Reclassification of a Medicine for consideration by the Medicine Classification Committee

Application for the reclassification of ibuprofen 300 mg in powder form from Prescription Medicine to Pharmacist Only Medicine

13 August 2021

Submitted by:

AFT Pharmaceuticals Ltd

Level 1, 129 Hurstmere Road, Takapuna, Auckland 0622, New Zealand

Once completed, this application should be sent to committees@moh.govt.nz by the deadline indicated on the Dates and Deadlines page on the Medsafe website.
By submitting this form, you are confirming that all information is true and accurate, and understand that this information and any appendices and/or supporting information that is not considered commercially confidential under the Official Information Act 1982 criteria will be published on the Medsafe website.

Contents

Executive summary 3

Part A 7

1. International Non-proprietary Name of the medicine. 7
2. Proprietary name(s) 7
3. Name and contact details of the company / organisation / individual requesting a reclassification. 7
4. Dose form(s) and strength(s) for which a change is sought 7
5. Pack size, storage conditions and other qualifications. 7
6. Indications for which change is sought. 8
7. Present classification of the medicine 8
8. Classification sought 9
9. Classification status in other countries (especially Australia, UK, USA, Canada). 10
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) 10
12. Labelling or draft labelling for the proposed new presentation(s) 10
13. Proposed warning statements (if applicable). 11
14. Other products containing the same active ingredient(s) and which would be affected by the proposed change 12

Part B 12

1. Indications and dose 12
2. Presentation 13
3. Consumer benefits 14
4. Contraindications and precautions 17
5. Undesirable effects 21
6. Overdose 22
7. Medication errors and abuse/misuse potential 24
8. Communal harm and / or benefit 25
9. Integrated benefit-risk statement 25
10. Risk mitigating strategies 26

Appendix 1 30

Maxigesic® Cold & Flu Hot Drink Double Strength powder for oral liquid -carton 12 sachets 30

Maxigesic® Cold & Flu Hot Drink Double Strength powder for oral liquid - sachet 30

Maxigesic® Cold & Flu Hot Drink powder for oral liquid -carton 24 sachets 30

Maxigesic® Cold & Flu Hot Drink powder for oral liquid - sachet 30

Executive summary

AFT Pharmaceuticals submitted a previous reclassification proposal to the 66th Medsafe Classification Committee meeting which proposed the reclassification of ibuprofen 300mg in powder form, from a Prescription Medicine to a Pharmacy Only medicine. The committee rejected this proposal in part due to the lack of market experience of ibuprofen presented in sachet form. However, the Committee indicated a willingness to consider restricted medicine as an alternative classification given that an interaction with a pharmacist would allow a consumer to receive advice and understand the risks associated with this dosage form. The following therefore presents a modified resubmission of this original proposal with the request for reclassification from Prescription Medicine to Pharmacist Only medicine.

This application seeks the reclassification of 300mg of ibuprofen in powder form, for use in the fixed dose combination of paracetamol/ibuprofen (1000mg/300mg; powder in sachets) to be dissolved for a hot drink formulation and used for the management of cold and flu symptoms. Packs will contain no more than 12 dose units (sachets) when sold in the manufacturer's original pack and will be labelled for use by adults and children over 12 years of age. We request the reclassification of ibuprofen 300mg in powder form from a Prescription Medicine to a Pharmacist Only Medicine. *Larger pack sizes containing 13 to 50 dose units (sachets) are to remain as a Prescription Medicine and are not the subject of this application.*

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) which works by inhibiting the enzyme cyclooxygenase (COX) which acts to reduce inflammation, relieve pain, and reduce fever. Ibuprofen has been used for decades (first available in New Zealand in 1975) and is one of the most commonly used NSAIDs around the world. Ibuprofen has been available for General Sale for many years and has the most extensive safety profile of all the NSAIDs, which have been on the market for the longest time. While there are several documented risks and contraindications for NSAID use, these risks are still considered to be very low, and many hundreds of millions of doses of ibuprofen are taken each year for the relief of pain. Maximum daily doses recommended for OTC use are 1200 mg/day but higher doses (up to 2400mg) are common under prescription and medical supervision.

The full dose of the *Maxigesic*® fixed dose combination of paracetamol and ibuprofen (1000mg and 300mg, respectively) has been shown to be a safe and effective analgesic that is more effective than either of the single active-ingredients alone. As a line extension of the *Maxigesic*® film-coated tablet range we have developed a hot drink formulation which is dedicated to the easier management of cold and flu symptoms; *Maxigesic*® *Cold & Flu Hot Drink* and *Maxigesic*® *Cold & Flu Hot Drink Double Strength*.

Our proposed dosage of the *Maxigesic*® *Cold & Flu Hot Drink* (containing 500mg paracetamol and 150mg ibuprofen) is 1 or 2 sachets per dose, to be in line with the posology for the *Maxigesic*® film-coated tablet which also has dosage instructions of 1 – 2 tablets per dose. We are requesting the reclassification of ibuprofen powder to allow for 300mg of ibuprofen powder to be contained per single dose unit (sachet) such that we can offer *Maxigesic*® *Cold & Flu Hot Drink Double Strength* sachets (containing 1000mg paracetamol and 300mg ibuprofen) which will contain the same effective dosage as taking the full dose of two sachets of *Maxigesic*® *Cold & Flu Hot Drink* or two tablets of the *Maxigesic*®-film coated tablets. We believe that this will provide consumers with an additional option for the relief of moderate to strong pain typically experienced by patients with cold and flu symptoms, in a more convenient formulation for when a hot drink formulation is preferred, and since the maximum daily dose of ibuprofen remains the same, offers no additional risk to the consumer.

The public health benefits of having a small pack (limited to no more than 12 dose units) of ibuprofen (300 mg in powder form) in a hot drink available as Pharmacist Only is however broader than the simple convenience of and preference for taking fewer sachets or tablets. The recent reclassification of all codeine-based analgesics in New Zealand to prescription medicines will also create a consumer need for alternative easily accessible analgesics to manage strong pain. The 300 mg ibuprofen powder used in the fixed combination of paracetamol/ibuprofen within *Maxigesic® Cold & Flu Hot Drink Double Strength* sachets are likely to be used by people seeking relief of moderate to strong pain associated with cold and flu symptoms, such as headaches or sore throat (Moore et al., 1999, 2002). The *Maxigesic®* formulation at the full dose (1000mg/300mg with 2 tablets of 500mg/150mg), has in clinical trials been shown to provide more effective pain relief than either component alone (Merry et al., 2010; Daniels et.al, 2018).

In addition, approximately 1 in 6 customers of retail pharmacies have difficulty swallowing oral solid medications. For the 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. In fact, this issue is expected to be amplified in a patient with a sore throat as is typically experienced with cold and flu symptoms. For these people, the benefit of taking the full dose of the medication in the powder form dissolved in water is meaningful and is not adequately addressed by the current scheduling as swallowing difficulties of oral solid formulations are not commonly discussed. We believe the offering a single product that provides adequate pain relief in situations where a hot drink formulation is preferred will decrease the need for consumers to seek additional or alternative forms or doses of pain relief and decrease the risk of double dosing with other products or formulations.

With regards to the safety profile, the maximum daily dose of ibuprofen for a Pharmacy Only or OTC product is 1200 mg per day. OTC ibuprofen (at doses ≤ 1200 mg/day) is well tolerated and when taken as directed has a gastrointestinal safety profile equivalent to paracetamol and superior to aspirin (Moore et al., 1999). 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 (Moore et al., 2017). With this reclassification we do not propose any changes to the maximum daily dose of ibuprofen, and the same maximum daily dose of 1200 mg of ibuprofen will be used for the *Maxigesic® Cold & Flu Hot Drink* (containing 150mg ibuprofen per sachet) and *Maxigesic® Cold & Flu Hot Drink Double Strength* (containing 300 mg ibuprofen per sachet). The pack size for ibuprofen powder at 300mg will be limited to a 4 day's supply (12 sachets per package), clearly labelled to indicate that the product is 'Double Strength', and will indicate not to consume more than the maximum daily dose of 1200 mg of ibuprofen per day. Also, the abuse potential for analgesic products has been closely related to its dosage form and there is a lack of evidence to suggest that powder formulations are misused. Multiple doses of powder would require the consumption of a large volume (many individual glasses) of liquid. Given the impracticalities of consuming multiple sachets at once for intentional or unintentional misuse, we believe that this powdered formulation does not present any greater risk to the consumer. Purchase behaviour is also considered to be different for cold and flu products where it is expected that the consumer will episodically purchase cold and flu products, as compared with continuous purchasing behaviour for regular pain medication which can lead to stockpiling of products and subsequent availability for misuse.

We believe that ibuprofen 300 mg in a powder form is appropriate for inclusion as a - Pharmacist Only medicine as it is considered to be one of the safest NSAIDs when used at the maximum daily dose of 1200mg or less. Ibuprofen at this full dose (300mg) combined with the full dose of paracetamol (1000mg) has been shown to be more effective than either single components alone. There is currently precedent for allowing the availability of 300 mg of ibuprofen in powder form per dose unit. Firstly, ibuprofen has a superior risk-benefit profile compared to paracetamol, and paracetamol at 1000mg per dose unit is already available in

powder form for both General Sale and as Pharmacy Only medicine in New Zealand. These sachets are often dosed with a single sachet therefore consumers are already familiar with taking a single sachet per dose. Secondly, a significant number of European countries have already introduced ibuprofen in powder form in doses up to 400mg as a Pharmacy Only medicine *(see section A.9 of the application)* and *Maxigesic® Cold & Flu Hot Drink Double Strength* (containing 300 mg ibuprofen per sachet) has been approved in Australia as a Pharmacist Only medicine. Thirdly, consumers are accustomed to seeing higher strength formulations at the pharmacy *(see section B.4, point 4 of the application*). Finally, within the pharmacy environment and with pharmacist interactions, additional information and guidance on appropriate product usage is available. With clear dosage instructions on the packaging to not exceed the maximum daily dose, we believe there is minimal additional risk to providing this commonly used dose of ibuprofen within a single sachet unit. Improving the availability of 300 mg ibuprofen in powder form in the fixed combination of paracetamol/ibuprofen by permitting classification as a Pharmacist Only medicine will provide consumers with an effective option which also has a very good benefit risk profile to relieve strong pain.

Previous literature demonstrates that doses of ibuprofen at a maximum of 1200 mg per day or less were not associated with an increased risk of cardiovascular events. (McGettigan & Henry, 2011; White et al., 2018). These reviews demonstrated that there is little risk of cardiovascular adverse events when used as per the product label and low-dose ibuprofen (i.e. OTC dose of 1200mg) appears to be free of cardiovascular risk and is one of the NSAIDs least likely to increase cardiovascular risk. Given the sachets containing ibuprofen powder at 300mg will have clear labelling identifying that the product is 'Double Strength' and not to consume more than 4 sachets per day (1200mg), there should be no additional risks for providing this dose within a single sachet.

Overall, the evidence enclosed in this submission demonstrates that ibuprofen 300 mg in the fixed combination of paracetamol/ibuprofen (1000mg/300mg) in primary packs limited to 12 dose units or less, is suitable for reclassification to a Pharmacist Only medicine:

- The approved indications for ibuprofen 300 mg are the same as that for regular ibuprofen 150 mg in the fixed combination of paracetamol/ibuprofen (500mg/150mg), 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 easily identified by the pharmacist who can offer guidance on appropriate product usage.
- Ibuprofen 300 mg with a maximum daily dose of 1200 mg (and limited to 12 sachets) has the same excellent safety profile as 150 mg ibuprofen in the fixed combination of paracetamol/ibuprofen (500mg/150mg).
- Pharmacist Only ibuprofen is restricted for oral use (tablets or capsules) up to 400 milligrams per dose form and in packs containing not more than 50 dose units. Therefore, the proposed reclassification would offer ibuprofen at a lower, yet still effective, dose compared to what is currently available in pharmacies, however in an alternative dose form.
- 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. This toxic dosage per kg is significantly more than the 3600 mg contained within a 12 sachet pack of *Maxigesic® Cold & Flu Hot Drink Double Strength* powder for oral liquid.
- Safety in at risk populations is effectively addressed by product labelling, and the proposed changes to the Pharmacist Only label for *Maxigesic® Cold & Flu Hot Drink Double Strength* powder for oral liquid, mitigate the risk of dosing confusion.

- The full dose of the *Maxigesic*® formulation contains 300 mg of ibuprofen (two film-coated tablets of 150 mg ibuprofen each, or two sachets of *Maxigesic*® *Cold & Flu Hot Drink* powder for oral liquid, each containing 150 mg ibuprofen each) hence availability of the 300 mg dose in a single sachet matches consumer choice of dosing to other products that are available as OTC or Pharmacy Only and is unlikely to alter overall medication usage.

Part A

1. International Non-proprietary Name of the medicine.

Ibuprofen (in the fixed combination of paracetamol/ibuprofen)

2. Proprietary name(s).

Maxigesic® Cold & Flu Hot Drink Double Strength powder for oral liquid in sachet

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

[redacted]
AFT Pharmaceuticals Ltd
PO Box 33203
Takapuna
Auckland 0740
[redacted]
AFT Pharmaceuticals Ltd
Level 1, 129 Hurstmere Road
Takapuna
Auckland 0622

Note: Contact details will be removed from the form prior to publication on the Medsafe website.

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

Dose form of the product: Powder 300mg ibuprofen (as lysine) in the fixed combination of paracetamol/ibuprofen.

5. Pack size, storage conditions and other qualifications.

Pack size: Up to 12 dose units - Sachets 300mg of ibuprofen (as lysine) powder in the fixed combination of paracetamol/ibuprofen, Storage below 30°C.

Qualifications: for oral use in powder form in the fixed combination of paracetamol/ibuprofen (containing up to 300 milligrams of ibuprofen (as lysine) powder per dose). The recommended daily dose of ibuprofen is not more than 1200mg and this product will be in packs containing not more than 12 dose units when sold in the manufacturer's original pack. Packs will be labelled for use by adults and children over 12 years of age.

Note, this application is not proposing any changes to the classification of ibuprofen 300 mg in larger pack sizes 13 to 50 dose units. These medicines are to remain unchanged as Prescription Medicines. Our product, Maxigesic® Cold & Flu Hot Drink Double Strength sachets will also contain 1000 mg of paracetamol to provide a fixed dose combination of 1000 mg paracetamol and 300 mg of ibuprofen (as lysine) per sachet.

6. Indications for which change is sought.

Maxigesic® Cold & Flu Hot Drink Double Strength (1000 mg paracetamol and **300 mg ibuprofen powder**) is indicated for the temporary relief of pain associated with: headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, sore throat, arthritis, tennis elbow, period pain, muscular pain, rheumatic pain, aches and pains associated with colds and flu. Reduces fever.

7. Present classification of the medicine.

The current classification of ibuprofen is summarised in Table 1.
Prescription. There is currently no classification for ibuprofen 300 mg in powder form. Ibuprofen in other formulations dosed at 200 mg (tablets and liquid form) has a maximum daily dose of 1200 mg is classified as General Sale and Pharmacy Only in New Zealand.

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.

Pharmacist only.

The classification sought is Pharmacist Only medicine, for oral use in powder form containing up to 300 milligrams of ibuprofen (as lysine) per dose. The recommended daily dose will be not more than 1.2 grams and will be in packs containing not more than 12 dose units when sold in the manufacturer's original pack. Packs will be 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 for oral use in powder form containing 300 milligrams per dose form with a recommended daily dose of not more than 1.2 grams, and sold in the manufacturers original packs containing not more than 12 dose units, and 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

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

Australia: Pharmacist Only Medicine
Germany, Belgium, France, Czech Republic: Pharmacy Only Medicine (Ibuflam 400mg powder).
UK, Sweden, Austria, Belgium, Bulgaria, Estonia, Spain, Hungary, Ireland, Slovakia, Slovenia, Romania, Netherlands, Luxemburg, Lithuania: Pharmacy Only Medicine (Brufen 400mg Effervescent granules)

Canada: Health Canada regulates ibuprofen in strengths of 200 mg, 300 mg and 400 mg as over-the-counter medicines. (Not available in powder form)

US: ibuprofen not available in powder form.

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

Maxigesic® Cold & Flu Hot Drink Double Strength powder for oral liquid has been recently approved in Australia on 07 Apr 2021 as a Pharmacist Only medicine.

Maxigesic® Cold & Flu Hot Drink Double Strength powder for oral liquid is not yet marketed in Australia and New Zealand.

Our High-level estimates for Australia in terms of sachets is as following:

[redacted]

Our High-level estimates for New Zealand in terms of sachets is as following:

[redacted]

Maxigesic® Cold & Flu Hot Drink Double Strength powder for oral liquid is dedicated to provide help with maintaining cold and flu symptoms therefore the main sale would be expected during winter season in New Zealand when the number of cold and flu cases is highest.

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).

A copy of the proposed Pharmacist Only label is included in Appendix 1 as well as copy of the current Pharmacy Only label for regular *Maxigesic® Cold & Flu Hot Drink* powder for oral liquid in sachet (for the purpose of comparison).

The label is clearly differentiated from the regular strength *Maxigesic® Cold & Flu Hot Drink* powder for oral liquid in sachet and makes it clear that *Maxigesic® Cold & Flu Hot Drink Double Strength* powder for oral liquid in sachet is a 'Double Strength' formulation, hence containing twice the amount of active ingredient vs. regular *Maxigesic® Cold & Flu Hot Drink* powder for oral liquid in sachet. There are three main components on the front panel and side panels which differ between the carton artwork for the regular and double strength product: different colour of the cup background, different colour of border spikes, and the bolded statement "DOUBLE STRENGTH" in red print on the light blue background. We believe these differences will be very obvious to the consumer and pharmacist. Furthermore, the individual sachet unit for the double strength product contains additional warning "Do not use more than 1 sachet per dose" (in bold print). Therefore, with these differences there is minimal risk of confusion for the customer between these two dose strengths.

13. Proposed warning statements (if applicable).

Maxigesic® Cold & Flu Hot Drink Double Strength powder for oral liquid [ibuprofen (as lysine) 300mg] in sachet has the same warning statements as that required for regular *Maxigesic® Cold & Flu Hot Drink* powder for oral liquid [ibuprofen (as lysine) 150mg} in sachet. (See Appendix 1).

Except for differences in dose strength and dosing directions, the back of pack medicines information panel for *Maxigesic® Cold & Flu Hot Drink Double Strength* powder for oral liquid in sachet ibuprofen 300 mg is essentially the same as that for regular *Maxigesic® Cold & Flu Hot Drink* powder for oral liquid in sachet ibuprofen 150 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. Therefore, given this is a label updated as per a Medsafe evaluator's request which meets the Medsafe labelling requirements it is reasonable to conclude that the current packaging and labelling for regular and double strength product effectively supports the quality and safe use of ibuprofen for selection under the pharmacist supervision.

Directions for use:

Maxigesic® Cold & Flu Hot Drink	***Maxigesic® Cold & Flu Hot Drink Double strength***
Adults and children over 12 years: 1 - 2 sachets every 4 - 6 hours, as required	Adults and children over 12 years: 1 sachet every 4 - 6 hours, as required.
Pour contents of 1 or 2 sachets into a mug and fill with hot, but not boiling water. Stir until dissolved.	Pour contents of 1 sachet into a mug and fill with hot, but not boiling water. Stir until dissolved.
Do not consume more than 8 sachets in 24 hours. Dissolved powder should be consumed immediately.	Do not consume more than 4 sachets in 24 hours. Dissolved powder should be consumed immediately.

Please note: the proposed warning statements relate specifically to the use of the fixed dose combination product Maxigesic® Cold & Flu Hot Drink Double Strength which contains two active ingredients, paracetamol 1000 mg and ibuprofen 300 mg (as lysine). Some of these warnings relate to the use of paracetamol, however will be present on the same product which also contains ibuprofen 300 mg in powder form.

Proposed Labelling

Warnings
Do not give to children under 12 years of age.
Do not exceed the maximum stated dose. Unless advised to by a doctor, adults should not take this medicine for longer than a few days at a time, and adolescents (12-17 years) should not take it for longer than 48 hours at a time.
Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.

Do not use if:
• you are pregnant or trying to become pregnant
• you have a stomach ulcer
• you have impaired kidney or liver function
• you have heart failure
• you are allergic to paracetamol, ibuprofen, aspirin or other anti-inflammatory medicines.
If you get an allergic reaction, stop taking and see your doctor immediately

Unless a doctor has told you to, do not use:
• if you have asthma
• if you are aged 65 years or over
• with other product containing paracetamol, ibuprofen, aspirin or other anti-inflammatory medicines, or with medicines that you are taking regularly.
If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.
Phenylketonurics are warned that this product contains aspartame (phenylalanine). It also contains sugars

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

N/A - Ibuprofen in powder form not available in NZ.

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?

The *Maxigesic® Cold & Flu Hot Drink Double Strength* containing 300 mg of ibuprofen (as lysine) is indicated for the temporary relief of pain associated with: headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, sore throat, arthritis, tennis elbow, period pain, muscular pain, rheumatic pain, aches and pains associated with colds and flu. Reduces fever. The reclassification of ibuprofen powder at 300 mg would apply to all of the above indications, and these are the same indications as the approved lower

dose of ibuprofen (150 mg) present in *Maxigesic® Cold & Flu Hot Drink*. These are common indications regularly treated with OTC pain-relief products and it is generally accepted that these short-term ailments are easily recognised by consumers and are unlikely to be confused with more serious conditions. We expect this product to be primarily aimed at people experiencing cold and flu symptoms such as sore throat, sinus pain, and headache and products for the treatment of these indications are appropriate and currently available for self-selection within a grocery and pharmacy environment.

Ibuprofen has been available for General Sale for many years has the most extensive safety monitoring record of all the NSAIDs having been on the market for the longest time. Considering the millions of doses of ibuprofen that are taken annually, the risks of severe reactions are very low and usually associated with either over dose, or with pre-existing conditions which enhance the susceptibility to a potential adverse effect of the drug. The *Maxigesic®* formulation utilises a ratio of paracetamol/ibuprofen that provides more effective pain relief than either the equivalent doses of paracetamol or ibuprofen alone, while minimising the dose of ibuprofen. This is consistent with the FDA guidance of using ibuprofen at the *"The lowest effective dose for the shortest duration consistent with individual patient treatment goals*" (FDA, 2005). One feature of this fixed-dose combination product containing both actives is that it avoids the opportunity for double drug confusion when supplementing paracetamol or ibuprofen with an additional active treatment when either of the drugs alone provides insufficient analgesia. This minimises the risk of accidently overdosing by supplementing with the same drug in a different packaging or having to take two different drugs on different time schedules. The dosing of the *Maxigesic®* formulation is simple with only one type of sachet required and administered at a single dosing regimen.

Above all, the dosage and labelling clearly advises the consumer to not exceed the approved maximum daily dose of ibuprofen approved internationally for OTC use. For *Maxigesic® Cold & Flu Hot Drink Double Strength* (containing 300 mg ibuprofen (as lysine) powder) the labelling advises patients should not consume more than 4 sachets in 24 hours, (thereby not exceeding 1200 mg per day).

The dose and dose frequency for this indication are as follows:
1 sachet every 4-6 hours, as required. Patients should not consume more than 4 sachets in 24 hours. Adults should not use *Maxigesic® Cold & Flu Hot Drink Double Strength* for more than a few days at a time, unless advised to by a doctor. Children and adolescents aged 12-18 years should not use *Maxigesic® Cold & Flu Hot Drink Double Strength* for longer than 48 hours at a time, unless advised to by a doctor. *Maxigesic® Cold & Flu Hot Drink Double Strength* is not recommended for children under 12 years.

The treatment population for the indications are adults and children over 12 years.

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 product for reclassification is ibuprofen in powder form at a dose of 300 mg. The ibuprofen powder (300 mg) will be packed in a sachet also containing 1000 mg of paracetamol for the *Maxigesic® Cold & Flu Hot Drink Double Strength* sachet product. This applies to all previously mentioned indications.

There are no special requirements for disposal recommended for the product.

The product is practical and easy to use. The product is in powder form and is to be dissolved in hot (not boiling) water and consumed immediately. The benefit of the presentation of the *Maxigesic® Cold & Flu Hot Drink Double Strength* product is that it would allow the consumer to receive the same dose of active ingredients in a single sachet as they would if they were consuming a full dose of either the approved fixed dose combination Maxigesic® tablets (500/150) or the maximum two sachets per dose of *Maxigesic® Cold & Flu Hot Drink* which is currently under evaluation. The *Maxigesic® Cold & Flu Hot Drink Double Strength* label clearly states that this product is 'Double Strength' and that only one sachet is required per dose. Consumers are accustomed to being able to obtain higher strength formulation in the pharmacy therefore the presentation of the product will be suitable for a pharmacist proposed selection as a Pharmacist Only medicine.

***In comparison, the posology for the Maxigesic® film coated tablets (500 mg paracetamol and ibuprofen 150 mg per tablet) is one to two tablets taken every four to six hours, up to a maximum of eight tablets (4000 mg paracetamol/1200 mg ibuprofen total) in 24 hours (for Adults and children over 12 years). Maxigesic® tablets are approved for OTC General Sale and Pharmacy Only sale in New Zealand.*

3. Consumer benefits

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

Ibuprofen has been used for decades (first available in New Zealand in 1975) and is one of the most commonly used NSAIDs around the world. Ibuprofen was the first drug of this class to be approved for OTC use in the UK in 1983 and the USA in 1984 and with widespread use, the efficacy and safety profiles are extensively reported and understood. While there are several documented risks and contraindications (see below in section B4), these risks are still considered to be very low, and many hundreds of millions of doses of ibuprofen are taken each year for the relief of pain. Maximum daily doses recommended for OTC use are 1200 mg/day but higher doses are common under prescription and medical supervision. 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 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.

Given its admirable safety record, ibuprofen was selected as the NSAID of choice for use in the fixed dose combination product *Maxigesic®* film coated tablet (paracetamol 500 mg and ibuprofen 150 mg) formulation. *Maxigesic®* was initially developed to provide more convenient and more effective product compared to using either paracetamol or ibuprofen alone. Physicians have supported the logic of paracetamol and ibuprofen combinations for many years by commonly co-prescribing the two drugs. Over 5 million co-prescriptions were made in the USA and UK in the 12 months to the end of 2007 (Table 1). This indicated a need recognised by practising doctors.

Table 1: IMS Medical Index Co-Prescription Data of paracetamol/ibuprofen by the end of 2007

Country	Approximate Population (Million) at end of 2007	Co-prescriptions	Co-prescriptions per million population
United Kingdom	60	1,448,083	24,134
USA	300	3,890,628	12,968
New Zealand	4	55,862	13,965
Australia	21	51,454	2450

Maxigesic® was launched in New Zealand in 2009 and as stated in the '*Maxigesic*® Periodic Safety Update Report' of August 2020 (AFT Pharmaceuticals, 2020), more than 370 million tablets have now been sold around the world (Australia, New Zealand, Italy, Nordic countries, UK, Israel, United Arab Emirates, Central America and Asia). *Maxigesic*® tablets have been registered for sale in 48 countries and has been classified as an OTC (either General Sale or Pharmacy Only) in 32 of these countries.

The Maxigesic® Cold & Flu Hot Drink (containing 150 mg ibuprofen powder) and *Maxigesic® Cold & Flu Hot Drink Double Strength* hot drink sachets, containing 300 mg ibuprofen powder, have been developed to extend the therapeutic advantage of *Maxigesic*® tablets to patients when administration in a hot drink form is preferred or clinically justified by a need to treat pain or fever primarily associated with cold and flu symptoms. The sachet and oral dose tablet forms *Maxigesic*® have been shown to be pharmacokinetically equivalent in terms of area under the plasma concentration-time curve (AUC) (Aitken et al., 2018). The lower dose *Maxigesic® Cold & Flu Hot Drink* (containing 150 mg of ibuprofen) would provide the equivalent of one *Maxigesic*® tablet, whereas *Maxigesic® Cold & Flu Hot Drink Double Strength* (containing 300 mg of ibuprofen) would provide the equivalent of a full dose of *Maxigesic*® tablets (2 tablets). The reclassification of ibuprofen at 300 mg in powder form to Pharmacist Only would therefore extend the robust clinical benefits of the existing *Maxigesic*® oral tablet formulation to patients where an oral liquid hot drink is preferable and if selected by the pharmacist would allow for the consumer to use the same dose as would be administered in the equivalent *Maxigesic*® tablet formulations while in a convenient single sachet formulation.

The benefit to the consumer of allowing pharmacist supported selection of the *Maxigesic® Cold & Flu Hot Drink Double Strength* containing 300 mg ibuprofen powder is therefore providing an equivalent product in a more convenient formulation.

Additionally, in a study in Australia it was reported that over 16.5% of consumers experienced difficulty swallowing solid dosage forms of medication such as tablets and capsules (Lau et al., 2015). It was also noted that it is common for these populations to make modifications to their medication dose forms which can result to unintentional alterations in dosing. Difficulties swallowing tablets is not exclusive to consumers with medicals conditions and is also not limited to people with dysphagia. It is also very common for patients to experience a sore throat and have difficulties swallowing when they have a cold or flu. **Therefore, an additional consumer benefit to the reclassification of ibuprofen 300 mg in powder form is that patients who have difficulties swallowing medicines for a variety of reasons could benefit from taking the same active ingredients and same equivalent doses in a hot drink formulation *Maxigesic® Cold & Flu Hot Drink Double Strength compared with a full dose of the already approved Maxigesic® film-coated tablets*.**

At this time of increasing regulatory concerns at the safety of drugs to relieve pain, the rationale for *Maxigesic® Cold & Flu Hot Drink Double Strength* sachets combination is robust and timely. The clinical trials conducted by AFT Pharmaceuticals with the oral fixed dose combination Maxigesic® product demonstrate that the efficacy of the fixed-dose combination (dosed at 1000 mg paracetamol and 300 mg ibuprofen) is superior to the two active drugs used on their own for the control of moderate to severe postoperative pain (Daniels et al., 2018; Atkinson et al.2015; Merry et al. 2010). Additionally, clinical studies with the fixed dose combination have

shown that the adverse effects of the combination drug product are similar to the individual active drugs (Aitken et al., 2019). The fixed-dose combination avoids the risks of increasing the dose of paracetamol consequently increasing the hazards of liver injury. It also reduces the need to combine either paracetamol or ibuprofen with an opioid, which is important given their side effects of constipation and dependence, and the recent reclassification of codeine in New Zealand. Addition of paracetamol to ibuprofen, in the form of *Maxigesic® Cold & Flu Hot Drink Double Strength* sachets, also adds to the efficacy of ibuprofen without having to increase the dose, which can increase the risk of gastric bleeding and thromboembolic events. **In summary, with the reclassification of ibuprofen powder at 300 mg, *Maxigesic® Cold & Flu Hot Drink Double Strength* sachets would deliver effective analgesia in cases where standard doses of primary drugs are inadequate, alongside an equivalent or superior safety profile. The *Maxigesic® Cold & Flu Hot Drink Double Strength sachets* would allow for an easy to consume formulation at the same strength as a full dose of currently approved fixed dose oral tablet formulation.**

4. Contraindications and precautions

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

There are no additional contraindications for the use of 300 mg ibuprofen powder over 150 mg ibuprofen powder. These warnings are the same as those present on the *Maxigesic® Cold & Flu Hot Drink* (containing 150 mg ibuprofen) and also on Maxigesic® film-coated tablets (for which a full dose is 300 mg of ibuprofen). *Please note also that since proposed warning statements relate specifically to the use of the fixed dose combination product which also contains paracetamol 1000 mg, some of these proposed warning relate to the use of paracetamol.*

Maxigesic® is contraindicated for use:

- in patients with known hypersensitivity to paracetamol, ibuprofen, aspirin, other NSAIDs or any other ingredients in the product;
- in patients with active alcoholism as chronic excessive alcohol ingestion may predispose patients to paracetamol hepatotoxicity (due to the paracetamol component);
- in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin, ibuprofen or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients
- in patients with active gastrointestinal bleeding, peptic ulceration or other stomach disorders;
- during pregnancy or in patients trying to become pregnant;
- in patients with impaired kidney function, impaired liver function or heart problems;
- in patients with heart failure;
- in patients undergoing treatment of perioperative pain in the setting of coronary artery bypass surgery (CABG).

− What are the precautions for this medicine and how easy are these to understand? − What class effects need to be considered and what are the risks?

The following is from the data-sheet for *Maxigesic® Cold & Flu Hot Drink* and *Maxigesic® Cold & Flu Hot Drink Double Strength.*

Maxigesic® Cold & Flu Hot Drink should not be taken with other products containing ibuprofen, paracetamol, aspirin, salicylates or with any other anti-inflammatory medicines unless under a doctor's instruction.

Gastrointestinal events

Upper gastrointestinal ulcers, gross bleeding or perforation have been described with NSAIDs. The risks increase with dose and duration of treatment, and are more common in patients over the age of 65 years. Some patients will experience dyspepsia, heartburn, nausea, stomach pain or diarrhoea. These risks are minimal when this product is used at the prescribed dose for a few days.

Maxigesic® Cold & Flu Hot Drink should be used with caution, and at the lowest effective dose for the shortest duration, in patients with a history of gastrointestinal haemorrhage or a history of peptic ulcers since their condition may be exacerbated. It is contraindicated in patients with active gastrointestinal bleeding and in those with peptic ulcers or other stomach disorders.

This product should be discontinued if there is any evidence of gastrointestinal bleeding.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Cardiovascular thrombotic events
Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk. *Maxigesic® Cold & Flu Hot Drink* is contraindicated in patients with heart problems.

Patients should be advised to remain alert for such cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Hypertension
Fluid retention, hypertension and oedema have been reported in association with NSAID therapy. NSAIDs may lead to onset of new hypertension or worsening of pre-existing hypertension and patients taking antihypertensive medicines with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing *Maxigesic®* to patients with hypertension. Blood pressure should be monitored closely during initiation of treatment with *Maxigesic® Cold & Flu Hot Drink* and at regular intervals thereafter.

Hepatic effects
As with other NSAIDs elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled trials in less than 1% of patients.

Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and “flu-like” symptoms). Excessive use can be harmful and increase the risk of liver damage.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics
The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients.

Severe skin reactions
NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Pre-existing asthma
Products containing ibuprofen should not be administered to patients with aspirin-sensitive asthma and should be used with caution in patients with pre-existing asthma.

Ophthalmological effects
Adverse ophthalmological effects have been observed with NSAIDs; accordingly, patients who develop visual disturbances during treatment with products containing ibuprofen should have an ophthalmological examination.

Aseptic meningitis
For products containing ibuprofen, aseptic meningitis has been reported only rarely, usually, but not always, in patients with systemic lupus erythematosus (SLE) or other connective tissue disorders.

Masking signs of infection
As with other drugs of this class containing ibuprofen, by reducing fever this may mask the usual signs of infection.

Haematological effects
Blood dyscrasias have been rarely reported. Patients on long-term therapy with ibuprofen should have regular haematological monitoring.

Coagulation defects
Like other NSAIDs, ibuprofen can inhibit platelet aggregation. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying haemostatic defects, ibuprofen should be used with caution in persons with intrinsic coagulation defects and those on anti-coagulation therapy.

Special precautions
In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

- Does the medicine have a low therapeutic index?

No, ibuprofen used either alone or in a fixed dose combination with paracetamol has a wide therapeutic index as evidenced by its long-standing excellent safety profile. The safety profiles of paracetamol and ibuprofen are well known and for each there is an extensive literature. Considering the millions of doses of ibuprofen that are taken annually, the risks of severe reactions are very low and usually associated with either over-dose, or with pre-existing conditions which enhance the susceptibility to a potential adverse effects of the drug, such as a peptic ulcer increasing the risk of gastro-intestinal bleeding with NSAIDs. There is no evidence to suggest that the safety profile or toxicity of ibuprofen has changed over time (see the latest Periodic Safety Update Report for *Maxigesic*® film-coated tablets for the period 1 Jan 2020 to 31st August 2020; AFT Pharmaceuticals, 2020). Since the product was launched in New Zealand and Australia (in 2009 and 2013 respectively), over 54 million tablets have been distributed in New Zealand, and over 96 million tablets have been distributed in Australia. Collectively since launch there have been only 6 Individual Case Safety Reports (ICSRs) received at AFT Pharmaceuticals from the New Zealand and Australian markets, including one serious case and five non-serious cases. Globally, over 370 million tablets have been distributed, and only 46 spontaneous ICSRs have been received by AFT, including 15 serious cases, none of which were classified as unexpected.

Since ibuprofen has a wide therapeutic index, toxicity would only be likely in situations of intentional overdose. Mild adverse effects may be observed at doses of 100 mg/kg with more serious effects occurring closer to or beyond 400 mg/kg. If a consumer was to take all 12 sachets of *Maxigesic® Cold & Flu Hot Drink Double Strength*, they would consume 3600 mg

of ibuprofen, and 12,000 mg of paracetamol. With this consumption, the 400 mg/kg dose of ibuprofen would only be reached in a person weighing 9kg, and a 70 kg adult would only reach a dose of 51mg/kg. Of more concern would be the consumption of paracetamol which would likely reach the threshold for potential paracetamol-induced hepatic injury in adults (>200 mg/kg within 24 hours) for those over 50kg. However, this being said, to date there have only been three reported cases from the global market of intentional misuse involving the fixed dose combination tablets, out of the 370 million tablets distributed globally.

This wide therapeutic range emphasises the relative safety for the reclassification of ibuprofen powder at 300 mg for use in the *Maxigesic® Cold & Flu Hot Drink Double Strength* Sachets.

− What are the risks of the medicine being used in an OTC environment?

In AFTs view, there is minimal risk associated with ibuprofen 300 mg powder being available as an OTC Pharmacy Only medicine when used in combination with 1000 mg of paracetamol for the following reasons:

- 300 mg of ibuprofen is the same amount of active ingredient used in the recommended full dose (2 tablets) of *Maxigesic*® film-coated tablets.
- The maximum dose as listed on the labelling of the *Maxigesic® Cold & Flu Hot Drink Double Strength* Sachets will state to not exceed 4 sachets within 24 hours. Therefore, despite using a higher single dose formulation, consumption should still not exceed the maximum recommended dose of ibuprofen of 1200 mg in 24 hours.
- 300 mg of ibuprofen in powder form is bioequivalent to the 300 mg of ibuprofen contained in a full dose (2 tablets) of *Maxigesic*® film-coated tablets.
- Additional advice and guidance on appropriate usage of the product is available within a Pharmacy environment.

Unlike conventional tablet formulations where consumers will often use 2 tablets, we expect that consumers are only likely to use a single sachet per cup of hot water. However additional risk may occur if consumers were to consume more than one Double Strength sachet at a time or consumed sachets more often than recommended. We intend to have both a limited pack size and clear labelling, and believe that if the product clearly says ‘Double Strength’ on the front panel, the consumers will understand that the product contains twice the active ingredient than the standard strength formulation.

Consumers are also accustomed to seeing double strength products alongside original strength products in the pharmacies, for example Pamol Double Strength, Paracare Double Strength suspension, Zantac Double Strength Tablet, and they understand that the dosing of these products is different. Moreover, the classifications of Pharmacist Only would ensure that professional healthcare advice and guidance for appropriate use will always be available at the point of sale, which would further mitigate any risk of consumer confusion between the products.

− What other drug interactions need to be considered?

The following interactions have been noted:

- anticoagulants, including warfarin: ibuprofen interferes with the stability of INR and may increase risk of severe bleeding and sometimes fatal haemorrhage, especially from the gastrointestinal tract. Ibuprofen should only be used in patients taking warfarin if absolutely necessary and they must be closely monitored.
- lithium: ibuprofen may decrease renal clearance and increase plasma concentration of lithium;

- ACE inhibitors, beta-blockers and diuretics: ibuprofen may reduce the anti-hypertensive effect of these drugs and may cause natriuresis and hyperkalaemia in patients under these treatments;
- methotrexate: ibuprofen reduces methotrexate clearance;
- cardiac glycosides: ibuprofen may increase the plasma levels of these drugs;
- corticosteroids: the risk of ibuprofen-induced gastrointestinal bleeding may be increased with concomitant use of oral corticosteroids;
- zidovudine: ibuprofen may prolong bleeding time in patients treated with this drug;
- probenecid, antidiabetic medicine and phenytoin: these medicines may interact with ibuprofen.

− What food and/or drink interactions need to be considered?

Ibuprofen can be taken with or without food. AFT Pharmaceuticals pharmacokinetic studies have demonstrated that in fasting conditions, the sachet formulation of ibuprofen (300 mg) has a higher C_{max} and shorter t_{max}, when compared to ibuprofen (300 mg) in the *Maxigesic*® film-coated tablet formulation, likely due to the nature of the dissolved sachet formulation skipping the disintegration and dissolution steps required by the tablet formulation. However, the sachet formulation is still bioequivalent to the tablet formulation in terms of AUC in both fasting and fed conditions therefore food/drink interactions do not need to be taken into consideration by the consumer.

− Are there any other restrictions when taking the medicine ie, driving restrictions or operating machinery?

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of product registration and there are no additional restrictions regarding the use of ibuprofen 300 mg in powder form.

− Are there any special populations where exposure to the medicine needs to be restricted?

Use in the elderly
No adjustment in labelled dosage is necessary for older patients who require paracetamol therapy. Those who require therapy for longer than a few days should consult their physician for condition monitoring; however, no reduction in recommended dosage is necessary. However, caution should be taken with regard to the use of ibuprofen as it should not be taken by adults over the age of 65 without consideration of co-morbidities and co-medications because of an increased risk of adverse effects, in particular heart failure, gastrointestinal ulceration and renal impairment

Paediatric use
Maxigesic® Cold & Flu Hot Drink is not recommended for children under 12 years

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?

Clinical trials with the fixed dose combination of paracetamol and ibuprofen (at a maximum daily dose of 4000mg paracetamol and 1200mg of ibuprofen) have not indicated any other undesirable effects other than those for paracetamol alone or ibuprofen alone.

Adverse effects with OTC or short-term use of ibuprofen are rare and may include:

- gastrointestinal – gastrointestinal bleeding, dyspepsia, heartburn, nausea, loss of appetite, stomach pain, diarrhoea; The risk of which is low at the maximum OTC dose of 1200 mg per 24 hours.
- central nervous system (CNS) – dizziness, fatigue, headache, nervousness;
- hypersensitivity reactions – skin rashes and itching. Rarely exfoliative dermatitis and epidermal necrolysis have been reported with ibuprofen;
- rare cases of photosensitivity;
- cardiovascular – risks of myocardial infarct and stroke. These risks are minimal at *Maxigesic® Cold & Flu Hot Drink* recommended OTC maximum daily doses. Risks increase with longer duration of treatment, and in the elderly. Fluid retention and in some cases, oedema have been reported with all NSAIDs. These effects are rare at the recommended OTC maximum dose of 1200 mg per 24 hours.

A meta-analysis of ibuprofen use and gastrointestinal bleeding has demonstrated that the risks of gastrointestinal bleeding after ibuprofen administration can be greater with higher doses (greater than 1200 mg) or long-term use, although the odds of experiencing gastrointestinal bleeding with doses <1200 mg is close to that of placebo (Lewis et al., 2002). However notably, even for longer administration ibuprofen is still considered to be one of the safest NSAIDs (Varrassi et al., 2020). Given *Maxigesic® Cold & Flu Hot Drink Double Strength* will be marketed as a Cold and Flu product, which are typically only required for 2 – 3 days at a time when cold and flu symptoms are most severe, and considering pack sizes will provide only enough for three days of dosing, the risks of experiencing more severe gastrointestinal symptoms with use of this product, is lowered. If reclassified, an interaction with a pharmacist would allow a consumer to receive advice and understand the risks associated with this dosage form. Additionally, all product labelling will clearly state that this product should not be used in patients with active gastrointestinal disorders.

− Are there any significant safety concerns for the medicine under review?

There are no additional safety concerns for the use of ibuprofen powder at 300 mg over and above the use of 150 mg of ibuprofen powder, or ibuprofen dosed between 150-300 mg in tablet formulation. Ibuprofen powder at 300 mg shows equivalent bioavailability to 300 mg ibuprofen in tablet formulation in terms of AUC, and in general ibuprofen is considered to be low risk when maximum daily doses are less than or equal to 1200 mg.
Identified contraindications and precautions for the use of ibuprofen have been listed above in section B4.

− 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)?

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

− Are there any withdrawal effects following cessation of use of the medicine?

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?

Excessive use or overdose of ibuprofen and paracetamol in combination can increase the risk of heart attack, stroke or liver damage. Symptoms of ibuprofen overdose include nausea, abdominal pain and vomiting, dizziness, convulsion and rarely, loss of consciousness. Clinical features of overdose with ibuprofen which may result are depression of the central nervous system and the respiratory system.

Firstly, the abuse potential for analgesic products is likely to be related to its dosage form. In comparison to solid-dose forms, there is a lack of evidence to suggest that granules and powder formulations are used for intentional overdose or misuse. Individual sachets first need to be opened, and then dissolved in water for ease of consumption. Multiple doses would require the consumption of a large volume (many individual glasses) of liquid. Consumption of the powder without dissolving firstly in water would also be difficult and unpleasant. Given these impracticalities of consuming multiple sachets at once for intentional or unintentional misuse, we believe that this powdered formulation does not present any greater risk to the consumer.

Secondly, we believe that purchase behaviour is different for cold and flu products where it is expected that the consumer will episodically purchase cold and flu products. In comparison, continuous purchasing behaviour for regular pain medication can lead to stockpiling of products and subsequent availability for misuse.

Finally, the practical potential for harm or overdose with ibuprofen itself is low given its wide therapeutic index. Widespread use of ibuprofen around the world has confirmed that ibuprofen has a wide margin of safety, and relatively low toxicity following overdose. More severe toxicity would only be likely in situations of excessive consumption for intentional overdose. Mild adverse effects may be observed at doses of 100 mg/kg with more serious effects occurring closer to or beyond 400 mg/kg. If a consumer was to take all 12 sachets of a box of *Maxigesic® Cold & Flu Hot Drink Double Strength*, they would consume 3600 mg of ibuprofen, and 12,000 mg of paracetamol. With this consumption, the 400 mg/kg dose of ibuprofen would only be reached in a person weighing 9.0kg, and a 70 kg adult would only reach a dose of 51 mg/kg. Of more concern would be the consumption of paracetamol which would likely reach the threshold for potential paracetamol-induced hepatic injury in adults (>200 mg/kg within 24 hours) for those over 50 kg if all 12 sachets were consumed at once.

Since the metabolic pathways of the two drugs are different and distinct there is no physiological reason why high doses or overdose of ibuprofen should increase the adverse effects or toxicity of an overdose of paracetamol. However, other monotherapy and combination cold and flu hot drink sachets such as Lemsip Max are currently available in pack sizes of 10 as OTC General Sale and contain up to 1000 mg of paracetamol per sachet, therefore there is precedent for the more dangerous ingredient to already be considered safe in this similar packaging size for General Sale. Given these sachets are often dosed with a single sachet we believe that consumers are already accustomed to only taking a single sachet per dose therefore the unintentional misuse potential is low. Therefore, with the additional information and guidance available from the pharmacist at the Pharmacy, there is little additional risk for the reclassification of ibuprofen powder at 300mg when included in *Maxigesic® Cold & Flu Hot Drink Double Strength* sachets.

While *Maxigesic® Cold & Flu Hot Drink Double Strength* are not yet on the market, to date there have only been three reported cases of intentional misuse globally involving the fixed dose combination tablets, out of the 370 million tablets distributed globally since launch in New Zealand in 2009.

Overall, improving the availability of ibuprofen powder at 300 mg (in combination with paracetamol in *Maxigesic*® *Cold & Flu Hot Drink Double Strength sachets*) by making it a Pharmacist Only medicine does not contribute to any increased risk of toxicity when the total daily dose remains the same (1200 mg/day).

7. Medication errors and abuse/misuse potential

− Would reclassification affect the risk of unnecessary use?

Reclassification will not increase the risk of unnecessary use considering that the maximum daily dose will remain at 1200 mg, and the dosage of one sachet will be equivalent to the full dose of the equivalent film coated tablets. AFT Pharmaceuticals have shown that the fixed dose combination therapy in the form of film coated tablets provides more effective pain relief than either component alone (Merry et al. 2010, Daniels et al., 2018), an effect which has also been noted previously with other paracetamol/ibuprofen combination products (R. A. Moore et al., 2015). Therefore, by allowing for 300 mg ibuprofen powder in *Maxigesic*® *Cold & Flu Hot Drink Double Strength* sachets, consumers are likely to experience more effective pain management for pain associated with cold and flu symptoms with a single dose, and may as a consequence take overall fewer doses resulting in a lower exposure to the drugs (R. A. Moore et al., 2015).

− Is the medicine be provided with necessary tools to allow correct dosing eg, liquids supplied with a measuring device?

The product is to be taken by dissolving the powder in hot water and then consumed immediately. The correct dose is included within each sachet and therefore no additional tools are required to ensure the correct dose is dissolved.

− What are the reported medication errors post-market? − What are the reported cases of abuse/misuse/accidental overdose?

Maxigesic® *Cold & Flu Hot Drink Double Strength* containing 300 mg of ibuprofen (as lysine) is not yet on the market, however the dose of ibuprofen is the same as for the full dose of the *Maxigesic*® film-coated tablets (2 tablets of 500 mg paracetamol/150 mg of ibuprofen). After distribution of over 370 million *Maxigesic*® tablets around the world since launch in New Zealand in 2009 there has been one report of a non-serious ADR due to a medical error (prescribed to patient with history of relevant drug allergy), one reported case of off-label use with no side effects, two reported cases of intentional overdose for self-injury, and one reported case of intentional misuse (exceeded recommended use duration).

− How would reclassification affect import considerations?

This reclassification to Pharmacist Only would not impact any import considerations.

− What is the addiction potential of the medicine?

There is no evidence that ibuprofen has addictive potential or would produce dependency, and ibuprofen is not a candidate for illicit or recreational use.

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)?

This is not applicable for this application. Pain is an individual and subjective experience and pain management varies from person to person.

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?

We have presented information demonstrating that in combination with 1000 mg of paracetamol, ibuprofen (as lysine) powder at a 300 mg dose with a maximum daily dose of 1200 mg in a pack of 12 sachets, is a safe medication for the relief of acute pain and fever, and will be beneficial for patients looking for effective management of pain associated with cold and flu symptoms. The *Maxigesic*® formulation utilises a ratio of paracetamol/ibuprofen that provides more effective pain relief than either the equivalent doses of paracetamol or ibuprofen alone, while minimising the dose of ibuprofen. This is consistent with the FDA guidance of using ibuprofen at the "*The lowest effective dose for the shortest duration consistent with individual patient treatment goals*" (FDA, 2005). Our formulation is also superior in this context to several other brands of ibuprofen tablets available for OTC sale in New Zealand since it is typical to recommend the usage of one to two (200 – 400 mg) tablets of ibuprofen, resulting in up to a full dose of 400mg. Since our proposed reclassification is for allowing for a lower full dose of ibuprofen (300 mg) in a single dose form we believe this is suitable for Pharmacist Only sale.

There is also a need for more self-selected OTC medicines for pain relief and pain management with the recent reclassification of codeine analgesics to Prescription medicines. The fixed dose combination product *Maxigesic® Cold & Flu Hot Drink Double Strength* fulfils this need. *Maxigesic® Cold & Flu Hot Drink Double Strength* sachets deliver a cumulative dose of the active ingredients that is equivalent to that provided in Maxigesic® tablets. AFT Pharmaceuticals sponsored pharmacokinetic studies demonstrated that the sachet and tablet forms of Maxigesic® are bioequivalent in terms of AUC for plasma concentration (Aitken et al., 2018). This dose combination has been shown in tablet formulation to provide more effective pain relief than the same dose of paracetamol or ibuprofen alone (Daniels et al., 2018; Merry et al. 2010)) Ultimately, if consumers can achieve better pain management for their pain associated with cold and flu with a single dose, they are less likely to require additional doses and will overall have a lower exposure to drugs (R. A. Moore et al., 2015).

The sachet formulation including 300 mg ibuprofen powder provides a convenient equivalent alternative to the approved tablet formulation for consumers where a hot drink formulation is preferred or clinically justified. It has been reported that around 16.5% of consumers experience difficulty swallowing solid dosage forms of medication such as tablets and capsules (Lau et al., 2015). Additionally, sore throat and difficulty swallowing is a common symptom experienced by patients with cold and flu. Therefore, this hot drink formulation provides an additional benefit of providing these consumers with a more accessible medication

formulation at the equivalent dosage of a full dose of tablets, without exceeding the recommended individual dose, or maximum daily dose.

Since ibuprofen has a wide therapeutic index, the potential for harm or overdose with ibuprofen is low. Widespread use of ibuprofen around the world has confirmed that ibuprofen has a wide margin of safety, and relatively low toxicity following overdose. More severe toxicity would only be likely in situations of intentional overdose, and in the case of the *Maxigesic® Cold & Flu Hot Drink Double Strength* sachets, toxicity is much more likely to be reached in an intentional overdose situation due to the paracetamol component rather than the ibuprofen component. While the sachet formulation is not yet marketed, the equivalent fixed-dose combination tablets have had only three reports of intentional overdose since 2009, with over 370 million tablets sold worldwide. Overall, improving the availability of ibuprofen powder at 300 mg (in combination with paracetamol in *Maxigesic® Cold & Flu Hot Drink Double Strength sachets*) by making it a Pharmacist Only medicine does not contribute to any increased risk of toxicity when the total daily dose remains the same (1200 mg/day).

With the minimal risk profile of ibuprofen when used at a maximum daily dose of 1200 mg a day and when available in limited pack sizes, and the benefits of more effective pain relief for symptoms of cold and flu, the convenient formulation, and accessibility of equivalent medicines to those where a hot drink is preferred, we believe that the benefit to risk profile of reclassification of ibuprofen powder at 300 mg in combination with 1000 mg paracetamol is very positive.

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 of ibuprofen powder at 300 mg to Pharmacist Only poses negligible risk considering that the maximum daily dose of ibuprofen remains at 1200 mg/day.

The primary risk mitigation strategy will be clear labelling. On the front display panel ‘Double Strength’ will be prominently positioned to indicate this is a full-strength product. Warning labelling as listed in Section A13 will be clearly visible on the back panels, and all contraindications will be available in the product data-sheet. The dosage instructions will also be clearly stated as a single sachet every six hours, and to not exceed more than 4 sachets a day. Customers understand that higher strength formulations are available from the pharmacy and know to examine the dosage requirements. Since the maximum daily dosage is the same as the approved *Maxigesic*® film-coated tablets, any customers who have previously used the tablet formulation will be familiar with the dosage and therefore there is unlikely to be any confusion between formulations.

By making this product available as a Pharmacist Only medicine, the interaction required with the pharmacist would allow a consumer to receive advice and understand the risks associated with this dosage form. This would enable better understanding of the safe use of this product and further minimise risk of adverse events associated with accidental overdose with other medications or with improper use of the product.

Since the risk associated with this reclassification is negligible, and the doses of this product are the same as already approved products we are not proposing any additional risk mitigation strategies or additional post-marketing surveillance studies.

As mentioned earlier in Section B3, health professionals have long been co-prescribing paracetamol and ibuprofen together and therefore there is precedent for additional formulations of fixed dose combinations products to improve availability of strong pain relief to those where a hot drink formulation may be preferable, and for better pain management of the symptoms of cold and flu.

References:

AFT Pharmaceuticals. (2020). *Maxigesic film coated tablets (paracetamol 500mg and ibuprofen 150mg) Periodic Safety Update Report.*

Aitken, P., Salem, I. I., Stanescu, I., Playne, R., & Atkinson, H. C. (2018). A single dose, four-way, open-label bioavailability study of oral acetaminophen and ibuprofen combinations (Maxigesic) under both fasting and fed conditions. *Journal of Bioequivalence & Bioavailability*, *10*(5), 84–91. https://doi.org/10.4172/0975-0851.1000383

Aitken, P., Stanescu, I., Playne, R., Zhang, J., Frampton, C. M. A., & Atkinson, H. C. (2019). An integrated safety analysis of combined acetaminophen and ibuprofen (Maxigesic® /Combogesic®) in adults. *Journal of Pain Research*, *12*, 621–634. https://doi.org/10.2147/JPR.S189605

Daniels, S. E., Atkinson, H. C., Stanescu, I., & Frampton, C. (2018). Analgesic efficacy of an acetaminophen/ibuprofen fixed-dose combination in moderate to severe postoperative dental pain: A randomized, double-blind, parallel-group, placebo-controlled trial. *Clinical Therapeutics*, *40*(10), Article 10. https://doi.org/10.1016/j.clinthera.2018.08.019

FDA. (2005). *Public Health Advisory—FDA Announces Important Changes and Additional Warnings for COX COX-2 Selective and Non Non-Selective Non Non-Steroidal Anti Anti-Inflammatory Drugs (NSAIDs)*. Rockville, MD: FDA Alerts.

Lau, E. T. L., Steadman, K. J., Mak, M., Cichero, J. A. Y., & Nissen, L. M. (2015). Prevalence of swallowing difficulties and medication modification in customers of community pharmacists. *Journal of Pharmacy Practice and Research*, *45*(1), 18–23. https://doi.org/10.1002/jppr.1052

Lewis, S. C., Langman, M. J. S., Laporte, J.-R., Matthews, J. N. S., Rawlins, M. D., & Wiholm, B.-E. (2002). Dose-response relationships between individual nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) and serious upper gastrointestinal bleeding: A meta-analysis based on individual patient data. *British Journal of Clinical Pharmacology*, *54*(3), 320–326. https://doi.org/10.1046/j.1365-2125.2002.01636.x

McGettigan, P., & Henry, D. (2011). Cardiovascular Risk with Non-Steroidal Anti-Inflammatory Drugs: Systematic Review of Population-Based Controlled Observational Studies. *PLoS Medicine*, *8*(9), e1001098. https://doi.org/10.1371/journal.pmed.1001098

Merry, A. F., Gibbs, R. D., Edwards, J., Ting, G. S., Frampton, C., Davies, E., & Anderson, B. J. (2010). Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: A randomized controlled trial. *British Journal of Anaesthesia*, *104*(1), 80–88. https://doi.org/10.1093/bja/aep338

Moore, A., Crossley, A., Ng, B., Phillips, L., & Sancak, Ö. (2017). *Use of Multi-Criteria Decision Analysis (MCDA) for assessing the Benefit and Risk of OTC Analgesics*. 29.

Moore, N., Ganse, E. V., Parc, J.-M. L., Wall, R., Schneid, H., Farhan, M., Verrière, F., & Pelen, F. (1999). The PAIN Study: Paracetamol, Aspirin and Ibuprofen New Tolerability Study. *Clinical Drug Investigation*, *18*(2), 89–98. https://doi.org/10.2165/00044011-199918020-00001

Moore, N., Le Parc, J. M., van Ganse, E., Wall, R., Schneid, H., & Cairns, R. (2002). Tolerability of ibuprofen, aspirin and paracetamol for the treatment of cold and flu symptoms and sore throat pain. *International Journal of Clinical Practice*, *56*(10), 732–734.

Moore, R. A., Wiffen, P. J., Derry, S., Maguire, T., Roy, Y. M., & Tyrrell, L. (2015). Non-prescription (OTC) oral analgesics for acute pain—An overview of Cochrane reviews. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD010794.pub2

Varrassi, G., Pergolizzi, J. V., Dowling, P., & Paladini, A. (2020). Ibuprofen Safety at the Golden Anniversary: Are all NSAIDs the Same? A Narrative Review. *Advances in Therapy*, *37*(1), 61–82. https://doi.org/10.1007/s12325-019-01144-9

White, W. B., Kloner, R. A., Angiolillo, D. J., & Davidson, M. H. (2018). Cardiorenal Safety of OTC Analgesics. *Journal of Cardiovascular Pharmacology and Therapeutics*, *23*(2), 103–118. https://doi.org/10.1177/1074248417751070

Appendix 1

Maxigesic® Cold & Flu Hot Drink Double Strength powder for oral liquid -carton 10 sachets

Maxigesic® Cold & Flu Hot Drink Double Strength powder for oral liquid - sachet

Maxigesic® Cold & Flu Hot Drink powder for oral liquid -carton 24 sachets

Maxigesic® Cold & Flu Hot Drink powder for oral liquid - sachet

Maxigesic Cold Flu Sachets CARTON DS 10's

e005261 Maxigesic Cold & Flu Hot Drink

Maxigesic Cold and Flu Hot Drink - Double Strength

Including artwork boundary

Directions for use

Adults and children over 12 years:

1 sachet every 6 hours, as required. Do not use more than 1 sachet per dose.

Pour contents of 1 sachet into a mug and fill with hot, but not boiling, water. Stir until dissolved.

Do not consume more than 4 sachets in 24 hours.

Do not give to children under 12 years.

Keep to the recommended dose.

Please refer to the outer carton for complete Medicine Information.

Dissolved powder should be consumed immediately

B :

EXP : ALFT *pharmaceuticals*

Bar code area

Minimum text height

24 Sachets

maxigesic®

COLD & FLU HOT DRINK

MEDICINE INFORMATION

Active ingredients (per sachet)

Paracetamol ..... 500 mg
Ibuprofen (as lysine) ..... 150 mg

Uses

For the temporary relief of:

- Headache
- Sinus pain
- Sore throat
- Aches and pains associated with colds and flu
- Reduces fever

Warnings

Do not give to children under 12 years of age.

Do not exceed the maximum stated dose. Unless advised to by a doctor, adults should not take this medicine for longer than a few days at a time, and adolescents (12–17 years) should not take it for longer than 48 hours at a time.

Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.

Do not use if:

- You are pregnant or trying to become pregnant
- You have a stomach ulcer
- You have impaired kidney or liver function
- You have heart failure
- You are allergic to paracetamol, ibuprofen, aspirin or other anti-inflammatory medicines.

If you get an allergic reaction, stop taking and see your doctor immediately.

Unless a doctor has told you to, do not use:

- If you have asthma
- If you are aged 65 years or over
- With other product containing paracetamol, ibuprofen, aspirin or other anti-inflammatory medicines, or with medicines that you are taking regularly.

If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

Phenylketonurics are warned that this product contains aspartame (phenylalanine). It also contains sugars.

Directions for use

Adults and children over 12 years: 1–2 sachets every 4–6 hours, as required.

Pour contents of 1 or 2 sachets into a mug and fill with hot, but not boiling, water. Stir until dissolved.

Do not consume more than 8 sachets in 24 hours.

Dissolved powder should be consumed immediately.

Store below 30°C.

AFT pharmaceuticals

DISTRIBUTED BY

AFT Pharmaceuticals Ltd
Auckland, New Zealand
customer.service@aftpharm.com
www.aftpharm.com

PHARMACY MEDICINE

KEEP OUT OF REACH OF CHILDREN

maxigesic®

COLD & FLU HOT DRINK

Paracetamol 500 mg
Ibuprofen (as lysine) 150 mg

DOUBLE ACTION

LEMON FLAVOUR

24 Sachets
Powder for oral solution

- Headache
- Sore throat
- Non-drowsy
- Body aches & pains
- Reduces Fever

24 Sachets

maxigesic®

COLD & FLU HOT DRINK

B :
EXP :

Made in India.

Directions for use

Adults and children over 12 years:

1–2 sachets every 4–6 hours.

Pour contents of 1 or 2 sachets into a mug and fill with hot, but not boiling, water. Stir until dissolved.

Do not consume more than 8 sachets in 24 hours.
Do not give to children under 12 years.
Keep to the recommended dose.
Please refer to the outer carton for complete Medicine Information.

B :

Dissolved powder should be consumed immediately.

EXP :

AFT *pharmaceuticals*