HEALTH • HYGIENE • HOME

9 October 2020

The Secretary
Advisory Committee on Medicines Scheduling
Therapeutic Goods Administration
medicines.scheduling@health.gov.au

Dear Sir/Madam,

Re: Interim decisions to amend (or not amend) the current Poisons Standard – ACMS Meeting #31, 3.5 Interim decision in relation to ibuprofen

Reckitt Benckiser supports the interim decision of the TGA delegate to amend the schedule for ibuprofen so that it is available in Schedule 2 in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 12 dosage units, when labelled not for the treatment of children under 12 years of age. However, we do not believe that this amendment should be limited to immediate release preparations and request that the amended entry revert to that originally proposed by Reckitt Benckiser, see Table 1 below. The only difference between the two entries is the deletion of the words "immediate release".

Table 1: Interim and proposed Schedule 2 Amended entry for ibuprofen.

Interim decision: Schedule 2 Amended Entry	**Proposed: Schedule 2 Amended Entry**
IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen: a) in liquid preparations when sold in the manufacturer's original pack containing 8 g or less of ibuprofen; or b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when: i. as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent); ii. packed in blister or strip packaging or in a container with a child-resistant closure; iii. in a primary pack containing not more than 25 dosage units; iv. compliant with the requirements of the Required Advisory Statements for Medicine Labels;	IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen: a) in liquid preparations when sold in the manufacturer's original pack containing 8 g or less of ibuprofen; or b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when: i. as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent); ii. packed in blister or strip packaging or in a container with a child-resistant closure; iii. in a primary pack containing not more than 25 dosage units; iv. compliant with the requirements of the Required Advisory Statements for Medicine Labels;

v. not labelled for the treatment of children 6 years of age or less; and vi. not labelled for the treatment of children under 12 years of age when combined with phenylephrine. c) in divided immediate release preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 12 dosage units, when labelled: i. not for the treatment of children under 12 years of age.	v. not labelled for the treatment of children 6 years of age or less; and vi. not labelled for the treatment of children under 12 years of age when combined with phenylephrine. c) in divided ~~immediate~~ release preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 12 dosage units, when labelled: i. not for the treatment of children under 12 years of age.

Reckitt Benckiser's original submission to the ACMS did not include any reference to the modified release (MR) ibuprofen preparations as there are no modified release preparations currently available in Australia in a dose that is 400 mg or lower. The only marketed modified release ibuprofen formulation available in Australia is GlaxoSmithKline's Advil 12 Hour Extended Release Tablet which contains 600 mg of ibuprofen per dosage unit and would not be impacted by this scheduling change. We do acknowledge that there are two modified release products listed on the Australian Register of Therapeutic Goods that contain ibuprofen 300 mg whose scheduling will be influenced by the above interim decision. Hence, we are taking this opportunity to address the issues raised in the interim decision in relation to the exclusion of modified release ibuprofen from Schedule 2.

It is important to recognise that only a single comment was received on the scheduling in relation to modified release ibuprofen [redacted] on the scheduling of modified release paracetamol they made a sound case as to the consumer benefits of modified release analgesics with longer duration of action compared to the immediate release preparations, including reduced pill burden, improved adherence and persistence, the potential to reduce the interference of pain on sleep and activities of daily living, whilst proposing equivalent safety profiles to the immediate release preparations.(1) These benefits are not exclusive to modified release paracetamol, but are also relevant to modified release formulations in general,(2) including modified release ibuprofen. The main difference between modified release paracetamol and modified release ibuprofen is that modified release ibuprofen has a better benefit-risk profile versus modified release paracetamol. In addition, management of overdose situations are not markedly different between modified release Ibuprofen and immediate release Ibuprofen whereas this is not the case with modified release paracetamol where specific overdose management guidelines are required for modified release paracetamol formulations.(3)

With respect to the decision to up-schedule modified release paracetamol from Schedule 2 to Schedule 3, the TGA delegate found that "the complex and unpredictable pharmacokinetic profile of MR paracetamol following an overdose poses an unacceptable risk to the

Australian population and that my concerns regarding the potential for abuse outweigh the arguments to retain the Schedule 2 entry." In addition, "I considered the compelling body of evidence, including data from the European Medicines Agency, that there is an increased risk of death or serious liver injury in people who overdose either deliberately or accidentally on MR paracetamol compared to immediate release paracetamol." "In making my decision I have had regard for the higher strength of MR, unpredictable pharmacokinetics, potential pharmacobezoar and that large pack size increase the risks associated with overdose with MR paracetamol. I have decided that there is reasonable evidence that the potential for harm from inappropriate use of MR Paracetamol is not low and that the Scheduling Factors for Schedule 2 are not met."(4) These issues are specific to paracetamol and are not relevant to the scheduling of modified release ibuprofen. There are clear and distinct differences between the two medicines and their presentations that support a superior benefit-risk profile for modified release ibuprofen making it suitable for inclusion in Schedule 2, including:

- Excellent safety profile in overdose for ibuprofen(5), which is safer than paracetamol(6, 7)
- Evidence suggesting a better safety profile of modified release ibuprofen in overdose than immediate release ibuprofen.(5)
- The management of rare cases of symptomatic ibuprofen overdose is the same irrespective if the person has taken immediate or modified release ibuprofen(3)
- The pack size of ibuprofen for inclusion in Schedule 2 is limited to 12 dosing units or less, representing a maximum of 3 days' supply, versus 96 dosing units for modified release paracetamol representing 16 days' supply.

In forming the interim the decision, that limited the scheduling change to immediate release formulations at the exclusion of modified release formulations, the ACMS raised the following issues:

1. There is limited clinical experience with modified release ibuprofen
2. There is a very different use profile with modified release ibuprofen. Ibuprofen modified release is designed to help manage recurrent or chronic pain and therefore requires pharmacist intervention to ensure the quality use of the medicine.
3. Ibuprofen modified release does not have the same safety profile as immediate release formulations.

These conclusions were reached without any formal submission of clinical evidence from Reckitt Benckiser regarding modified release ibuprofen or any supporting data presented by the Committee. This submission provides evidence that addresses these issues. Once this evidence is considered, we believe there will be no reason to exclude modified release ibuprofen in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 12 dosage units, when labelled not for the treatment of children under 12 years of age from Schedule 2 medicines.

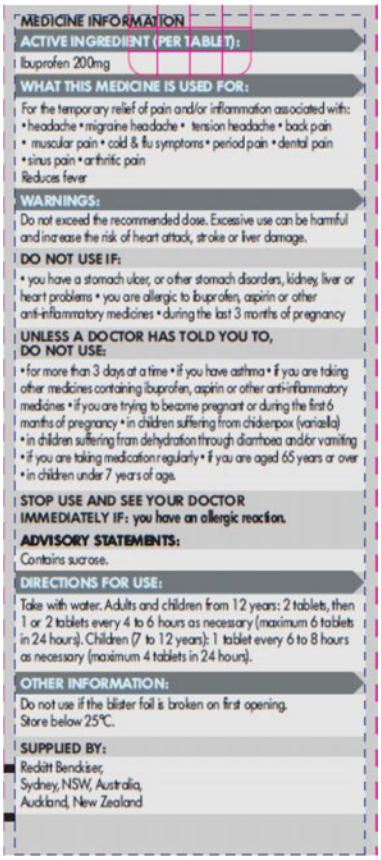
Background

There are two modified release 300 mg ibuprofen formulations listed on the ARTG, of which one is sponsored by Reckitt Benckiser, Nurofen® 12 HOUR. Modified release Nurofen® 12 HOUR is indicated for the **temporary relief** of persistent pain and/or inflammation likely to last more than 6 hours associated with sinus pain, toothache, dental procedures, backache, muscular aches and pains, arthritis, osteoarthritis, rheumatic pain, period pain, fibrositis, neuralgia, sore throat, tennis elbow, and colds and flu.

This formulation is yet to be marketed in Australia. The proposed label for this product is shown in Figure 1 and for comparison purposes, Figure 2 is the current pack for regular immediate release Nurofen® (200 mg).

Figure 1: Nurofen® 12 HOUR label

Figure 2: Schedule 2 immediate release Nurofen® 200 mg label



MEDICINE INFORMATION

ACTIVE INGREDIENT (PER TABLET):
Ibuprofen 200mg

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

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

DO NOT USE IF:
• you have a stomach ulcer, or other stomach disorders, kidney, liver or heart problems • you are allergic to ibuprofen, aspirin or other anti-inflammatory medicines • during the last 3 months of pregnancy

UNLESS A DOCTOR HAS TOLD YOU TO, DO NOT USE:
• for more than 3 days at a time • if you have asthma • if you are taking other medicines containing ibuprofen, aspirin or other anti-inflammatory medicines • if you are trying to become pregnant or during the first 6 months of pregnancy • in children suffering from chickenpox (varicella) • in children suffering from dehydration through diarrhoea and/or vomiting • if you are taking medication regularly • if you are aged 65 years or over • in children under 7 years of age.

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

ADVISORY STATEMENTS:
Contains sucrose.

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

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

SUPPLIED BY:
Reckitt Benckiser,
Sydney, NSW, Australia,
Auckland, New Zealand

In reviewing these labels, it is important to recognise the following:

- The pack has been designed to emphasize the differences between the modified release formulation and regular immediate release Nurofen® products.
- The longer duration of action and differences in dosing are clearly communicated on front of pack as well as in the dosing instructions. The formulation being a MODIFIED RELEASE tablet is also clearly communicated.
- The modified release product has the same warnings and precautions as regular immediate release ibuprofen (200 mg), which is widely acknowledged as a safe and effective analgesic that has been safely and appropriately used as a self-section medicine in both the pharmacy and general sales environment since 2003 in Australia.

Limited clinical experience

It is acknowledged that the Australian clinical experience with modified release ibuprofen is less than that for immediate release ibuprofen. However, there is considerable experience in comparable overseas markets.

The first modified release Nurofen® product (300 mg modified release capsule) was launched in France in October 1998 as a prescription only medicine. In the United Kingdom, this same product was launched in 2006 as a Pharmacy Only medicine and it has been available as an OTC medicine since this launch. This product was also launched as an OTC medicine in Poland in April 2010.

In these three markets, there has been significant consumer experience with 300 mg modified release ibuprofen. For the period of 1st January 2006 to 31st May 2019 the estimated total patient exposure was [redacted] (see Table 2).

Table 2: Patient exposures to 300 mg modified release ibuprofen (1st January 2006 to 31st May 2019)

Country	Scheduling Status	Patient Exposure
France	Prescription	[redacted]
Poland	OTC	
United Kingdom	Pharmacy Only	
Total		

During this period, there has been a very low incidence of adverse events reported to Reckitt Benckiser with the modified release products. As an OTC medicine (UK and Poland), 15 adverse events have been reported from 7 cases. Of these, 6 adverse events were considered serious (from 1 case) and these events were assessed as possibly related to the medication (Table 3). 9 non-serious adverse events were reported (from 6 cases), of which 8 were assessed as possibly related and 1 as unlikely related to ibuprofen (Table 4).

Table 3: Serious adverse events associated with the use of branded Nurofen® LL Capsules (300 mg modified release) in Poland and the United Kingdom from 01 January 2006 to 31 May 2019

Case Seriousness	System Organ Class	Preferred Term	Total adverse events
Serious	Serious Ear and labyrinth disorders	Tinnitus	1
	Gastrointestinal disorders	Abdominal distension	1
		Nausea	1
	General disorders and administration site conditions	Malaise	1
	Investigations	Blood pressure increased	1
	Nervous system disorders	Tremor	1
Total			6

Table 4: Non-serious adverse events associated with the use of branded Nurofen® LL Capsules (300 mg modified release) in Poland and the United Kingdom from 01 January 2006 to 31 May 2019

Case Seriousness	System Organ Class	Preferred Term	Total adverse events
Non-serious	Gastrointestinal disorders	Diarrhoea	1
		Nausea	1
	General disorders and administration site conditions	Drug ineffective	5
		Malaise	1
	Injury, poisoning and procedural complication	Lip injury	1
Total			9

In France, were the product has only been available as a prescription medicine there has been a similar very low incidence of adverse events associated with the use of modified release ibuprofen 300 mg, with 12 adverse events from 3 cases reported since 1998. (Table 5)

Table 5: All adverse events associated with the use of branded Nurofen® Modified Release Capsules (300 mg) in France since 1998

System Organ Class	Preferred Term	Total adverse events
Blood and lymphatic system disorders	Anaemia	1
Gastrointestinal disorders	Rectal haemorrhage	1
	Abdominal pain	1
	Abdominal pain upper	1
	Abdominal wall haematoma	1
General disorders and administration site conditions	Pain	1
Investigations	Malaise	1
Injury, poisoning and procedural complication	Intentional overdose	1
	Toxicity to various agents	1
	Wrong technique in product usage process	1
Skin and subcutaneous tissue disorders	Ecchymosis	1
Vascular disorders	Haemorrhage	1
		12

Hence, international experience with modified release ibuprofen 300 mg is considerable and post-marketing surveillance data indicates a very low incidence of adverse events, with 1 patient experiencing adverse events per [redacted] patient exposures. The ability of consumers to use this product appropriately in a pharmacy self-selection environment is further supported by the observation that the rate of adverse events was lower with its OTC

use (UK and Poland) than with prescription use (France); [redacted] patient exposures, respectively.

In addition, post-marketing surveillance data from the United Kingdom has identified no cases of overdoses, including accidental overdoses, associated with the use of modified release Nurofen® (300 mg) since its Pharmacy Only availability in 2006.

Different use profile

The interim decision for excluding modified release ibuprofen from Schedule 2 was in part due to the belief that use profile with modified release ibuprofen is very different to immediate release ibuprofen. It was suggested that ibuprofen modified release is designed to help manage recurrent or chronic pain and therefore requires pharmacist intervention to ensure the quality use of the medicine. Reckitt Benckiser respectfully disagrees with this position for a number of reasons outlined below.

Minimal differences in the approved indications

The approved indications for modified release ibuprofen 300 mg are very similar to that for the immediate release ibuprofen 200 and 400 mg products (See Table 6). It is accepted that these pain conditions are suitable for self-selection in both the pharmacy and non-pharmacy setting, hence pharmacist intervention is not necessary for the short-term management of these conditions irrespective of whether the formulation selected is immediate or modified release ibuprofen.

Table 6: Comparison of approved indications

Product	Approved indication
Ibuprofen 200 mg and 400 mg (immediate release)	The temporary relief of 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.
Ibuprofen 300 mg modified release	For the temporary relief of persistent pain and/or inflammation likely to last more than 6 hours associated with: sinus pain, toothache, dental procedures, backache, muscular aches and pains, arthritis, osteoarthritis, rheumatic pain, period pain, fibrositis, neuralgia, sore throat, tennis elbow, and colds and flu.

The main differences in the types of painful conditions that can be treated with the modified release ibuprofen are:

- The exclusion of headaches
- The inclusion of osteoarthritis, fibrositis and neuralgia

Given that people with headaches are generally seeking fast pain relief,(8) it is unlikely that they will consider the longer-acting modified release product and will not need pharmacist intervention to support this appropriate product selection process.

Given that both formats are indicated for the management of arthritis, and many consumers use the term arthritis to also describe osteoarthritis, the differences between the types of pain consumers would use either product for is further reduced. Hence, when considering the types of pain being treated the usage profiles are not significantly different.

The product is not intended to manage continuous chronic pain, but is for the temporary relief of pain likely to last more than 6 hours

It is important to recognise that the modified release product is indicated for the **temporary relief** of persistent pain and that persistent pain is defined within the indication **as pain likely to last more than 6 hours**. This is distinctly different to the standard medical definition of chronic or persistent pain, which is defined by the International Association for the Study of Pain (IASP)(9) as pain which persists past the normal time of healing, commonly defined as pain present for at least 3 months. Hence, it is clear that the intended use of over-the-counter modified release ibuprofen 300 mg is for temporary relief of pain expected to persist for more than 6 hours and it is not intended for long-term continuous use. This short-term use is reinforced by:

- On pack instructions to limit use to 3 days at a time, unless advised by your doctor
- Limiting the proposed Schedule 2 pack size to a maximum of 12 dosing units which represents only 3 days' supply.

It is clearly not practical or economical for patients with continuous chronic pain to use the Schedule 2 product to manage long-term chronic pain as it would necessitate repurchase at least twice weekly. As such pharmacist intervention is not needed to ensure the quality use of modified release ibuprofen 300 mg in this limited pack size for the approved indication. In addition, if this frequent purchase behaviour were to occur, it would be unlikely not to be detected and addressed by pharmacy staff even in the Schedule 2 setting.

Moreover, prior to the up-schedule of modified release paracetamol it was a Schedule 2 medicine with the approved indication of **'**Effective relief from **persistent pain for up to 8 hours.** Effective for the relief of persistent pain associated with osteoarthritis and muscular aches and pains such as backache.' This indication was clearly considered acceptable and not the reason for why modified release paracetamol was up-scheduled. Given the acceptability of this indication as a Schedule 2 indication it would seem appropriate that the proposed indication for modified release ibuprofen is also appropriate for Schedule 2 availability.

Relative safety profile

The interim decision for excluding modified release ibuprofen from Schedule 2 was in part due to the belief that ibuprofen modified release does not have the same safety profile as immediate release ibuprofen formulations. Reckitt Benckiser respectfully disagrees with this position and provides the following clinical evidence to support its position.

The total ibuprofen exposure per day is unchanged at ≤ 1200 mg/day, hence dose-related safety is unchanged

The safety profile of NSAIDs is widely recognised as being dose-related, with ibuprofen having the best gastrointestinal safety profile.(3, 10) The maximum daily dose available in Australia for self-selection immediate release ibuprofen products, either as an Unscheduled or Pharmacy Only medicine, is 1200 mg/day for people 12 years and older. The maximum dose of modified release ibuprofen is 2 x 300 mg (600 mg) every 12 hours, with a maximum of 4 tablets in 24 hours or 1200 mg per day. Hence, the total daily exposure to ibuprofen is the same for the modified release 300 mg formulation and the immediate release ibuprofen products.

The safety of ibuprofen at OTC doses (≤ 1200 mg/day) is well-established(6, 11, 12) and has been evaluated by the TGA and its evaluation committees over several decades. The NDPSC and ACMS have previously accepted that ibuprofen has a lower risk of adverse events and serious effects after overdose than over-the-counter aspirin or paracetamol. This was reflected by the NDPSC decision in 2003 to exempt from scheduling products

containing ibuprofen (in primary pack ≤ 25 dosage units) of unit doses of up to 200 mg with a maximum daily dose of 1200 mg/day.(13) Since this time there is no evidence indicating that the safety profile of ibuprofen including modified release formulations has changed(12) and from a safety perspective the modified release product is appropriate for inclusion in Schedule 2 medicine in primary pack ≤ 12 dosage units.

Modified release ibuprofen has a flatter pharmacokinetic profile with no difference in total exposure (AUC)

It is well established that one of the potential benefits of modified release analgesic formulations is that they deliver a more consistent steady-state plasma levels without the more pronounced peaks and troughs associated with short-acting immediate release formulations, leading to reduced adverse events.(2)

Even though a larger single dose of ibuprofen is taken with modified release ibuprofen (2 x 300 mg) to provide its longer duration of action, due to the modified release properties of the formulation, Nurofen® 12 HOUR exhibits a smoother pharmacokinetic profile in comparison to regular immediate release ibuprofen.

This has been demonstrated in a bioequivalence study of Ethypharm ibuprofen sustained release (SR) capsules 300 mg (identical to the modified release Nurofen® formulations marketed in Europe) and Nurofen® 200 mg immediate release tablets. This pharmacokinetic study was conducted in 12 healthy male volunteers who received a single 600 mg dose of ibuprofen (three immediate release Nurofen® 200 mg tablets or two modified release Ethypharm ibuprofen 300 mg capsules). In addition to the single dose study, dosing was continued for 5 consecutive days and the pharmacokinetic profile at steady-state was assessed on day 5. Note the dosing regimen for the steady-state pharmacokinetics was 2 x 300 mg modified release capsules twice daily compared to 2 x 200 mg immediate release ibuprofen tablets three times daily.(14)

The pharmacokinetic profiles of the s (active)-isomer of the two formulations following a single dose (600 mg each) are shown in Figure 3 and at steady-state (day 5) with multiple dosing Figure 4. Both pharmacokinetic profiles demonstrate that the modified release formulation results in a longer time to peak concentration (Tmax) and a lower peak plasma concentration (Cmax), and no change in bioavailability or exposure (AUC).

Figure 3: Pharmacokinetic profile for s-ibuprofen from single doses of 2 x 300 mg ibuprofen modified release capsules (600 mg) compared with 3 x 2 mg immediate-release ibuprofen tablets (600 mg).(14)

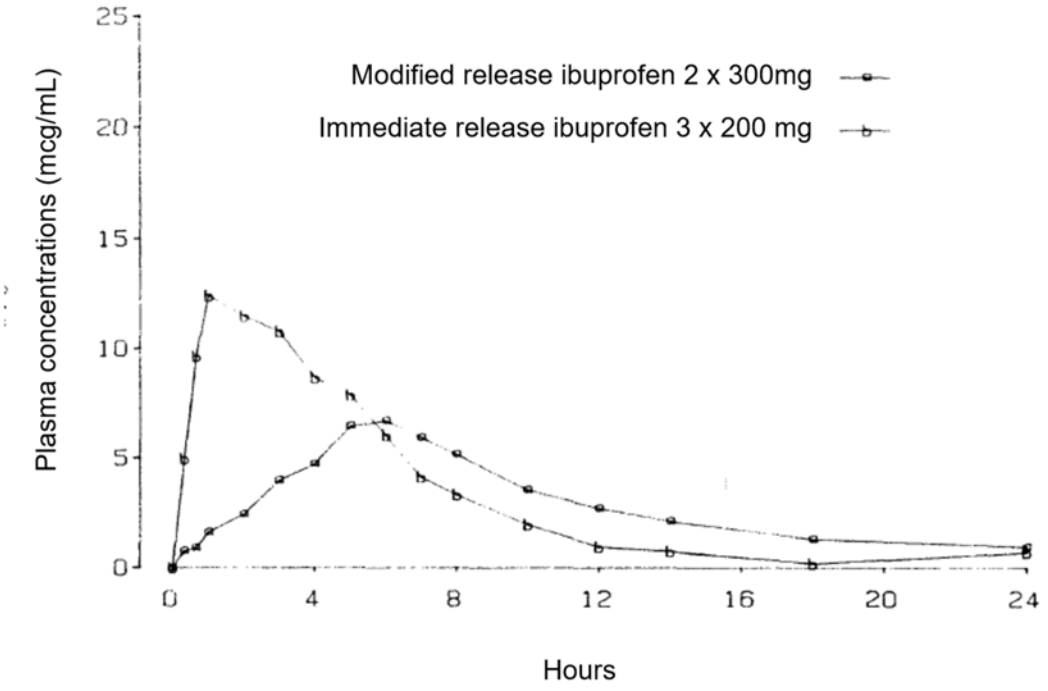
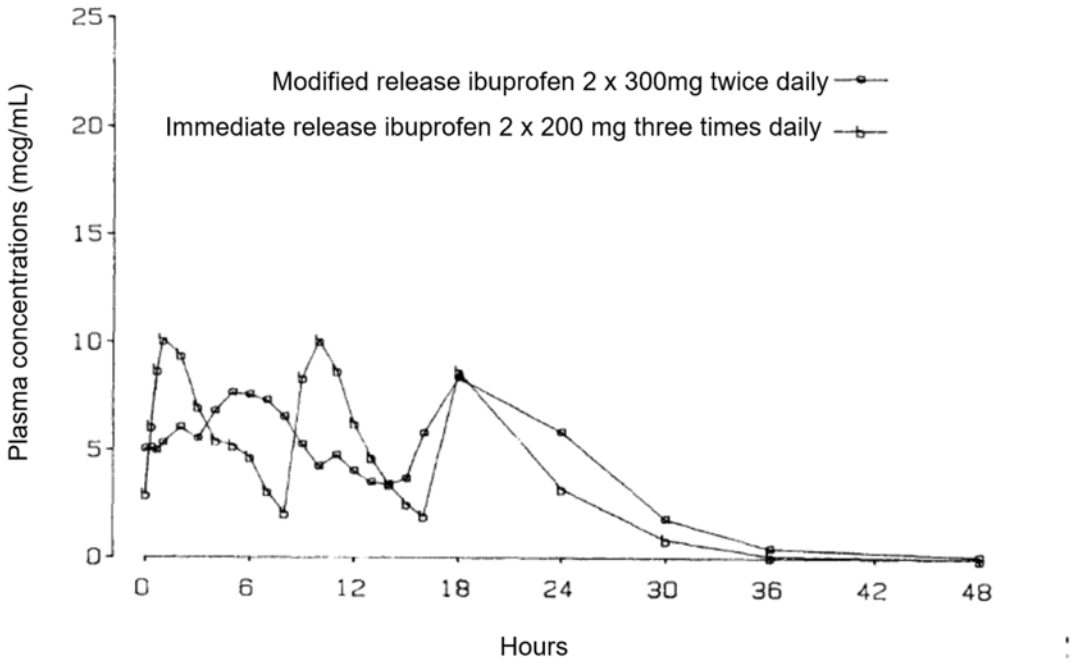


Figure 4: Pharmacokinetic profile for s-ibuprofen Day 5 following multiple doses of ibuprofen modified release capsules 2 x 300 mg twice daily compared with immediate-release ibuprofen tablets 2 x 200 mg three times daily(14)



Linear dose proportionality was demonstrated and there was no difference in the extent of exposure (AUC) between the formulations after a single dose on day 1 or after five days use.(14) (See Table 7)

Table 7 Mean Pharmacokinetic Parameters for S-ibuprofen (active isomer) on Day 5.(14)

	Enantiomer	Ethypharm MR 300 mg	Nurofen® 200 mg
Dose		2 x 300 mg twice daily	2 x 200 mg three times daily
Cmax (µg/mL)	S	10.3 ± 2.3*	14.3 ± 3.9
	R	7.0 ± 2.4	10.6 ± 4.9
Tmax (h)	S	4.8 ± 2.2*	2.3 ± 2.0
	R	4.4 ± 1.6*	1.6 ± 1.0
Cmin (µg/mL)	S	5.1 ± 3.0*	2.9 ± 2.1
	R	2.9 ± 2.0	1.3 ± 1.2
AUC 24 hour (µg/mL*h)	S	144.3 ± 24.3	140.3 ± 35.0
	R	82.6 ± 15.8	86.9 ± 26.4

* Significantly different to immediate release ibuprofen

As there is no difference in ibuprofen exposure (AUC), and there is a lower peak concentration with the modified release formulation, the safety profile of the modified release ibuprofen formulation (2 x 300 mg) is expected to be equivalent to regular immediate release ibuprofen.

Post-marketing surveillance data signals no difference in safety profile with modified release ibuprofen

To enable an assessment of the relative safety profile of modified release ibuprofen (300 mg) to regular immediate release ibuprofen an analysis of adverse events reported in the United Kingdom has been performed for the period from the 1st January 2006 to 31st May 2019. During this period 300 adverse events (141 serious and 159 non-serious) were reported for immediate release branded Nurofen® tablets (200 mg) from an estimated patient exposure of [redacted]. Over the same period, 15 adverse events (6 serious and 9 non-serious) were reported for modified release branded Nurofen® tablets (300 mg) from an estimated patient exposure of [redacted]. (See Tables 8 and 9). Five of 15 adverse events reported for the modified release preparation was the medication was reported to be ineffective, which is not a safety issue. Overall, this data supports the very low incidence of adverse events with the modified release 300 mg formulation as a self-selection Pharmacy Only medicine.

Table 8: Comparison of the serious adverse events reported for the branded Nurofen® Modified Release 300mg Capsules and the branded Nurofen® Tablets 200mg in the United Kingdom from 01 January 2006 to 31 May 2019

Country of Incidence	Case Seriousness	Event SOC	Event PT	200 mg	300 mg	Grand Total
UNITED KINGDOM	**Serious**	Blood and lymphatic system disorders	Anaemia	1		1
			Leukocytosis	1		1
			Aplastic anaemia	1		1
		Cardiac disorders	Palpitations	1		1
			Ventricular tachycardia	1		1
			Tachyarrhythmia	1		1
		Ear and labyrinth disorders	Tinnitus		1	1
			Deafness	1		1
		Eye disorders	Eyelid thickening	1		1
			Visual impairment	1		1
			Swelling of eyelid	1		1
			Eye disorder	1		1
			Blindness	1		1
			Eye haemorrhage	1		1
		Gastrointestinal disorders	Abdominal pain upper	5		5
			Nausea	2	1	3
			Abdominal pain	3		3
			Diarrhoea	3		3
			Haematemesis	2		2
			Abdominal distension	1	1	2
			Melaena	2		2
			Dyspepsia	2		2
			Gastric ulcer	2		2
			Dysphagia	2		2

			Odynophagia	1		1
			Peptic ulcer haemorrhage	1		1
			Oesophageal perforation	1		1
			Vomiting	1		1
			Rectal haemorrhage	1		1
			Duodenal ulcer	1		1
			Abdominal discomfort	1		1
			Flatulence	1		1
		General disorders and administration site conditions	Malaise	4	1	5
			Hypothermia	3		3
			Chest pain	2		2
			Death	2		2
			Asthenia	1		1
			Pyrexia	1		1
			Peripheral swelling	1		1
			Discomfort	1		1
			Swelling	1		1
			Feeling abnormal	1		1
			Feeling hot	1		1
		Immune system disorders	Hypersensitivity	3		3
			Anaphylactic reaction	1		1
		Injury, poisoning and procedural complications	Overdose	6		6
			Inappropriate schedule of product administration	3		3
			Contusion	2		2
			Expired product administered	2		2

			Accidental exposure to product	1		1
		Investigations	Respiratory rate decreased	3		3
			Heart rate decreased	3		3
			Platelet count decreased	1		1
			Blood pressure increased		1	1
			Red blood cell count decreased	1		1
			Urine output decreased	1		1
			Cardiac output decreased	1		1
			Blood lactic acid increased	1		1
			Liver function test abnormal	1		1
		Metabolism and nutrition disorders	Hyponatraemia	1		1
			Hyperkalaemia	1		1
		Musculoskeletal and connective tissue disorders	Neck pain	1		1
			Muscle spasms	1		1
		Nervous system disorders	Depressed level of consciousness	3		3
			Paraesthesia	2		2
			Dizziness	2		2
			Headache	2		2
			Tremor	1	1	2
			Syncope	1		1
			Somnolence	1		1
			Migraine	1		1
			Formication	1		1
			Loss of consciousness	1		1

		Product issues	Product lot number issue	1		1
		Psychiatric disorders	Disorientation	1		1
			Psychotic disorder	1		1
			Emotional distress	1		1
			Completed suicide	1		1
			Anxiety	1		1
			Confusional state	1		1
		Renal and urinary disorders	Renal failure	1		1
			Chronic kidney disease	1		1
		Respiratory, thoracic and mediastinal disorders	Dyspnoea	2		2
			Wheezing	1		1
			Throat tightness	1		1
		Skin and subcutaneous tissue disorders	Pruritus	2		2
			Erythema	1		1
			Papule	1		1
			Subcutaneous emphysema	1		1
			Swelling face	1		1
			Toxic epidermal necrolysis	1		1
			Urticaria	1		1
			Rash generalised	1		1
			Skin burning sensation	1		1
		Vascular disorders	Hypotension	3		3
			Circulatory collapse	3		3
Grand Total				**141**	**6**	**147**

Table 9: Comparison of the non-serious adverse events reported for the branded Nurofen® Modified Release 300mg Capsules and the branded Nurofen® Tablets 200mg in the United Kingdom from 01 January 2006 to 31 May 2019

Country of Incidence	Case Seriousness	Event SOC	Event PT	200 mg	300 mg	Grand Total
UNITED KINGDOM	**Non-Serious**	Cardiac disorders	Palpitations	1		1
			Cardiac flutter	1		1
		Eye disorders	Eye swelling	1		1
		Gastrointestinal disorders	Lip swelling	5		5
			Abdominal pain upper	4		4
			Dysphagia	2		2
			Oral discomfort	2		2
			Swollen tongue	2		2
			Diarrhoea	1	1	2
			Vomiting	1	1	2
			Abdominal discomfort	1		1
			Oral pain	1		1
			Abdominal distension	1		1
			Tongue discomfort	1		1
			Gastrointestinal haemorrhage	1		1
			Glossitis	1		1
		General disorders and administration site conditions	Drug ineffective	18	5	23
			No adverse event	9		9
			Malaise	5	1	6
			Peripheral swelling	4		4
			Discomfort	3		3
			Chest pain	2		2
			Pain	2		2

			Drug effect delayed	2		2
			Feeling hot	1		1
			Condition aggravated	1		1
			Drug effect decreased	1		1
			Therapeutic product ineffective	1		1
			Adverse event	1		1
			Feeling abnormal	1		1
		Immune system disorders	Hypersensitivity	5		5
		Infections and infestations	Urinary tract infection	1		1
			Cystitis	1		1
		Injury, poisoning and procedural complications	Accidental exposure to product by child	5		5
			Overdose	3		3
			Inappropriate schedule of product administration	2		2
			Incorrect product administration duration	2		2
			Exposure via breast milk	2		2
			Foreign body in respiratory tract	2		2
			Poor quality product administered	1		1
			Exposure during pregnancy	1		1
			Accidental exposure to product	1		1
			Lip injury		1	1
		Metabolism and nutrition disorders	Decreased appetite	1		1

		Musculoskeletal and connective tissue disorders	Flank pain	1		1
		Nervous system disorders	Dizziness	3		3
			Paraesthesia	1		1
			Burning sensation	1		1
			Somnolence	1		1
			Speech disorder	1		1
			Dysarthria	1		1
			Loss of consciousness	1		1
		Product issues	Product physical issue	3		3
			Product quality issue	1		1
		Psychiatric disorders	Insomnia	2		2
			Emotional distress	1		1
		Reproductive system and breast disorders	Menstrual disorder	1		1
		Respiratory, thoracic and mediastinal disorders	Throat irritation	3		3
			Oropharyngeal pain	3		3
			Throat tightness	1		1
			Dyspnoea	1		1
			Choking	1		1
			Pharyngeal oedema	1		1
		Skin and subcutaneous tissue disorders	Swelling face	6		6
			Rash	4		4
			Pruritus	4		4
			Urticaria	2		2
			Erythema	2		2
			Rash generalised	2		2

			Blister	1		1
			Hair growth abnormal	1		1
			Skin irritation	1		1
			Rash macular	1		1
			Rash erythematous	1		1
			Rash maculo-papular	1		1
			Skin disorder	1		1
		Social circumstances	Contraindication to medical treatment	1		1
Grand Total				**159**	**9**	**169**

There have been no adverse events reported for extended release ibuprofen (600 mg) in Australia

A search of the Database of Adverse Event Notifications (DAENs) for the period of 1st January 1971 to 29th June 2020 also supports a low incidence of adverse events with modified release ibuprofen as there have been no reports attributed to the OTC use of Advil 12 hour (600 mg extended release tablets).

Similarly, adverse events reported in surveillance data from Canada from 1st January 1965 to 31st May 2020 indicate a very low incidence of adverse events associated with the of Advil 12 hour (600 mg extended release tablets). During this period there have been 54 reports of non-serious adverse events (from 42 patients) and 18 reports of serious adverse events (from 3 patients). However, the most common adverse events reported related to the medication being ineffective or the product effect being incomplete, decreased or delayed. As these reports are not safety issues, when these cases are removed the number of non-serious adverse events reported decrease from 54 to 13 and the serious adverse events decrease from 18 to 17. During this time there was one death reported that was related to intentional product misuse.(15) (See Table 10) Note, Health Canada regulates modified release ibuprofen in strengths of 600 mg or less as over-the-counter medicines.

Table 10: Non-serious and serious adverse events reported for the branded Advil 12 hour (600 mg extended release ibuprofen tablets) in Canada from 1st January 1965 to 31st May 2020

Event SOC	Event PT	Non-serious	Serious	Total
Gastrointestinal disorders	Gastric disorder	1		1
	Dysgeusia	1		1
	Dysphagia		1	1
	Flatulence		1	1
	Diarrhoea	1	1	2

General disorders and administration site conditions	Drug ineffective	30	1	31
	Therapeutic product effect incomplete	9		9
	Therapeutic product effect delayed	1		1
	Therapeutic product effect decreased	1		1
	Feeling abnormal	2		2
	Death		1	1
	Feeling hot	1		1
Injury, poisoning and procedural complications	Intentional product misuse	1	1	2
	Intentional product use issue	1		1
Investigations	Heart rate increase		1	1
Musculoskeletal and connective tissue disorders	Arthritis		1	1
	Muscle spasms		1	1
Nervous system disorders	Headache	2		2
	Tremor		1	1
Product issues	Product taste abnormal	1		1
	Product size issue		1	1
	Product use complaint		1	1
Psychiatric disorders	Insomnia		1	1
	Initial insomnia	1		1
	Anxiety	1		1
	Nervousness		1	1
Renal and urinary disorders	Urine flow decrease		1	1
Respiratory, thoracic and	Choking		1	1

mediastinal disorders				
	Dyspnoea		1	1
Vascular disorders	Haemorrhage		1	1
Total		54	18	72

Safety in overdose

It is well established that ibuprofen has a wide therapeutic index and a good safety profile in overdose.(7) 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.(5) If the entire 12 pack of 300 mg modified release ibuprofen was taken as a single dose, the total dose would be 3600 mg and the 400 mg/kg dose would only be experienced by a patient weighing 9 kg or less. An adult weighing 70 kg would be exposed to a non-toxic, asymptomatic dose of 51 mg/kg.

Unlike paracetamol, suspected overdoses with modified release NSAIDs are managed the same as if the overdose occurred with an immediate release formulation. This is reflected in the management guidelines for NSAID overdoses published in the Therapeutic Guidelines Complete. Management of NSAID overdoses involves providing supportive care and investigating for the presence of paracetamol, to exclude the ingestion of paracetamol or coformulations of ibuprofen and paracetamol. Patients are observed for 4 to 8 hours dependent on the dose taken (whether it is less or greater than ibuprofen 400 mg/kg) before discharge (if the patient has good kidney function, is well hydrated and is asymptomatic). This is distinctly different to poisonings associated with modified release paracetamol which have a greater risk of acute liver injury than with immediate release paracetamol irrespective of treatment.(3) This safety in overdose concern for modified release paracetamol is reflected by its recent up-scheduling to Schedule 3.(4) However, the overdose safety issue only relates to modified release paracetamol and is not applicable to modified release ibuprofen.

The safety of modified release ibuprofen is further supported with data from the United Kingdom. 99% of all cases of suspected ibuprofen poisoning reported to the UK National Poisons Centre involve conventional, immediate-release tablets or capsules. During a period where more than 63,000 cases of poisoning were reported involving ibuprofen tablet formulations, only 23 cases involved sustained-release formulations (300 or 800 mg). An analysis of data from these cases suggested that there was less evidence for toxic effects with modified release formulations than with immediate release tablets.(5)

In addition, post-marketing surveillance data from the United Kingdom has identified no cases of overdoses, including accidental overdoses, associated with the use of modified release Nurofen® (300 mg) since its Pharmacy Only availability in 2006.

Conclusion

Reckitt Benckiser believes that the evidence tabled above demonstrates that there is extensive clinical experience with modified release ibuprofen 300 mg in comparable markets to Australia and that this experience has confirmed that the modified release product has an

equivalent safety profile to immediate release ibuprofen, with a very low incidence of adverse events. This excellent safety profile includes its safety in overdose. In contrast to modified release paracetamol which poses greater risks than immediate release paracetamol in overdose, the safety profile of modified release ibuprofen in overdose appears to be superior, or at a minimum equivalent, to immediate release ibuprofen formulations. Hence, from a safety perspective modified release ibuprofen 300 mg tablets is suitable for inclusion in Schedule 2.

The modified release product is indicated for the **temporary relief** of persistent pain and that persistent pain is defined within the indication **as pain likely to last more than 6 hours**. The pain states that are listed within the approved indication, are overall comparable to that for Schedule 2 immediate release ibuprofen solid dose formulations, with the main difference being the exclusion of headaches. Hence, the use profile for OTC modified release ibuprofen 300 mg is consistent with the short-term management of common pain states and is suitable for inclusion is Schedule 2. In addition, the Schedule 2 listing limits pack sizes to 12 dosage units or less, which represents 3 days' supply of modified release ibuprofen 300 mg. This pack size only supports short-term use and it is extremely unlikely that a consumer would choose to use this format to manage long-term chronic pain. As such pharmacist intervention is not needed to ensure the quality use of modified release ibuprofen 300 mg in these limited pack sizes.

Reckitt Benckiser requests that the TGA delegate reconsider the exclusion of modified release Ibuprofen from the interim decision to amend the schedule for ibuprofen so that it is available in Schedule 2 in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 12 dosage units, when labelled not for the treatment of children under 12 years of age. In Reckitt Benckiser's view the scheduling decision should apply to both immediate release and modified release formulations and as such Reckitt Benckiser requests that the final decision reflects this.

Yours sincerely,

DocuSigned by:
[redacted]

Reckitt Benckiser (Australia) Pty Limited

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