people with cardiovascular and renal disorders are currently using this product.

The label of regular ibuprofen and Nurofen 400 DOUBLE STRENGTH also states – DO NOT USE UNLESS A DOCTOR HAS ADVISED YOU if you are 65 years and older. There is currently no evidence to suggest that the elderly are actually using OTC ibuprofen.
Even if it was considered that the 400 mg dose marginally increased risk of harm, this risk is reduced by limiting Pharmacy Only pack sizes to 12 units, equivalent to 4 day’s supply.

From a potential total exposure perspective, the relative risk of harm is likely to be lower with Pharmacy Only ibuprofen 400 mg as the maximum duration of use of 4 days is lower than other Pharmacy Only analgesics; naproxen (30 tablets) 5 day’s supply, diclofenac 12.5 mg

(30 tablets) 5 day's supply and ibuprofen 200 mg options, 8 (48 tablets) or 16.6 (100 tablets) day's supply.

Data from the New Zealand Suspected Medicine Adverse Reaction Search (SMARS) database for the period of 1st January 2000 to 25 April 2020 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.(22) (See Table 6).

Table 6: Renal and cardiovascular adverse events reported on the Suspected Medicine Adverse Reaction Search database(22)

System	MedDRA reaction term	Number of reports for ibuprofen
Cardiac disorders	Atrial fibrillation	1
	Bradycardia	1
	Cardiac failure	1
	Cardiomyopathy	1
	Myocardial infarction	2
	Palpitations	2
	Tachycardia	3
Renal disorders	Acute kidney injury	13
	Nephropathy	1
	Renal failure	3
	Renal impairment	8
	Renal tubular disorder	1
	Renal tubular necrosis	3
	Tubulointerstitial nephritis	5

Data from the Australian Database of Adverse Event Notifications (DAENs) for the period of 1st January 1971 to 1st November 2019 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 (400 mg dose in doses up to 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, noting that the data does not allow analysis by dose.(23)

Table 7: Selected renal and cardiovascular adverse events reported on the Database of Adverse Event Notifications(23)

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	19	9	0	4	0	0
Renal failure	7	1	1	0	0	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	1	0	1	0	0	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.

Risks of the medicine used in the OTC setting

In RB's view, there is minimal risk associated with use of 400 mg tablets of ibuprofen (maximum daily dose of 1200mg) for the following reasons;

- The 400 mg dose is the dose most commonly used by consumers to manage acute pain(13, 14)
- The maximum daily dose (1200 mg/day) is the same as currently available for unscheduled and Pharmacy only ibuprofen options
- Pack size limitation is 4 day's supply
- Ibuprofen has a wide therapeutic index and for an adult weighing 70 kg, six of the proposed Pharmacy Only packets of ibuprofen 400 mg would need to be taken as a single dose to result in moderate to severe toxicity(12)
- Ibuprofen at OTC doses has a favourable risk-benefit profile which is superior to paracetamol and aspirin.(6)

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.
- Some individuals may take two 400 mg tablets rather than one, due to dosage confusion between double and regular strength. (This issue is addressed in detail in Part B Section 7).

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.(13, 14)

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.(13)

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.(1-3) Hence, the evidence indicates that the dose-related risk (200 mg versus 400 mg) of adverse events with short term use is negligible. In addition, when the risks of adverse events are considered from the perspective of the total daily exposure (maximum of 1200 mg), the amount of ibuprofen taken per dose (i.e. 200mg vs 400mg) is not relevant.

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(24) offering an alternative for strong 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.(6) In fact, if a consumer did accidentally or intentionally take a higher dose than recommended on pack e.g. 2 x 400 mg four times a day (maximum 6 tablets in 24 hours) as per the current 200 mg product posology, the 12 tablet pack of 400 mg ibuprofen will have been consumed in 2 days. In addition, in order for ibuprofen to have a harmful effect in overdose one would need to take 100-400 mg/kg for mild effects, and greater than 400 mg/kg for moderate to severe effects,(12) much more than can be taken if a 12 pack of 400 mg ibuprofen is purchased and taken incorrectly. 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 dose of 68 mg/kg.(12)

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.(13) This is further supported by UK consumer research that found that 78.4% used the 2 x 200 mg dose.(14) In addition, the Australian research indicated that in the majority of cases Nurofen 400 DOUBLE STRENGTH would be considered for the relief of strong pain.(13) 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 addition, 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. In New Zealand and Australia, the use of double strength has been increasing without any local signals of adverse consequences. This is not unexpected as the safety profiles associated with the short-term use of ibuprofen 400 mg and 200 mg are essentially the same,(1, 3) for the minority of occasions where individuals may have been able to manage their pain with the 200 mg dose, the short term use of the 400 mg dose is unlikely to increase the risk of harm.

The risk of dosage confusion is mitigated by the product label. The product name Nurofen 400 DOUBLE STRENGTH makes it clear that this product has twice the amount of active

ingredient (also emphasised by the 400) as regular Nurofen. In addition, the active ingredient and dose is very clearly listed as per TGO 92. To avoid any further confusion with dosing Reckitt Benckiser proposes to amend the current Medsafe approved label for Nurofen 400 DOUBLE STRENGTH and will be calling out the 'one tablet dose' on front of pack as text as well as with a pictorial of one tablet (see Appendix 1).

In addition, as previously mentioned consumers are accustomed to seeing double strength products alongside original strength products in pharmacy and understand that the dosing of these is different.

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.(9)

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:(10)

- 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.(10)

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.(21)

Other restrictions

There are no additional restrictions regarding the use of ibuprofen 400 mg.(21)

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 an unscheduled 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 Unscheduled 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.(6, 8) 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.(24)

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).(1)

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.(2)

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).(3)

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 2019. This report confirms that no new safety concerns or potential risks have emerged, and that ibuprofen's risk-benefit profile remains positive.(15)

In addition, a comprehensive assessment of the cardiovascular and renal 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.(10) In addition, ibuprofen at 1200 mg/day is well tolerated and suitable for medicines available for self-selection. The favourable risk-benefit profile of OTC ibuprofen has been acknowledged by Medsafe in their 2015 review of the cardiovascular safety ibuprofen.(9)

Data from the New Zealand Suspected Medicine Adverse Reaction Search (SMARS) database for the period of 1st January 2000 to 25 April 2020 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.(22) (See Table 8)

Table 8: Summary of SMARS reports for ibuprofen, paracetamol and aspirin(22)

Adverse event	Ibuprofen	Paracetamol	Aspirin
Number of reports (cases)	364	509	307
Number of reactions	706	879	551
Number of cases where death was a reported outcome	2	5	31

Equivalent data from the Database of Adverse Event Notifications (DAENs) for the period of 1st January 1971 to 1st November 2019 also supports the good overall safety profile of OTC and prescription ibuprofen in Australia (see Table 9).(23) 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.

Table 9: Summary of DAEN reports for ibuprofen, paracetamol and aspirin(23)

Adverse event	OTC ibuprofen	Prescription ibuprofen	OTC paracetamol	OTC aspirin
Number of reports (cases)	1043	498	2493	2803
Number of cases with a single suspected medicine	681	327	1058	539
Number of cases where death was a reported outcome	43	9	179	154

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

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.(6)

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.(12)

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.(25) 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.

A search of the Suspected Medicine Adverse Reaction Search (SMARS) database for the period of 1st January 2000 to 25 April 2020 identified no reports of overdose with ibuprofen in New Zealand.(22)

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.(12)

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 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.(12) 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(24) 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 (1200 mg/day) does not contribute to an increased risk of toxicity. In addition, limiting pack size to 12 tablets further minimises 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.(13) 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.(1-3) 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 when used as per the dosage instructions.

Potential for medication errors

As the dosage regimen for regular Nurofen 200 mg is to take 2 tablets and then 1 or 2 tablets every 4 to 6 hours as necessary (maximum 6 tablets per 24 hours), there is a theoretical risk that some consumers could apply the same dosage to the double strength product and take a higher dose up to 2,400 mg/day instead of 1,200 mg/day.

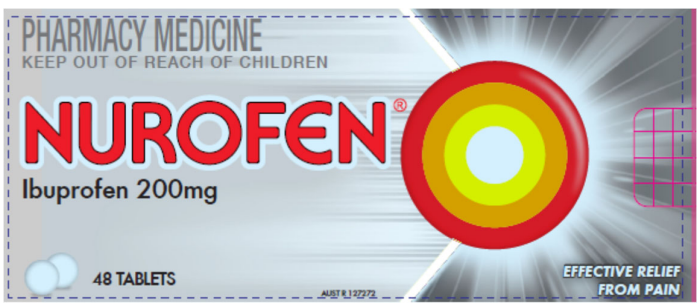
The ability of consumers to correctly use ibuprofen double strength 400 mg was assessed in a US study (Meeves 2017). At the time of the study the 400 mg strength was not available for OTC use and this allowed the researchers to investigate the use amongst consumers who were only previously exposed to the 200 mg strength. In this study, 95.2% of users exhibited correct or acceptable behaviour with respect to adhering to a total daily ibuprofen dose of no more than 1200 mg/day. In terms of not taking more than a single 400 mg tablet at one time, 84.4% of participants exhibited correct or acceptable behaviour. Amongst those who took greater than 1 tablet per dose, 60% were aware that the package directions was to only take a single tablet at a time, and the most common reason for this behaviour was a desire for greater pain relief.(16) Hence, one could assume that for these people, a higher dose would have also been taken if they were using another analgesic such as regular ibuprofen (200 mg).

This potential for dosage confusion is mitigated by the product name Nurofen 400 DOUBLE STRENGTH which clearly calls out that this product has twice the amount of the active ingredient versus the regular Nurofen product. In addition, the proposed amendments to the label for Nurofen 400 DOUBLE STRENGTH (see Appendix 1 and Figures 1 and 2 below) which include changes to the design elements on the front pack, will further mitigate the risk of potential dosing confusion:

- Ibuprofen 400 mg is also clearly listed on front of pack directly under the brand name.
- The front of the NUROFEN 400 DOUBLE STRENGTH pack calls out that it is a single tablet dose.
- A single tablet is pictured on the Nurofen 400 DOUBLE STRENGTH pack vs two tablets pictured on the regular Nurofen formulation.

Figure 1: Proposed front of pack for Pharmacy Only Nurofen 400 DOUBLE STRENGTH

Figure 2: Front of pack for Pharmacy Only Nurofen 200 mg



The availability of “extra strength” or “double strength” products alongside the regular strength products for self-selection is something that consumers are accustomed to seeing and would not be unique to ibuprofen. Other self-selection examples include:

- Aspro Clear Regular Strength 300 mg and Extra Strength 500 mg, which are available for general sale as Unscheduled medicines
- Zantac 150 mg and Zantac Double Strength 300 mg tablets which are available as Pharmacy Only medicines. Zantac also has a difference in posology between the regular strength 150mg (1-2 tablets) versus double strength 300mg (1 tablet). There is no evidence that this has caused confusion amongst consumers.

The availability of Aspro Clear is most relevant to this application as the product indications are essentially the same as for ibuprofen, that is for acute pain and fever. However, it is well established that the safety profile of OTC aspirin is inferior to that of ibuprofen.(8) Hence, any risk of taking the incorrect dose would be magnified if this was to occur with aspirin relative to ibuprofen. The posology of these two products is also different with Aspro Clear Extra Strength (500 mg) stating that 1-2 tablets to be dissolved in water while Aspro Clear Regular Strength (300 mg) requiring 3-4 tablets to be dissolved in water. Both strengths of Aspro Clear are available for general sale, with maximum pack size of 24 for the regular strength and 16 for the extra strength and where there is no opportunity for pharmacist intervention. This switch application proposes to make 400 mg ibuprofen Pharmacy Only and to limit the pack size to 12 tablets per pack .

The clinical implications of taking the incorrect dose with Pharmacy Only availability ibuprofen 400 mg in pack sizes limited to 12 dose units or less, is likely to pose minimal risk of harm. If a consumer did take the incorrect dose that is 2 x 400 mg tablets every 4 to 6 hours (maximum 6 tablets in 24 hours) as per the instructions for regular strength Nurofen, this would limit use to 2 days. Therefore, the period of exposure to the higher dose is restricted and this amount of ibuprofen over a short period of time is unlikely to result in harm, since this amount is a current approved prescription dose of ibuprofen and is well below that expected to cause side effects. From an analysis of acute overdoses a person would need to take 100 to 400mg/kg ibuprofen to cause mild side effects, and over 400mg/kg to cause moderate to severe effects.(12) As previously stated, taking the entire proposed Pharmacy Only pack of Nurofen 400 DOUBLE STRENGTH equates to 4800 mg of ibuprofen. For the average 70 kg adult this represents a non-toxic dose of 68.6 mg/kg.(12)

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.(6)

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 25 April 2020.(22) In addition, data from the Reckitt Benckiser PSUR for the period from 19 February 1969 to 31 October 2019 reported 171 cases of accidental overdose from over 7.5 billion patient exposures.(15)

Import considerations

This reclassification to Pharmacy Only would not impact any import considerations. Please note that an equivalent application for reclassification has been applied for in Australia and will be considered by the Advisory Committee on Medicines Scheduling at the June 2020 meeting.

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.

The public health benefits of having a small pack (limited to no more than 12 dose units) of ibuprofen 400 mg as a Pharmacy Only medicine is broader than the convenience of and preference for taking fewer tablets. There is a need for more self-select OTC treatments to manage strong pain, with the upcoming implementation of the rescheduling of all codeine-based analgesics to Prescription medicines.(17) Ibuprofen 400 mg represents a more effective analgesic option than ibuprofen 200 mg(1, 2) with equivalent tolerability.(1, 3) Ibuprofen 400 mg has been demonstrated to be 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.(4, 5) As the vast majority of Nurofen users report taking the 400 mg dose (taking 2 x 200 mg),(13, 14) the proposed switch of 400 mg ibuprofen to Pharmacy Only aligns with current patterns of use by consumers and as such fills the consumer need. Ibuprofen 400mg has a favourable risk-benefit profile one which is better than other OTC NSAIDs and paracetamol.(6) It has a wide therapeutic index with minimal to no risk of overdose. Approximately 1 in 6 pharmacy customers have difficulty swallowing oral medications,(7) and having the option to take one small 400mg tablet will provide these people the benefit of taking fewer tablets to help manage their pain.

Pain is a personal and individual experience. The most commonly used dose of regular 200 mg ibuprofen is two x 200 mg (400 mg).(13, 14) It is expected that the majority people using the Nurofen 400 DOUBLE STRNGTH presentation are doing so to manage strong pain.(13) Thus, in the vast majority of cases the 400 mg dose will be the correct dose and the 200 mg dose would be inadequate. This is supported by consumer research that indicates that the 200 mg was considered a sufficient dose only by a minority of people and most people used

two x 200 mg.(13, 14) Therefore, risk of unnecessary use of a higher ibuprofen dose is likely to be low and an infrequent occurrence. If it was to occur the risk of harm associated with this use is expected to be negligible as the acute safety profile of the 400 mg dose is equivalent to the 200 mg dose.(1, 3)

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.(1, 3) 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.(10) 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.(9)

The labelling proposed makes it clear that Nurofen 400 DOUBLE STRENGTH contains more (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.

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 day's exposure than other Pharmacy Only NSAIDs and paracetamol and equivalent patient exposure to Unscheduled ibuprofen. (See Table 9) Given that that OTC ibuprofen has a favourable risk-benefit profile compared to these other analgesic options.(6)
The proposed reclassification is appropriate and poses negligible change in risk.

Table 9: Relative exposure to self-selection analgesics

Analgesic	Classification	Maximum pack size	Patient exposure (day's 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 scheduling 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 day's 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.(12)

To minimise the risk of taking the incorrect dose, the proposed Pharmacy Only label has been modified to include multiple indicators that the 400 mg product is double strength and that the correct dose is one tablet. (See Part B Section 7 Medication errors)

The ability of consumers to correctly use ibuprofen double strength 400 mg has been assessed in a US study (Meeves 2017). In this study, 95.2% of users exhibited correct or acceptable behaviour with respect to adhering to a total daily ibuprofen dose of no more than 1200 mg/day.(16) In addition, global use of the double strength formulations has not resulted in any signals of a change in the risk-benefit profile of ibuprofen.(15)

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 an effective OTC treatment for strong pain, that is more effective than ibuprofen 200 mg with equivalent tolerability.(1, 3) The 400 mg ibuprofen dose is the most commonly used dose of ibuprofen to manage pain, hence one tablet containing 400 mg offers convenience.(13) The one tablet posology is also more suitable for the 1 in 6 people who have difficulty swallowing oral medicines(7) and for those who prefer to take fewer tablets.

Ibuprofen 400 mg 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.(6)

The proposed labelling makes it clear that Nurofen 400 DOUBLE STRENGTH contains more (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 availability of Nurofen 400 DOUBLE STRENGTH in limited pack sizes (≤ 12 dose units) as a Pharmacy Only medicine will benefit consumers without altering overall medication usage patterns or the excellent safety of OTC ibuprofen.

References

1. Moore RA, Wiffen PJ, Derry S, Maguire T, Roy YM, Tyrrell L. Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2015(11):CD010794.
2. Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. Cochrane Database Syst Rev. 2009(3):CD001548.
3. Moore RA, Derry S, Aldington D, Wiffen PJ. Adverse events associated with single dose oral analgesics for acute postoperative pain in adults - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2015(10):CD011407.
4. Mehlisch DR, Aspley S, Daniels SE, Southerden KA, Christensen KS. A single-tablet fixed-dose combination of racemic ibuprofen/paracetamol in the management of moderate to severe postoperative dental pain in adult and adolescent patients: a multicenter, two-stage, randomized, double-blind, parallel-group, placebo-controlled, factorial study. Clin Ther. 2010;32(6):1033-49.
5. Thybo KH, Hagi-Pedersen D, Dahl JB, Wetterslev J, Nersesjan M, Jakobsen JC, et al. Effect of Combination of Paracetamol (Acetaminophen) and Ibuprofen vs Either Alone on Patient-Controlled Morphine Consumption in the First 24 Hours After Total Hip Arthroplasty: The PANSAID Randomized Clinical Trial. JAMA. 2019;321(6):562-71.
6. Moore A CA, Ng B, Phillips LD, Sancak Ö, Rainsford KD. Use of multi-criteria decision analysis (MCDA) for assessing the benefit and risk of OTC analgesics. J Pharm and Pharmacol. 2017(ISSN 2042-7158.).
7. Lau ETL, Steadman KJ, Mak M, Cichero JAY, Nissen LM. Prevalence of swallowing difficulties and medication modification in customers of community pharmacists. Journal of Pharmacy Practice and Research. 2015;45(1):18-23.
8. Moore N, Van Ganse E, Le Parc JM, Wall R, Schneid H, Farhan M, Verrière F, Pelen F. The PAIN Study: Paracetamol, Aspirin and Ibuprofen new tolerability study a large-scale, randomised clinical trial comparing the tolerability of aspirin, ibuprofen and paracetamol for short-term analgesia. Clin Drug Invest. 1999;18(2):89-98.
9. Medsafe. Ibuprofen and Cardiovascular Risk. Prescriber Update. 2015;36(3):42.
10. White WB, Kloner RA, Angiolillo DJ, Davidson MH. Cardiorenal Safety of OTC Analgesics. J Cardiovasc Pharmacol Ther. 2018;23(2):103-18.
11. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med. 2011;8(9):e1001098.
12. Volans G, Monaghan J, Colbridge M. Ibuprofen overdose. IJCP. 2003;Sup 135:54-60.
13. Reckitt Benckiser. Data on File, Nurofen 400 DOUBLE STRENGTH Omnibus. 2020.
14. Reckitt Benckiser. UK Data on File, Waterfall Omnibus. 2009.
15. Reckitt Benckiser. Periodic Safety Update Report - Ibuprofen. 2020.
16. Meeves S, Leyva R, Richardson C, Wilson B, Savastano DM. Actual use of and adherence to ibuprofen 400 mg tablet dosing instructions in a simulated OTC environment. Int J Clin Pharmacol Ther. 2017;55(7):547-57.
17. Mishriky J, Stupans I, Chan V. Pharmacists' views on the upscheduling of codeine-containing analgesics to 'prescription only' medicines in Australia. Int J Clin Pharm. 2019;41(2):538-45.
18. Daniels SE, Goulder MA, Aspley S, Reader S. A randomised, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. Pain. 2011;152(3):632-42.
19. Marquis J, Schneider MP, Payot V, Cordonier AC, Bugnon O, Hersberger KE, et al. Swallowing difficulties with oral drugs among polypharmacy patients attending community pharmacies. Int J Clin Pharm. 2013;35(6):1130-6.
20. Nguyen T LE, Steadman KJ, Cichero JAY, Dingle K, Nissen LM. Pharmacist, general practitioner, and nurse perceptions, experiences, and knowledge of medication dosage form modification. Integrated Pharmacy Research and Practice. 2014;3:1-9.

21. Reckitt Benckiser. NUROFEN 400 Double Strength Data Sheet. 2018.
22. Medsafe. Suspected Medicine Adverse Reaction Search - Ibuprofen. 2020.
23. Therapeutic Goods Administration. Database of adverse event notifications - medicines. 2020.
24. Cairns R, Brown JA, Wylie CE, Dawson AH, Isbister GK, Buckley NA. Paracetamol poisoning-related hospital admissions and deaths in Australia, 2004-2017. Med J Aust. 2019;211(5):218-23.
25. Frei MY, Nielsen S, Dobbin MD, Tobin CL. Serious morbidity associated with misuse of over-the-counter codeine-ibuprofen analgesics: a series of 27 cases. Med J Aust. 2010;193(5):294-6.

Appendix 1: Labelling

Proposed label for Schedule 2 Nurofen 400 DOUBLE STRENGTH

MEDICINE INFORMATION

ACTIVE INGREDIENT (PER TABLET):

Ibuprofen 400mg

WHAT THIS MEDICINE IS USED FOR:

For the temporary relief of pain and/or inflammation associated with:
- headache
- migraine headache
- tension headache
- muscular pain
- cold & flu symptoms
- period pain
- dental pain
- sinus pain
- back pain
- arthritic pain
- 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 give to children under 12 years of age.

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

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:
1 tablet every 4 to 6 hours as necessary (Maximum 3 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

9 300711 852495 >

(B)
EXP:

PRINT FREE

0318011

NUROFEN®
400 DOUBLE STRENGTH
12 TABLETS

EFFECTIVE RELIEF FROM PAIN

12 TABLETS
NUROFEN®
400 DOUBLE STRENGTH

PHARMACY MEDICINE
KEEP OUT OF REACH OF CHILDREN

NUROFEN®
400 DOUBLE STRENGTH
Ibuprofen 400mg

12 TABLETS

AUST R 141996

EFFECTIVE RELIEF FROM PAIN INCLUDING:
- OSTEOARTHRITIS
- MUSCULAR & BACK PAIN
- GENERAL PAIN

1 TABLET DOSE

NUROFEN®
400 DOUBLE STRENGTH
12 TABLETS

HEALTH • HYGIENE • HOME

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

Pharmacode Reads This Way
First Bar
Last Bar

X60SN

Current label of Schedule 2 regular Nurofen 200 mg tablets

Ink & varnish free area

MEDICINE INFORMATION

ACTIVE INGREDIENT (PER 1 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

Ⓑ
EXP:

PRINT FREE

3048941

NUROFEN®
48 TABLETS

EFFECTIVE RELIEF FROM PAIN

PHARMACY MEDICINE
KEEP OUT OF REACH OF CHILDREN

NUROFEN®
Ibuprofen 200mg

48 TABLETS

AUST R 127272

EFFECTIVE RELIEF FROM PAIN

NUROFEN®
48 TABLETS

9 300711 055155 >

NUROFEN®
48 TABLETS

HEALTH • HYGIENE • HOME

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