Public submissions on proposed amendments to the *Poisons Standard*

Subdivision 3D.2 of the *Therapeutic Goods Regulations 1990* (the Regulations) sets out the procedure to be followed where the Secretary receives an application under section 52EAA of the *Therapeutic Goods Act 1989* (the Act) to amend the current *Poisons Standard* and decides to refer the proposed amendment to an expert advisory committee. These include, under regulation 42ZCZK, that the Secretary publish (in a manner the Secretary considers appropriate) the proposed amendment to be referred to an expert advisory committee, the committee to which the proposed amendment will be referred, and the date of the committee meeting. The Secretary must also invite public submissions to be made to the expert advisory committee by a date mentioned in the notice as the closing date, allowing at least 20 business days after publication of the notice. Such a notice relating to the scheduling proposals initially referred to the November 2017 meeting of the Advisory Committee on Medicines Scheduling (ACMS #22) was made available on the TGA website on 6 September 2017 and closed on 6 October 2017.

Public submissions received on or before 6 October 2017 are published here in accordance with regulation 42ZCZL of the Regulations. Also in accordance with regulation 42ZCZL, the Secretary has removed information that the Secretary considers confidential.

Under regulation 42ZCZN of the Regulations, the Secretary, after considering the advice or recommendation of the expert advisory committee, must (subject to regulation 42ZCZO) make an interim decision in relation to the proposed amendment. If the interim decision is to amend the current *Poisons Standard*, the Secretary must, in doing so, take into account the matters mentioned in subsection 52E(1) of the Act (including, for example, the risks and benefits of the use of a substance, and the potential for abuse of a substance) and the scheduling guidelines as set out in the *Scheduling Policy Framework for Chemicals and Medicines* (SPF, 2015), available on the TGA website.

Under regulation 42ZCZP of the Regulations, the Secretary must, among other things, publish (in a manner the Secretary considers appropriate) the scheduling interim decision, the reasons for that decision and the proposed date of effect (for decisions to amend the current *Poisons Standard*, this will be the date when it is expected that the current *Poisons Standard* will be amended to give effect to the decision).

Also in accordance with regulation 42ZCZP of the Regulations, the Secretary must also invite the applicants and persons who made a submission in response to the original invitation under paragraph 42ZCZK(1)(d), to make further submissions to the Secretary in relation to the interim decisions by a date mentioned in the notice as the closing date, allowing at least 10 business days after publication of the notice. Such a notice relating to the interim decisions of substances initially referred to the November 2017 meeting of the Advisory Committee on Medicines Scheduling (ACMS # 22) was made available on the TGA website on 5 February 2017 and closes on 5 March 2018. Public submissions received on or before this closing date will be published on the TGA website in accordance with regulation 42ZCZQ.

Privacy statement

The Therapeutic Goods Administration (TGA) will not publish information it considers confidential, including yours/other individuals' personal information (unless you/they have consented to publication) or commercially sensitive information. Also, the TGA will not publish information that could be considered advertising or marketing (e.g. logos or slogans associated with products), information about any alleged unlawful activity or that may be defamatory or offensive.

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The TGA collects this information as part of its regulatory functions and may use the information to contact the individual who made the submissions if the TGA has any queries.

As set out above, the TGA is required to publish these submissions unless they contain confidential information.

If you request for your submission to be published in full, including your name and any other information about you, then the TGA will publish your personal information on its website. However, if at any point in time, you change your mind and wish for your personal information to be redacted then please contact the Scheduling Secretariat at medicines.scheduling@health.gov.au so that the pubic submissions can be updated accordingly.

Please note that the TGA cannot guarantee that updating the submissions on the TGA website will result in the removal of your personal information from the internet.

Please note that the TGA will not publish personal information about you/others without your/their consent unless authorised or required by law.

Cathinones, methylone (MDMC) and alpha-pyrrolidinovalerophenone (alpha-PVP)

A request has been made to schedule

The NSWPIC supports the inclusion of cathinones, MDMC and alpha-PVP in schedule 9. The NSWPIC and toxicology units in NSW continue to be contacted for advice on poisonings from these agents. Features of these poisonings include agitation, tachycardia, hypertension and in severe cases delirium, aggressive behaviour, hallucinations, hyperthermia, cardiac dysrhythmias and seizures. Deaths have occurred.[1]

These substances have no currently established therapeutic value and have demonstrated high risks of dependency, abuse, misuse and illicit use; and possess a significant toxicity profile which fits the criteria for schedule 9.

1. Sellors K, Jones A and Chan B. Death due to intravenous use of α-pyrrolidinopentiophenone. Med J Aust 2014; 201 (10): 601-603.

Clotrimazole

A request has been made to amend the scheduling.

The NSW PIC does not support the inclusion of clotrimazole pessaries in schedule 2. The NSWPIC continues to receive calls from members of the public who have inadvertently ingested the vaginally pessary (Table 2 and Poster 1). Current packaging is not sufficiently clear and the word “pessary” is not widely understood in the community to ensure patients are using these products correctly. Inclusion in Schedule 2 would allow greater access and increased likelihood of errors with oral treatments for vaginal thrush. These errors may result in possible gastrointestinal symptoms from ingestions of the pessary, but more importantly result in delays in effective treatment for the patient, leading to increased discomfort from and duration of symptoms. The economic cost of these errors is seen in cost of additional treatment for the patient, increased sick leave and greater use of health resources in the form of GP visits, hospital presentation and calls to the NSWPIC.

Current risks could be minimised by improved packaging and labelling to clarify method of administration and training of pharmacists to clarify administration method with the patients at the time of purchase.

Table 2. Calls to the NSWPIC relating to ingestion of clotrimazole pessary in therapeutic error

2014	63
2015	80
2016	64
2017 (to 27/09/17)	60

The NSWPIC neither supports nor opposes the amendment to the scheduling of clotrimazole cream for vaginal use.

Therapeutic errors involving ingestion of clotrimazole pessaries by women

[redacted]

Jared Brown

New South Wales Poisons Information Centre
The Children's Hospital at Westmead, Sydney, Australia

Introduction

- Over the past decade there has been an increasing number of over-the-counter products marketed for vaginal thrush in Australia.
- In 2004, single-dose fluconazole was downscheduled to be available without a prescription from a pharmacist and can be advertised to consumers. [redacted] was first available, followed by [redacted] in 2006 when the patent expired and since then numerous generics have appeared.
- [redacted] markets the only brand of clotrimazole pessaries (vaginal tablets) in Australia. [redacted] currently market the following products in solid dosage forms for vaginal thrush:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]

[redacted]

Aims: To investigate if there has been a change in the rates of clotrimazole pessary ingestions and discuss the possible reasons.

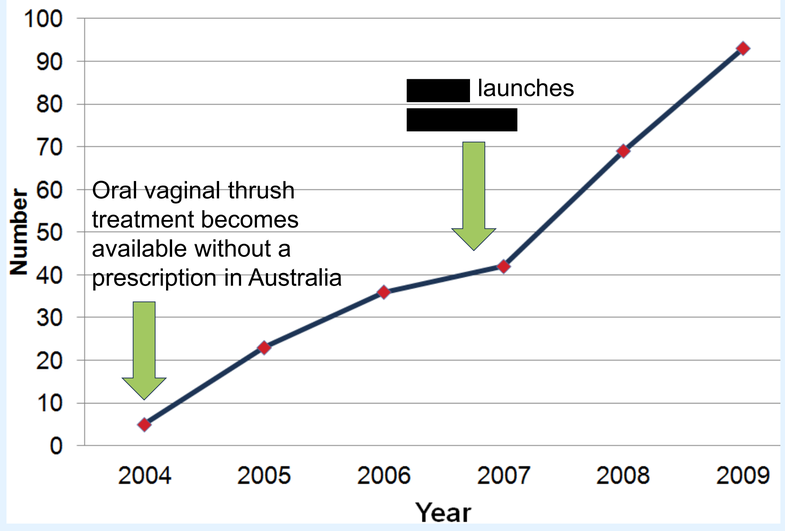
Methods

- Retrospective review of calls made to the NSW Poisons Information Centre during 2004–2009, involving females aged 12 years or older accidentally ingesting a clotrimazole pessary.

Results

- 268 therapeutic errors reported.
- Massive increase from 5 ingestions in 2004 to 93 in 2009 with less than 10% increase in calls.
- 11 women had presented to a hospital and 13 consulted a general practitioner for advice prior to contact with the PIC.
- Only 35 reports had the pessary strength noted:
  - 26 were 500mg once only pessaries
  - 9 were 100mg 6 day pessaries.

Clotrimazole pessary ingestions by women reported to NSW Poisons Information Centre



Adverse events

- 17 women reported minor symptoms associated with clotrimazole pessary ingestion.

Adverse effects	N
Nausea	8
Nausea with vomiting	3
Flushing	3
Abdominal pain	1
Lip swelling	1
Shaking	1
Headache	1
Weakness	1

Discussion

- Most calls are made soon after the ingestion when the woman has decided to read the packaging and information leaflet. This suggests that 'DO NOT SWALLOW' pack warnings need to be improved to ensure they are read before the pessary is removed.
- A common scenario is asking the pharmacist for the 'once thrush treatment' intending to purchase the oral fluconazole product but were given the [redacted] Clotrimazole Pessary instead.
- Possible explanations behind the increased incidence include:
  - Increased availability of non-prescription behind-the-counter vaginal thrush treatments.
  - Since approval in 2004, direct-to-consumer advertising of oral fluconazole has been more common than clotrimazole pessaries.
  - Fluconazole changed in 2006 to a first-line treatment option for vulvovaginal candidiasis leading to less questioning by pharmacists.
  - Similar sounding brand names and packaging causing consumer and pharmacist confusion between [redacted] and [redacted]
  - Lack of consumer familiarity with the term *pessary.*
  - Inadequate or absent pharmacist counselling of consumers.
  - Inadequate outer packaging and blister foil strip for pessary products.

Recommendations

- Educational campaign for pharmacists to ensure they are aware of the importance of counselling patients on the correct usage of vaginal thrush treatments. They also need to clarify the exact product the consumer is after in direct product requests.
- Manufacturers need to review the current packaging and labelling of clotrimazole pessary products:
  - Clearer wording on the front of the main packaging is required to ensure consumers know the product is for intravaginal use.
  - Improve blister foil packaging with the current warning 'Do not take by mouth' in larger print, different colour and also printed on the reverse to ensure it is seen.
- Pharmacists should affix an ancillary label to the pack to improve the current packaging. Example warning stickers available are:

Limitations

- This dataset is not a complete collection of accidental ingestions of clotrimazole pessaries. In Australia, there are also three other Poisons Information Centres and an Adverse Medicine Events Phone Line. [redacted] is the only phone number listed on the packet which would have collected additional cases.
- The nature of spontaneous reporting means that many adverse events are not recorded, particularly those which are not serious.
- Age of women, specific product ingested and circumstances of exposure were not recorded in many cases and outcome was not followed up.
- We were not able to ascertain the nature of the pharmacy purchasing scenario in most cases and were unable to verify the story described with the pharmacist. This needs to be the focus of further research.

Conclusions

- There has been a 19-fold increase in the rates of accidental ingestion of clotrimazole pessaries from 2004 to 2009 in Australia.
- Although clotrimazole ingestion is essentially benign, some adverse reactions have been reported and treatment failure will result.
- Increased rates are likely due to increased availability of an oral product for the same indication, predominance of consumer marketing for oral fluconazole and similar sounding product names creating confusion.
- Simple steps should be relatively easy to implement to reduce the incidence and involve more consistent pharmacist counselling and improved product packaging by the manufacturer.

Further information
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[redacted]

Orphenadrine

A request has been made to reschedule orphenadrine from Schedule 4 to Schedule 3 when compounded with paracetamol in oral preparations containing 35 mg or less of orphenadrine per dosage unit in packs containing 24 or less dosage units when used for the relief of pain associated with skeletal muscle spasm in adults and children over 12 years of age.

The NSWPIC opposes the inclusion of orphenadrine in schedule 3 in any form. Orphenadrine is a highly toxic medication. Within the group of anticholinergic medications it appears to have the greatest risk of death as a result of ventricular dysrhythmias, respiratory depression, seizures and hypoglycaemia.[2] Orphenadrine is significantly over represented in deaths when compared to other antimuscarinics or antipsycotics (71.5 deaths per million prescriptions compared to 0-6.1 deaths per million prescriptions for other anticholinergics).[3]

Inclusion in schedule 3 would allow greater access to orphenadrine for inappropriate use. This is particularly important in the current climate of reducing availability of over the counter pain relief due to codeine rescheduling. Patients will soon be seeking alternatives and pharmacists looking to assist with their pain management through over the counter options.

The NSWPIC has seen an increase in calls relating to orphenadrine in recent years as opiate free alternatives are sought. In the period 6/1/14 to 27/9/17 there have been 45 deliberate self poisonings, 16 therapeutic errors and 11 accidental exposures involving orphenadrine.

Table 3. Calls to the NSWPIC regarding exposures to orphenadrine

2014	15
2015	24
2016	29
2017 (to 27/09/17)	13

The Hunter Area Toxicology Service in NSW has reported on their experience with orphenadrine overdose at the Asia Pacific Association of Medical Toxicology 2016 Scientific Congress (Poster 2).

2. Dawson AH. Antimuscarinic drugs in Dart RC (ed). Medical Toxicology 3rd Ed.

3. Buckley N, McManus P. Fatal toxicity of drugs used in the treatment of psychotic illnesses. Br J Psychiatry. 1998 Jun;172:461-4.

Poster Abstracts

PO-68

ORPHENADRINE INGESTION : A CASE SERIES

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[1] Clinical Toxicology Research Group, University of Newcastle, NSW, Australia, [2]Department of Clinical Toxicology, Calvary Mater Newcastle, NSW, Australia; [3] School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia

Objectives: Orphenadrine is an antihistamine possessing both anticholinergic and sodium channel blocking properties. Orphenadrine overdose has been relatively rare because it has been superseded by better therapeutic alternatives. However, the trend toward utilising non-opioid agents to treat chronic pain has seen a resurgence in the therapeutic use of orphenadrine for its antispasmodic This study aimed to describe orphenadrine ingestions presenting to a regional toxicology service.

Methods: The Hunter Area Toxicology Service database (HATS) was searched for ingestions involving orphenadrine from 2000 to 2015. Data extracted included age, sex, dose ingested, coingested toxins, disposition ward, length of hospital stay and any complications which occurred.

Results: There were a total of 14 presentations to HATS within the database. Of these, 4 occurred prior to 1996 and 10 occurred from 2008 onward. Of the latter 10, six were male and median age was 44 years old (range 31-51). Ingested dose was in three cases, one of which was supratherapeutic use rather than acute an acute monointoxication. Less than 500mg was ingested in three cases and greater than 3g in four cases. The median length of stay was 35 hours (range: 16-378h). Intubation and intensive care was required in three cases all of whom ingested 3g or greater. Seizures occurred in four cases, three whom ingested greater than 3g, with multiple seizures occurring in 2 of these cases. In the case of seizure ingesting less than 3g, tramadol, a potential confounding pro-convulsant had been co-ingested. Delirium occurred in seven cases including all four ingestions greater than 3g. Quetiapine, a potential confounder, was ingested in one of these. Of the other three, one case reported ingesting 300 mg but the dose was in the other 2 cases. The QRS was greater than 120ms on electrocardiogram in two cases which were treated with hypertonic $NaHCO_3$. Although both cases were intubated, they did not develop any arrhythmias or hypotension. This information is presented in more detail in table 1. Orphenadrine was detected in blood in two patients. In the patient ingesting 9g the elimination half-life was 60h.

Conclusion: Based on this small case series, large ingestions of orphenadrine are associated with multiple seizures and profound anticholinergic delirium. Sedative medications are likely to be required and the clinical picture may necessitate intubation and ventilation to manage the behavioural state.

Table 1

Case	Sex	Dose ingested (mg)	Length of stay (hrs)	Delirium	Seizures	Ventilation	Peak QRS length	Confounding co-ingestants
1	M	4000	46	Yes	1	No	<120 ms	Yes
2	M	NQ*	16	No	1	No	<120 ms	Yes
3	F	300	75	Yes	0	No	<120 ms	No
4	F	300	14.5	No	0	No	<120 ms	No
5	F	7200	58	Yes	0	Yes	160 ms	No
6	M	3000	101	Yes	>1	Yes	130 ms	No
7	M	NQ*	27	Yes	0	No	<120 ms	No
8	M	NQ*	35	Yes	0	No	<120 ms	No
9	M	200	27	No	0	No	<120 ms	No
10	F	9000	380	Yes	>1	Yes	<120 ms	No

*Not

[redacted]

Consultation on proposed amendments to the Poisons Standard

NOV
2017

Purpose

The Pharmaceutical Society of Australia (PSA) makes this submission on proposed amendments to the Poisons Standard being referred to the November 2017 meeting of the Advisory Committee on Medicines Scheduling (ACMS) for scheduling advice.

PSA's comments relate to proposed amendments to: clotrimazole, orphenadrine and ibuprofen.

About PSA

PSA is the peak national professional pharmacy organisation representing Australia's 30,000 pharmacists[1] working in all sectors and locations.

PSA's core functions relevant to pharmacists include:

- providing high quality continuing professional development, education and practice support to pharmacists
- developing and advocating standards and guidelines to inform and enhance pharmacists' practice, and
- representing pharmacists' role as frontline health professionals.

PSA is also a registered training organisation and offers qualifications including certificate and diploma-level courses tailored for pharmacists, pharmacy assistants and interns.

[1] Pharmacy Board of Australia. Registrant data. Reporting period: 1 Apr 2017 – 30 Jun 2017. At: **www.pharmacyboard.gov.au/About/Statistics.aspx**

[redacted]

Recommendations

Clotrimazole *– PSA recommends that vaginal preparations of clotrimazole remain in Schedule 3 so that pharmacist intervention and support can minimise the risk of misdiagnosis and help deliver optimal patient health outcomes.*

Orphenadrine *– PSA supports the proposal to reschedule orphenadrine when compounded with paracetamol from Schedule 4 to Schedule 3 in the low dosage range and for short-term therapy. It is essential that relevant practice resources and tools are made available to pharmacists to support the implementation of Schedule 3.*

Ibuprofen *– PSA recommends that ibuprofen be rescheduled as proposed so that over-the-counter availability of ibuprofen-containing products is restricted to a pharmacy setting. This will provide the opportunity for pharmacist intervention, support a quality use of medicines approach to the use of ibuprofen and enhance patient care overall.*

Comments on specific substances

Clotrimazole

Proposal to:

- ***amend the Schedule 2 entry for clotrimazole to include the phrase "in vaginal preparations"***
- ***delete the Schedule 3 entry and Appendix H listing for clotrimazole***
- ***amend the Schedule 4 entry for clotrimazole to delete the reference to Schedule 3, and***
- ***amend the Appendix F listing for clotrimazole to change the reference from Schedule 3 to Schedule 2.***

Over-the-counter antifungal products have been available for many years for minor conditions amenable to self-diagnosis. The inherent safety and risk profile of clotrimazole and its efficacy data are well established and favourable.

While vaginal candidiasis may be self-diagnosed in some cases, studies have shown that caution is required due to concerns around the accuracy of self-diagnosis.[2,3] Tenni et al.[3] cited figures and findings from other research reports as follows:

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[2] Ryan-Wenger NA, Neal JL, Jones AS et al. Accuracy of vaginal symptom self-diagnosis algorithms for deployed military women. Nurs Res 2010;59(1):2–10.

[3] Tenni P, Hughes J, McCloskey J, Hilmi S. Ensuring the appropriateness of topical over-the-counter antifungal agents for clients with self-diagnosed vaginal thrush (the TAFT Project). Canberra: Pharmacy Guild of Australia; 2005.

- Of women who presented with a self-diagnosed initial episode of candidiasis, only 59% actually had the condition.
- Only 34% who self-diagnosed vaginal candidiasis were correct.
- Women who had previously had an episode of clinically diagnosed vaginal candidiasis were no more accurate in their diagnosis than women without previous episodes.

Common vaginal infections include bacterial vaginosis, candida vaginitis and trichomoniasis with different first-line treatment options. The use of antifungal products in non-fungal vaginal infections is ineffective, may worsen the condition, and can delay diagnosis and commencement of appropriate therapy.

PSA believes that Schedule 3 remains the most appropriate schedule for vaginal antifungal preparations including clotrimazole. Pharmacist advice and intervention can assist, for example, in:

- considering the patient's symptoms, treatment history, current medications, other health conditions
- minimising the potential for misdiagnosis
- referring to a medical practitioner where other vaginal conditions may be suspected
- discussing treatment options with the patient and making an appropriate selection
- advising on the management of repeated episodes of vaginal candidiasis
- providing recommendations on ways to minimise the risk of vaginal infections in the future
- monitoring and providing follow-up advice.

In summary, PSA does not support the proposed rescheduling of clotrimazole in vaginal preparations from Schedule 3 to Schedule 2. Careful consideration of patient factors through Schedule 3 arrangements provides the best option for optimal patient health outcomes.

Orphenadrine

Proposal to reschedule orphenadrine from Schedule 4 to Schedule 3 when compounded with paracetamol in oral preparations containing 35 mg or less of orphenadrine per dosage unit in packs containing 24 or less dosage units when used for the relief of pain associated with skeletal muscle spasm in adults and children over 12 years of age.

Current approved indications for orphenadrine combined with paracetamol are:

- tension headache, occipital headaches associated with spasm of skeletal muscles in the region of the head and neck
- acute and traumatic conditions of the limbs and trunk: sprains, strains, whiplash injuries, acute torticollis, prolapsed intervertebral disc.

The orphenadrine and paracetamol combination product has been available in Australia for many years, however, pharmacists report it is not widely used. This may be due to low level awareness of prescribers since the product is not listed on the Pharmaceutical Benefits Scheme (PBS). Even if the product was an appropriate therapeutic option, patients may prefer other PBS-listed options.

The rescheduling proposal outlined is for short-term therapy. Although anticholinergic effects of orphenadrine may require some caution, the proposed dosage is in the low range and orphenadrine has an overall well-established safety and efficacy profile.

The proposed indication for Schedule 3 can be regarded to be recognisable by the patient, and further, a pharmacist will be able to consider the patient's circumstance to discuss whether orphenadrine and paracetamol would be the most appropriate analgesic. This combination product would provide an alternative analgesic when codeine-containing products are rescheduled to Schedule 4.

PSA is supportive of the rescheduling of orphenadrine when combined with paracetamol from Schedule 4 to Schedule 3 with the proposed restrictions. This would be contingent on appropriate support being provided to pharmacists with regards to any necessary education and relevant practice tools for the implementation of Schedule 3.

Ibuprofen

Proposal to:

- ***amend the Schedule 2 entry for ibuprofen to restrict no more than 30 dosage units when in divided preparations containing 200 mg or less of ibuprofen in a primary pack (down from current 100 dosage units)***
- ***delete the exemptions in the Schedule 2 entry for ibuprofen that currently allow general sale of up to 25 dosage units of 200 mg ibuprofen, and***
- ***amend the Schedule 3 entry for ibuprofen to allow up to 100 dosage units containing 200 mg or less of ibuprofen in a primary pack.***

Ibuprofen has a good safety profile for use at over-the-counter (OTC) doses and short term therapy. This was confirmed in a comprehensive review of non-steroidal anti-inflammatory drugs (NSAIDs) with regards to cardiovascular safety.[4]

Nevertheless, PSA has consistently held the view that NSAIDs are potent substances, particularly for individuals with risk factors. The wide availability and use of OTC and prescription NSAIDs ultimately pose risks to patients who may inadvertently take different NSAIDs concurrently or continue therapy for a longer period than clinically necessary. Some patients are known to increase their OTC dose when analgesia is suboptimal.

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[4] Therapeutic Goods Administration. Review of cardiovascular safety of non-steroidal anti-inflammatory drugs. 2014. At: **https://www.tga.gov.au/sites/default/files/medicines-review-nsaid.pdf**

With regards to cardiovascular risk of non-selective NSAIDs, it is reported that naproxen may have the most favourable safety profile.[5] PSA notes that OTC-dose naproxen is currently listed in Schedule 2 and, in our view, it is logical to extend consideration of the appropriateness of applying similar restrictions to all OTC-dose ibuprofen given the similar safety profiles.

Patients with conditions such as asthma, hypertension, renal impairment or heart failure are particularly vulnerable and can experience significant adverse consequences if they take NSAIDs in an unsupervised manner.[6]

In a study,[7] researchers found that at least 50% of all patients and at least 60% of patients diagnosed with a musculoskeletal disorder had at least one NSAID-relevant coexisting medical condition. The frequency of NSAID-relevant coexisting medical conditions also increased with age. The researchers reinforced the important role of primary healthcare professionals in providing guidance on appropriate choice and use of OTC analgesics.

To provide optimal patient care and from a quality use of medicines perspective, PSA firmly believes it is preferable and beneficial for patients to be able to access ibuprofen only through a pharmacy setting where health care advice and intervention are available. This would allow consideration of and discussion with individuals seeking pain relief to confirm, for example, baseline risk factors, comorbidities and medication use, and apply evidence-based decision-making which is tailored to the patient.

Some stakeholders will state that ibuprofen products carry relevant and adequate warning statements and dosing advice on the product packaging and labelling. For example, ibuprofen currently has the following requirements listed in Appendix F of the Poison Standard.

- Warning statement 101: Don't use (*this product*):
    - if you have a stomach ulcer
    - in the last three months of pregnancy
    - if you are allergic to (*ibuprofen*) or anti-inflammatory medicines.
- Warning statement 104: Unless a doctor has told you to, don't use (*this product*):
    - for more than a few days at a time
    - with other medicines containing (*ibuprofen*) or other anti-inflammatory medicines
    - if you have asthma
    - if you are pregnant.

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[5] Schmidt M, Lamberts M, Schjerning Olsen AM et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J 2016;37:1015–23.

[6] Adams RJ, Appleton SL, Gill TK et al. Cause for concern in the use of non-steroidal anti-inflammatory medications in the community – a population-based study. BMC Family Practice 2011;12:70

[7] Bloom L, Blacketer M, Boyle K et al. Aging and the frequency of NSAID-relevant coexisting medical conditions in the primary care setting. Innovation in Aging 2017;1(suppl_1):875.

While these are designed to support safe and appropriate use of the medicine by the patient, PSA believes that the requirement to include many messages can be confusing for some patients and impact on understanding and adherence. In addition, the availability of a particular medicine from locations with varying restrictions to access is less than ideal in conveying and genuinely supporting a quality use of medicines approach.

In connection with a recent Danish publication,[8] the researchers voiced concerns about possible public perception that NSAIDs are harmless given the association they found between NSAID use and increased risk of cardiac arrest. Based on the fact that NSAIDs are widely available, commonly used and have significant potential for adverse cardiovascular effects, the researchers strongly advocated that "NSAIDs should only be available at pharmacies, in limited quantities, and in low doses".[9]

PSA firmly supports having OTC-dose ibuprofen-containing products available only through a pharmacy setting where the opportunity to consult with a pharmacist will assist with appropriate and optimal use. This could include patients who may continue to self-select analgesics through a non-pharmacy setting and not achieve optimal pain management or risk adverse outcomes.

Submitted by:

Pharmaceutical Society of Australia
[redacted]

Contacts:

Dr Lance Emerson, Chief Executive Officer

[redacted]

6 October 2017

[8] Sondergaard KB, Weeke P, Wissenberg M, et al. Non-steroidal anti-inflammatory drug use is associated with increased risk of out-of-hospital cardiac arrest: a nationwide case-time-control study. Cardiovascular Pharmacotherap 2017;3:100–7.

[9] European Society of Cardiology. 'Harmless' painkillers associated with increase risk of cardiac arrest [media release]. 15 Mar 2017.

From: [redacted]
To: Medicines Scheduling
Subject: Consultation: Proposed amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017, Proposed Amendments to the Poisons Standard (Medicines) [SEC=No Protective Marking]
Date: Friday, 6 October 2017 4:45:07 PM

Dear Sir or Madam,

With regards to the upscheduling of ibuprofen, I make this submission.

I am [redacted]

Restricting access to ibuprofen to S2 distribution comes with real costs to consumers with questionable benefits to safety. First, restricted distribution is likely to associate with higher costs of ibuprofen to consumers. Supermarket retailers currently have been following aggressive price-oriented strategies across most of their range and eliminating them as competitors for pharmacy will invariably take competitive pressure off pharmacies to offer low prices. Also, supermarket retailers have more aggressive pricing strategies regarding store brands. Most pharmacy store brands generally use "umbrella pricing" or going just under the major brands' prices. Supermarket store brands tend to be more aggressive relative to the packet size.

At the same time possible enhancements to consumers' safe use of medicines seems questionable and based on a misconception that lower scheduling implies higher likelihood of misuse. For several years now, I have been researching consumer use of OTC medicines using both national surveys and in-store eye tracking of real consumers buying medicines for themselves. There are risk concerns that come out of this research, but it does not directly related to the intensity of distribution.

For example, the most at-risk for misuse of medicines is a segment of the population, whom I call "Double Trouble". They have a noticeable tendency to ignore directions for medicines. Although only 7% of the population and sicker than average, they ignore directions across both OTC *and* prescription drugs. Yet while they worry whether or not they are buying the right medicine and find choosing hard, one would think that they would take advantage of pharmacy staff to direct their questions, but they are not any more than average to do so. Interestingly, they claim to have high knowledge of medicines, which I really don't believe is correct, but it's what they say. Double Troubles are big users across the board of OTC and prescription medicines as well as MVS. For example, they are five times more likely than average Australians to use obesity medicines, three times more likely to use migraine medicines, twice as likely to use oral contraceptives. However, this groups is no more likely than average to want to take advantage of wider distribution of medicines.

It is important to understand the reasons for misuse before we determine an amelioration strategy. For example, Double Troubles may just be obese individuals who erroneously believe they should be taking higher dosages than recommended. Other serious behavioural problems may be present as well. My data indicates that just over half of all Double Troubles have used NRT medicines and hence we can infer they have a high level of smoking—already flagrantly choosing to ignore the highly graphic warnings on cigarette packets. I strongly suspect, but

cannot yet prove that Double Troubles tend to have “cheetah” behaviours in-store. That is, they are quick-in/quick-out consumers offering little potential for in-store controls on their behaviour. Most of this research uses eye tracking equipment and the typical research venue is pharmacies. “Cheetahs” barely even look at packaging, including the brand name. Of the many consumers I have tested, only one “cheetah” has ever asked for assistance from a pharmacy employee—and that was where to find NRT medicines (which he was standing right in front of and was in too much of a rush to notice). More research is needed on Double Troubles to genuinely understand what will affect their behaviour and any move to restricting access seems premature.

While restricting access may be a well-intended control to be placed on consumers, it does present problems for middle-of-the-night medicine needs. In general, pharmacies close earlier than most supermarkets, with many supermarkets staying open all night. Such access at a time of great need is certainly appreciated by many consumers. However, if their preferred OTC pain medicine is restricted, my research estimates that 23.5% of the population will do nothing and just suffer through it, which clearly is not a suitable option for most consumers who can’t get to an open pharmacy. That is, many ibuprofen consumers will not switch to paracetamol and may “tough it out” instead. Even more alarming is that 2% of the population say they will present at an Emergency Department if they can’t get access to their preferred OTC pain medicine. Given the overstressed state of Australia’s EDs this again is not a reasonable option.

Although I discuss only the “top-line” findings of various research activities, I am happy to elaborate on more of these research details if so required.

Thanks,

[redacted]

[redacted]

PROPOSED AMENDMENTS TO POISONS STANDARD

ACMS Meeting November 2017

Comments by the Pharmacy Guild of Australia

1. Clotrimazole– Schedule 2 amendment

Date October 2017
Contact [redacted]

[redacted]
National Secretariat
[redacted]

CLOTRIMAZOLE

Amend the Schedule 2 entry to include the phrase 'in vaginal preparations'

Overview

The Guild does not support this proposal and believes the current scheduling remains appropriate. The risk of inaccurate self-diagnosis and subsequent delay in treatment for more serious underlying conditions warrants the continued mandatory oversight of a pharmacist. A pharmacist can also discuss more suitable treatment options where required.

The purposes for which a substance is to be used and the extent of use of a substance[1]

A 2002 study[2] showed only a third of women who self-diagnosed vaginal candidiasis were accurate and that prior clinician-based diagnosis and reading the label do not improve women's ability to properly diagnose vulvovaginal candidiasis. It showed that vulvovaginal candidiasis is more commonly misdiagnosed than are vaginal trichomoniasis and bacterial vaginosis. It also showed that ready access to these products is associated with wasted financial expenditures, unfulfilled expectations, and a delay in correct diagnosis for a substantial number of women.

Other studies indicate that the relapse rate for these types of infections is high, possibly due to poor diagnosis.[3]

Susceptibility to these infections can be caused by an underlying medical condition such as diabetes, obesity, hormonal fluctuations or prolonged use of antibiotics or steroids.[4] Consequently, the downscheduling of clotrimazole for this indication increases the risk of delayed or missed diagnosis of a potential serious underlying medical condition.

Given the high error rate in self-diagnosis and risk of delayed diagnosis, the Guild considers pharmacist intervention is required to improve the likelihood of accurate diagnosis and referral to a doctor to investigate any underlying causes of the infection if necessary.

A pharmacist may also recommend more suitable treatment options. Some studies have suggested oral anti-fungal regimes are more acceptable because of the ease of administration and avoidance of potentially messy creams and suppositories.[5] The potential for more suitable treatment options to be recommended is reduced if vaginal clotrimazole treatments are made available as a Schedule 2 medicine.

Other matters necessary to protect public health[6]

While some woman may feel uncomfortable discussing such conditions with a pharmacist or have privacy concerns, the Guild does not consider this sufficient reason to downschedule clortimazole in vaginal preparations, particularly given the risks highlighted above. The majority of pharmacies have private

[1] Therapeutic Goods Act 1989 – Sect 52E(b)

[2] Ferris DG, Nyirjesy P, Sobel JD et al; Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis; Obstetrics & Gynecology 2002; 99:419-425

[3] Schwiertz, Andreas, et al. "Throwing the dice for the diagnosis of vaginal complaints?." Annals of clinical microbiology and antimicrobials 5.1 (2006): 4.

[4] https://www.nps.org.au/medical-info/medicine-finder/canesten-clotrimazole-thrush-treatment-6-day-cream

[5] Nwokolo, Nneka C., and Fiona C. Boag. "Chronic vaginal candidiasis." *Drugs & aging* 16.5 (2000): 335-339.

[6] Therapeutic Goods Act 1989 – Sect 52E(f)

consultation areas and the Guild encourages pharmacies to offer these areas to consumers where appropriate. Consumers can also request to have these conversations discreetly in a more private area.

In addition, June 2017 Pharmacy Board of Australia registrant data[7] indicates that the majority of registered pharmacists are female. In most cases, this should enable consumers to speak with a female pharmacist if they are more comfortable discussing this condition with a pharmacist of the same gender.

Summary

The Guild believes the current scheduling remains appropriate.

[7] http://www.pharmacyboard.gov.au/About/Statistics.aspx

[redacted]

Comment on proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Chemicals Scheduling in November 2017

Contents

[redacted]

Introductory statement

This submission supports retention of the current scheduling arrangements for ibuprofen. However, it is not possible to address the specific issues raised in the amendment proposal and the data behind it because these details have not been released. Consequently we request the Delegate to either decide that the current scheduling remains appropriate or defer any rescheduling decision to a subsequent meeting to allow stakeholders sufficient time to address in detail the issues that have been raised and the data behind them.

Executive summary

1. Ibuprofen has a well-established safety and efficacy profile as an analgesic and has been used for many years as an effective over-the-counter (OTC) and prescription only medication. Reckitt Benckiser (Australia) Pty Ltd ('RB') is the sponsor of the 'Nurofen' range of ibuprofen-containing products in Australia, many of which are marketed in small packs through general retail / grocery, pharmacies and convenience outlets and through pharmacies in larger packs and liquid dose forms.

2. The current proposal, if implemented, would restrict sales of oral dose forms of ibuprofen to pharmacy outlets. This restriction is unnecessary and would have a significant impact on consumers, retailers and sponsors with possible public health consequences arising from increased consumption of paracetamol with its attendant risk from accidental or deliberate overdose.

3. Ibuprofen has a wide therapeutic window and when taken orally, the propensity for toxicity in overdose is low. The consequences of misuse of paracetamol are substantially worse than with ibuprofen.

4. In the UK, the switch to GSL licence in 1996 doubled sales of ibuprofen but this was without a corresponding increase in ADRs reported to the MHRA. Ibuprofen in solid dose forms was first exempted from scheduling in 2003 at low dose (up to 1200 mg per day) in small packs (up to 25 dose units) and with strict label warnings. The shift to GSL in Australia in January 2004 has not resulted in increasing reports of poisonings.

5. Since that time the TGA has re-evaluated the benefit / risk ratio in relation to cardiovascular risk (2014) and pregnancy risk (2016). In both cases it was decided that the current scheduling remained appropriate, subject to some tightening of label warning statements. An EMA review in 2015 found no increase in cardiovascular risk with ibuprofen at doses of up to 1,200 mg per day (see page 6 for details).

[redacted]

6. In June 2017 RB commissioned an independent literature review to investigate the statement: “Ibuprofen is as well tolerated as paracetamol” with a key focus on gastrointestinal effects. The review concluded that this statement is supported by the available literature i.e. ibuprofen is as well tolerated as paracetamol with respect to gastrointestinal effects (see page 12 for details).

7. Reckitt Benckiser’s Periodic Safety Update Report (PSUR) for the period 01 March 2014 to 28 February 2017 reported a total patient exposure with the caplet / tablet / meltlet formulations of 350,364,524 and an estimated total cumulative exposure since the International Birth Date (19 February 1969) of 5,785,143,653 patients exposed.

   The PSUR was based on clinical trials, cumulative exposure and sales data, post-market data and a review of the scientific literature for the reporting period. In summary the report’s findings were that:

   - There have been no new important, potential or identified risks associated with use of products containing ibuprofen;
   - No particular issues or safety concerns have been investigated by Reckitt Benckiser Healthcare (UK) Limited during the reporting period and it is concluded from evaluation of the cumulative safety data and benefit-risk analysis that the safety data remain in accordance with the Reference Safety Information (RSI) and no new information has come to light which would require an amendment;
   - On the evidence available to the Marketing Authorisation Holder (MAH), the benefit-risk balance for the company compounds containing ibuprofen remains positive;
   - The evaluation of the case reports received by Reckitt Benckiser Healthcare (UK) Limited during the reporting period has not revealed any new safety concerns for the product. The overall benefit-risk profile of ibuprofen remains positive”.
   - Ibuprofen has a better risk:benefit profile with fewer serious consequences with regard to adverse events and misuse than other commonly used unscheduled analgesics such as paracetamol and aspirin. The adverse event profile of OTC ibuprofen (up to 1200 mg per day) is comparable to that of paracetamol and placebo and is better than that of aspirin (see page 12 for details).

8. Data commissioned by RB from Quantium[1], based on sales of ibuprofen per shopping 'basket' in Woolworths supermarkets over a 12 month period, show that the vast majority of consumers adopt a responsible and conservative approach to analgesic purchases in general retail / grocery. Therapeutic Goods Order No 92 ('TGO 92') came into effect in August 2016 with a 4 year transition period. The labelling requirements in TGO 92 will further help consumers to find and understand the information they need on medicine labels (see page 14 for details).

9. RB maintains that the current scheduling of ibuprofen remains appropriate given that:

    - TGA reviews in 2014 (cardiovascular risk) and 2016 (pregnancy risk) found that the current scheduling of ibuprofen remained appropriate subject to some tightening of label statements;
    - An EMA review in 2015 found no increase in cardiovascular risk with ibuprofen at doses of up to 1,200 mg per day;
    - RB is not aware of any new published data in relation to cardiovascular risk that would justify further restrictions on the use of ibuprofen at OTC doses and durations;
    - RB's independent literature review (June 2017) found that ibuprofen is as well tolerated as paracetamol with respect to gastrointestinal effects;
    - RB's PSUR for the period 01 March 2014 to 28 February 2017 found that the overall benefit-risk profile of ibuprofen remains positive;
    - 12 month general retail / grocery sales data show that the vast majority of shoppers buy single packs of ibuprofen. RB is not aware of any evidence to suggest that these consumers use ibuprofen inappropriately;
    - The introduction of TGO 92 compliant labels from August 2016 will make it easier for consumers to find and understand the information they need on medicine labels.

10. There seems to be little foundation for the current proposal to restrict ibuprofen sales to pharmacy or limit schedule 2 pack sizes to 30. RB requests the delegate to confirm that the current scheduling remains appropriate or defer any scheduling decision to a subsequent meeting to allow RB sufficient time to address in detail the issues and data that have been presented as part of this proposal.

[1] https://www.quantium.com/

[redacted]

Body of the submission

Background

Scheduling history

Ibuprofen was first included in Schedule 4 in February 1973. Ibuprofen in packs of 24 or less tablets or capsules for the relief of dysmenorrhoea or of pain associated with inflammation was rescheduled to Schedule 3 in May 1989.

In May 1995, 200 mg or less of ibuprofen per dosage unit in a pack containing 50 or less dosage units and labelled with a recommended daily dose of not more than 1200 mg, was rescheduled from Schedule 3 to Schedule 2.

In October 2002, ibuprofen for external use was exempt from scheduling based on the safety data reviewed at the time.

In June and October 2003, the NDPSC decided that ibuprofen in divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 25 or less dosage units when labelled with a recommended maximum daily dose of 1200 mg of ibuprofen and compliant with the mandatory label requirements, would be exempt from scheduling on the following basis:

- The indications for low dose (<1200 mg/day) oral administration of ibuprofen are suitable for self-identification and treatment without professional advice;
- Ibuprofen has a comparable safety profile to existing unscheduled analgesic products (aspirin and paracetamol in small pack sizes) indicated for the same use;
- Ibuprofen products have been available for general sale in the USA since 1984, and in the UK since 1996 with no significant safety issues arising over that time, and there is considerable OTC marketing experience in Australia as an S2 medicine;
- Ibuprofen has a wide therapeutic index, and the risk of masking a serious disease is very low;
- Appropriate warning statements for GI complications, pregnancy, asthma and use in certain age groups have been included to reduce the risks in sensitive sub-populations;
- Ibuprofen has a very low to absent potential for abuse.

In February 2006, ibuprofen containing 400 mg per dose unit in packs of not more than 50 dose units and labelled not for the treatment of children aged less than 12 years was rescheduled form Schedule 4 to Schedule 3.

In June 2011, the delegate decided to increase the maximum amount of ibuprofen in liquid preparations in Schedule 2 from 4 g to 8 g.

TGA reviews

Cardiovascular safety

In October 2014 TGA released the 'Review of cardiovascular safety of non-steroidal anti-inflammatory drugs V2.1'[2]. In relation to OTC medicines the Review concluded as follows (page 10):

> *"Based on the current evidence, there are no major changes required to the availability and warnings on labels for over-the-counter (OTC) diclofenac, ibuprofen and naproxen. These drugs provide effective pain relief when used according to the label at recommended doses for short durations. However, inappropriate, unsafe and overuse of these OTC NSAIDs could pose a significant health hazard. Hence, there is a need to increase consumer awareness about the CV profile of OTC NSAIDs (diclofenac, ibuprofen and naproxen), just as the knowledge about their GI risks is widespread.*
>
> *The labelling of these OTC products needs to include:*
>
> - *Warnings that NSAIDs may cause an increased risk of serious CV thrombotic events, MI and stroke, which can be fatal, this risk may increase with duration of use, and consumers with CV disease or risk factors for CV disease may be at greater risk;*
> - *Stronger reminders that patients with CV disease and/or CV risk factors should seek the advice of a physician before using these drugs, and that consumers should be made aware of the signs and symptoms of serious CV toxicity. Consumers should remain alert for CV events even in absence of previous CV symptoms and also be made more aware of the need to limit the dose and duration of treatment in accordance with the package instructions, unless otherwise advised by a physician".*

The Review was summarised in a Q&A on the TGA website (25 September 2017) as follows (underlining added):

> *"The TGA has completed a review of the cardiovascular risks associated with the use of NSAIDs. <u>This review found that the benefit-risk profile for NSAIDs remains positive, meaning the health benefits of these medicines outweigh the known risks for most people</u>. However, the review also found that there is a need to raise awareness among consumers and health professionals of these risks, including that they also relate to OTC NSAID products. The TGA undertook a public consultation regarding options to reduce the risks associated with OTC NSAIDs.*

[2] https://www.tga.gov.au/sites/default/files/medicines-review-nsaid.pdf

Since 1 July 2016 (or 1 January 2017 in some cases where extensions were granted), all sponsors of OTC oral NSAIDs have been required to include updated warnings on their product labelling from 'Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful' (or words to that effect), to 'Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage' (or words to that effect)".

In October 2014 TGA put forward options for response to the Review[3] including an option for OTC NSAIDs to be considered for rescheduling. This option was considered and decided as follows:

> *"The TGA concluded that the current scheduling and availability of OTC NSAIDs are appropriate and that the addition of stronger warning statements on the labels should be sufficient to alert and inform consumers about the risks associated with excessive use of those products. Thus no changes to scheduling are proposed at this time".*

The updated label warning statements came into effect in the *Medicines Advisory Statements Specification 2017*[4].

EMA review 2015

The EMA issued an '*Updated advice on use of high-dose ibuprofen*' on 22 May 2015. This advice followed a review carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which confirmed a small increased risk of cardiovascular problems, such as heart attacks and strokes, in patients taking high doses of ibuprofen (at or above 2,400 mg per day).

The Review also found (underlining added) that:

- No increase in cardiovascular risk is seen with ibuprofen at doses of up to 1,200 mg per day, which is the highest dose generally used for over-the-counter (OTC) preparations taken by mouth in the European Union (EU); and

- Experimental data suggest long-term use of ibuprofen/dexibuprofen may reduce the cardioprotective effect of low-dose acetylsalicylic acid (typically 75 mg per day). This is because ibuprofen may competitively inhibit the effect of low dose acetylsalicylic

[3] https://www.tga.gov.au/consultation/consultation-review-cardiovascular-safety-non-steroidal-anti-inflammatory-drugs-and-safety-review-diclofenac

[4] https://www.tga.gov.au/medicines-advisory-statements-specification-updates

acid on platelet aggregation when they are used concomitantly. No clinically relevant effect is considered to be likely for occasional ibuprofen use.

Additional cardiovascular safety data

RB is aware of three studies published since 2015 that have data relating to the cardiovascular safety of ibuprofen. These data are not relevant to the availability of ibuprofen in general retail / grocery outlets in Australia because the doses were higher or the duration longer than a few days or the trial subjects had medical conditions that are contraindicated for OTC use in Australia. Summary details are included below.

Bally 2017

This was a systematic review followed by a one stage bayesian individual patient data meta-analysis on data sourced from Canadian and European healthcare databases. The objective was to characterise the determinants, time course, and risks of acute myocardial infarction associated with use of oral non-steroidal anti-inflammatory drugs (NSAIDs).

Eligible studies were sourced from computerised drug prescription or medical databases, conducted in the general or an elderly population, documented acute myocardial infarction as specific outcome, studied selective cyclo-oxygenase-2 inhibitors (including rofecoxib) and traditional NSAIDs, compared risk of acute myocardial infarction in NSAID users with non-users, allowed for time dependent analyses, and minimised effects of confounding and misclassification bias.

Drug exposure was modelled as an indicator variable incorporating the specific NSAID, its recency, duration of use, and dose. The outcome measures were the summary adjusted odds ratios of first acute myocardial infarction after study entry for each category of NSAID use at index date (date of acute myocardial infarction for cases, matched date for controls) versus non-use in the preceding year and the posterior probability of acute myocardial infarction.

A cohort of 446 763 individuals including 61 460 with acute myocardial infarction was acquired. Taking any dose of NSAIDs for one week, one month, or more than a month the probability of increased myocardial infarction risk (posterior probability of odds ratio >1.0) was 92% for celecoxib, 97% for ibuprofen, and 99% for diclofenac, naproxen, and rofecoxib. The corresponding odds ratios (95% credible intervals) were 1.24 (0.91 to 1.82) for celecoxib, 1.48 (1.00 to 2.26) for ibuprofen, 1.50 (1.06 to 2.04) for diclofenac, 1.53 (1.07 to 2.33) for naproxen, and 1.58 (1.07 to 2.17) for rofecoxib. Greater risk of myocardial infarction was documented for higher dose of NSAIDs. With use for longer than one month, risks did not appear to exceed those associated with shorter durations.

The study concluded that all NSAIDs, including naproxen, were found to be associated with an increased risk of acute myocardial infarction. Risk of myocardial infarction with celecoxib

was comparable to that of traditional NSAIDS and was lower than for rofecoxib. Risk was greatest during the first month of NSAID use and with higher doses.

Relevance to OTC ibuprofen
The results of this study are have no relevance to the safety of ibuprofen in OTC medicines in Australia for the following reasons:

- Ibuprofen in OTC medicines is labelled not to be used "for more than 3 days at a time". While the study did include subjects who had used ibuprofen for 1 – 7 days it did not quantify the dose used over this period or the number of days of use.
- The mean age of subjects across the 4 databases was 77.8, 68.9, 70.2 and 58.1 years meaning the majority were aged >65 years. Ibuprofen in OTC medicines is labelled not to be used in people ≥ 65 years unless on a doctor's advice.
- 7.3% of subjects had 'previous myocardial infarction' and 34% had 'coronary heart disease' (RAMQ database). Ibuprofen in OTC medicines is labelled not to be used in people with "heart problems".
- 29.1% of subjects had 'gastrointestinal ulcer disease' (RAMQ database). Ibuprofen in OTC medicines is labelled not to be used by people who "have a stomach ulcer or other stomach disorders".
- 23% of subjects (RAMQ database) were taking 'cardioprotective aspirin'. Ibuprofen in OTC medicines is labelled not to be used by people who are taking aspirin except on a doctor's advice.
- 1.8% of subjects had 'acute or chronic renal failure'. Ibuprofen in OTC medicines is labelled not to be used by people who have "kidney problems".

The data in this study do not reliably reflect cardiovascular risk in people using ibuprofen under the conditions that apply to OTC use in Australia (i.e. low dose, short duration, without concurrent risk factors for heart, kidney or liver disease).

Nissen 2016

This was a study of the cardiovascular safety of celecoxib, as compared with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs).

Patients who required NSAIDs for osteoarthritis or rheumatoid arthritis and were at increased cardiovascular risk were randomly assigned to receive celecoxib, ibuprofen, or naproxen. The goal of the trial was to assess the non-inferiority of celecoxib with regard to the primary composite outcome of cardiovascular death (including hemorrhagic death), nonfatal myocardial infarction, or nonfatal stroke. Non-inferiority required a hazard ratio of 1.12 or lower, as well as an upper 97.5% confidence limit of 1.33 or lower in the intention-to-treat population and of 1.40 or lower in the on-treatment population. Gastrointestinal and renal outcomes were also adjudicated.

A total of 24,081 patients were randomly assigned to the celecoxib group (mean [±SD] daily dose, 209±37 mg), the naproxen group (852±103 mg), or the ibuprofen group (2045±246 mg) for a mean treatment duration of 20.3±16.0 months and a mean follow-up period of 34.1±13.4 months. During the trial, 68.8% of the patients stopped taking the study drug, and 27.4% of the patients discontinued follow-up. In the intention-to-treat analyses, a primary outcome event occurred in 188 patients in the celecoxib group (2.3%), 201 patients in the naproxen group (2.5%), and 218 patients in the ibuprofen group (2.7%) (hazard ratio for celecoxib vs. naproxen, 0.93; 95% confidence interval [CI], 0.76 to 1.13; hazard ratio for celecoxib vs. ibuprofen, 0.85; 95% CI, 0.70 to 1.04; P<0.001 for non-inferiority in both comparisons). In the on-treatment analysis, a primary outcome event occurred in 134 patients in the celecoxib group (1.7%), 144 patients in the naproxen group (1.8%), and 155 patients in the ibuprofen group (1.9%) (hazard ratio for celecoxib vs. naproxen, 0.90; 95% CI, 0.71 to 1.15; hazard ratio for celecoxib vs. ibuprofen, 0.81; 95% CI, 0.65 to 1.02; P<0.001 for non-inferiority in both comparisons). The risk of gastrointestinal events was significantly lower with celecoxib than with naproxen (P = 0.01) or ibuprofen (P = 0.002); the risk of renal events was significantly lower with celecoxib than with ibuprofen (P = 0.004) but was not significantly lower with celecoxib than with naproxen (P = 0.19).

The study concluded that at moderate doses, celecoxib was found to be non-inferior to ibuprofen or naproxen with regard to cardiovascular safety.

Relevance to OTC ibuprofen
The results of the study have no relevance to the safety of ibuprofen in OTC medicines in Australia for the following reasons:

- The dose was 1800 mg / day administered for 20 months ± 16 months. The maximum dose of Ibuprofen in OTC medicines is 1200 mg / day and OTC products are labelled not to be taken for more than 3 days at a time.
- “Increased cardiovascular risk” or “established cardiovascular disease” or “an increased risk of the development of cardiovascular disease” were inclusion criteria and 72.2% of subjects were in cardiovascular risk category ‘primary prevention’ with 22.8% in the ‘secondary prevention’ category. Ibuprofen in OTC medicines is labelled not to be used in people with “heart problems”.
- The age of the ibuprofen group (ITT population) was 63.2 ± 9.4 years, meaning many subjects were aged >65 years. Ibuprofen in OTC medicines is labelled not to be used in people ≥ 65 years unless on a doctor’s advice.

The data in this study do not reflect cardiovascular risk in people using ibuprofen under the conditions that apply to OTC use in Australia (i.e. low dose, short duration without concurrent risk factors for heart, kidney or liver disease).

Gonzalez-Valcarcel 2016

This study examined whether paracetamol or ibuprofen use is associated with major cardiovascular events (MACE) or major bleeding in 19,120 patients with recent ischemic

stroke or transient ischemic attack of mainly atherothrombotic origin included in the 'Prevention of cerebrovascular and cardiovascular events of ischemic origin with terutroban in patients with a history of ischemic stroke or transient ischemic attack' (PERFORM) trial.

A 2 nested case–control analysis was performed (2153 cases with MACE during trial follow-up and 4306 controls matched on Essen stroke risk score; 809 cases with major bleeding matched with 1616 controls) and a separate time-varying analysis.

12.3% of subjects were prescribed paracetamol and 2.5% ibuprofen. Median duration of treatment was 14 (interquartile range 5–145) days for paracetamol and 9 (5–30) days for ibuprofen. Paracetamol, but not ibuprofen, was associated with increased risk of MACE (odds ratio 1.21, 95% confidence interval [CI] 1.04–1.42) or a major bleeding (odds ratio 1.60, 95% CI 1.26–2.03), with no impact of daily dose and duration of paracetamol treatment. Time-varying analysis found an increased risk of MACE with both paracetamol (hazard ratio 1.22, 95% CI 1.05–1.43) and ibuprofen (hazard ratio 1.47, 95% CI 1.06–2.03) and of major bleeding with paracetamol (hazard ratio 1.95, 95% CI 1.45–2.62).

The study concluded that there was a weak and inconsistent signal for association between paracetamol or ibuprofen and MACE or major bleeding, which may be related to either a genuine but modest effect of these drugs or to residual confounding.

Relevance to OTC ibuprofen
The study was inconclusive for both ibuprofen and paracetamol. The data in this study have little relevance to the use of ibuprofen under OTC conditions in Australia.

Safety in pregnancy

In October 2016 TGA released a safety review of the known association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the increased risk of miscarriage. The review focused on ensuring that consistent information on this risk was available for all products.

In relation to OTC NSAIDs the TGA recommendation was to:

> "*Require all OTC non-aspirin NSAIDs, including those exclusively indicated for dysmenorrhoea, to include an advisory statement on their packaging which appropriately addresses the risk of spontaneous abortion*".

This recommendation was implemented in the *Medicines Advisory Statements Specification 2017*[5]*.* The existing and updated label warning statements follow below (underlining added):

[5] https://www.tga.gov.au/medicines-advisory-statements-specification-updates

Existing label warning statement	*New label warning statement (mandatory from 1 January 2019)*
Do not use [this product/insert name of product] during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.	*Do not use if trying to become pregnant, or during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy. [underlining added]*

Reckitt Benckiser reviews

Gastro-intestinal risk

Ibuprofen is clinically proven to be as well-tolerated as paracetamol (Moore N 2015, Moore 1999) and is safer at OTC doses with less serious consequences in overdose.

RB commissioned a literature review (June 2017) to investigate the statement: "*Ibuprofen is as well tolerated as paracetamol"* with a key focus on gastrointestinal effects. The review concluded that there is "*that ibuprofen is as well tolerated as paracetamol, including with respect to gastrointestinal effects, when used at the dosages and durations approved for OTC use, and provided consumers comply with all relevant contraindications, precautions and dosage instructions for the relevant OTC products*".

Periodic Safety Update Report (PSUR)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Labelling of analgesics

Consumer behaviour

The Quantium multiple-purchase data above reflect a high level of compliance with the warning statements that must appear on the packs of all unscheduled products for oral use that contain ibuprofen:

> "*Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage*" (Ref: Medicines Advisory Statements Specification 2017 (MASS 2017)).

[redacted]

[redacted]

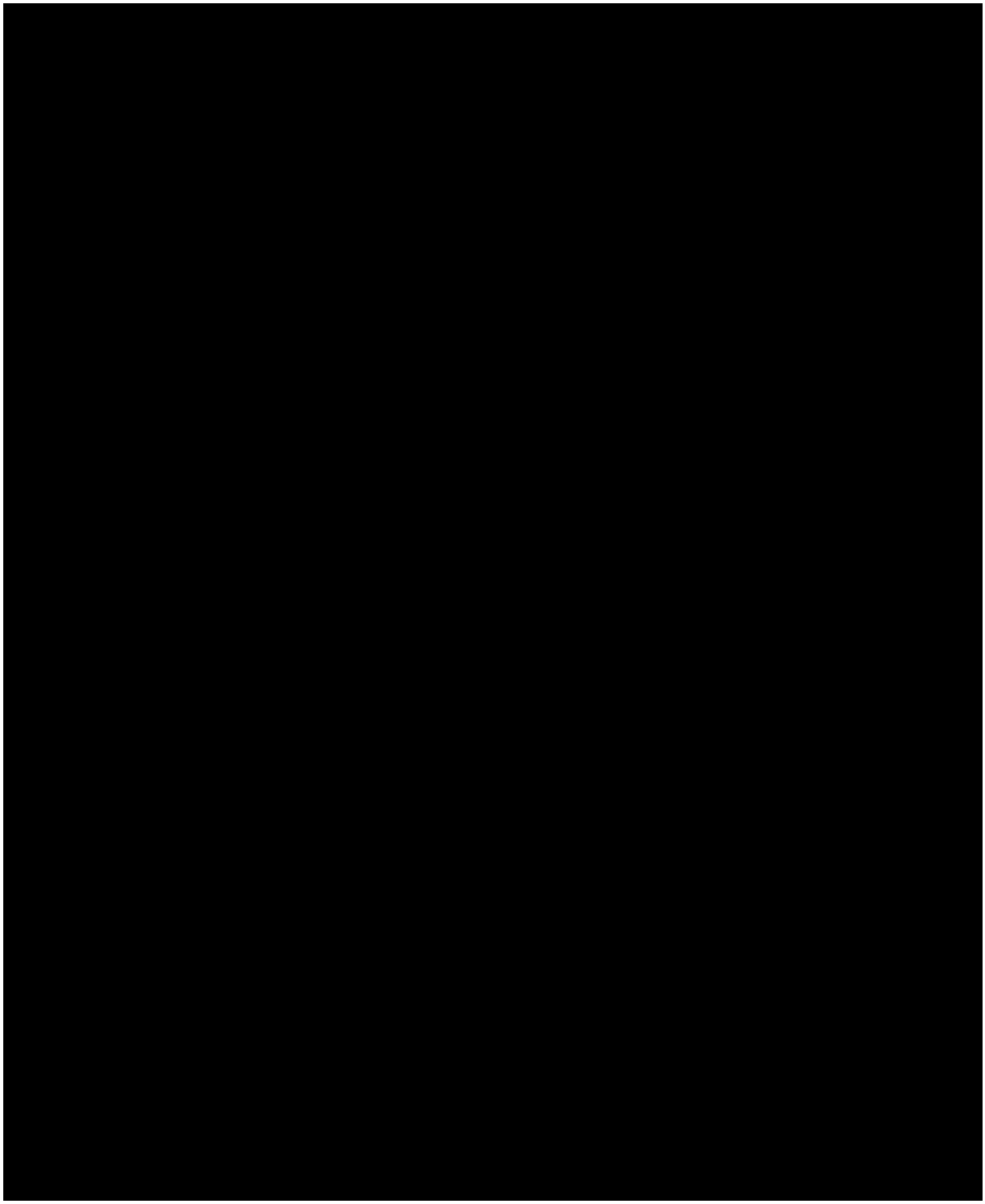
Label requirements – TGO 92

Therapeutic Goods Order No 92 ('TGO 92') came into effect on 31 August 2016 with a 4 year transition period. A statement on TGA's website[7] (28 July 2017) explains the changes as follows:

> "*Over the next four years labels are changing to make it easier to find the information you need. We are changing medicine labels to make important information about your medicine easier to find. These changes are the result of many years of consultation - they bring Australian medicine labels up to date with international best practice. They will help Australians to make more informed choices about their medicines and use them more safely.*
>
> *Under the new labelling rules active ingredients need to be more prominent. You will usually be able to find them below or next to the product name on the front of the medicine pack. Active ingredients will often be in a larger print size on the front label to make them easier to read. Make sure to look for the active ingredients on your medicine labels so you know what you are taking.*
>
> *Most over the counter medicines will have* ***critical health information*** *in distinctive tables to help you use your medicine safely. Over the counter medicines are medicines that you buy without a prescription. The new rules mean that critical health information will always be displayed in a consistent order and will be easy to recognise. Always check the critical health information before you take your medicine.*
>
> *Labelling requirements for Australian medicines are being updated after many years of consultation with industry, health professionals and the community. The changes help bring Australian medicine labels up to date and align them with international best practice*".

The Quantium consumer purchase data (page 14 above) reflect pre-TGO 92 labelling. Further improvements in consumer comprehension and safety are expected as the new packs become available. [redacted]

[7] https://www.tga.gov.au/australias-medicine-labels-are-becoming-clearer



Unintended public health consequences

The removal of ibuprofen from sale in general retail / grocery is likely to result in substantially increased sales and consumption of paracetamol with unpredictable effects on consumption and the attendant public health risk from accidental or deliberate paracetamol overdose. In addition limiting schedule 2 pack sizes to 30 will mean that every consumer who is seeking more than 5 days' supply of ibuprofen must be counselled by the pharmacist. This seems illogical given paracetamol is available in packs of 96 for relief of symptoms of osteoarthritis and that the safety and tolerability profiles are essentially similar (Moore 1999, Moore 2015).

In fact ibuprofen has a wide therapeutic window and when taken orally, the propensity for toxicity in overdose is low. The consequences of misuse of paracetamol are substantially worse than with ibuprofen.

Summary and conclusion

RB requests the Delegate to either decide that the current scheduling remains appropriate or defer any scheduling decision to a subsequent meeting. This will give stakeholders the opportunity to address in detail the issues that have been raised in the current submission and the data behind it.

RB maintains that the current scheduling of ibuprofen remains appropriate for the following reasons:

- TGA reviews in 2014 (cardiovascular risk) and 2016 (risk in pregnancy) concluded that the current scheduling remained appropriate subject to some tightening of label statements (which has been implemented);
- An EMA review in 2015 that found no increase in cardiovascular risk with ibuprofen at doses of up to 1,200 mg per day;
- RB is not aware of any data published since the TGA and EMA reviews with evidence of increased cardiovascular risk from ibuprofen use at OTC doses and durations;
- RB's independent literature review (June 2017) found that ibuprofen is as well tolerated as paracetamol with respect to gastrointestinal effects;
- Ibuprofen is clinically proven to be as well-tolerated as paracetamol (Moore 1999, Moore N 2015) and is safer at OTC doses with less serious consequences in overdose;
- RB's PSUR for the period 01 March 2014 to 28 February 2017 found that the overall benefit-risk profile of ibuprofen remains positive;
- 12 month supermarket sales data show that consumers take a responsible attitude to ibuprofen purchases with the vast majority of supermarket shoppers buying single packs;

- The introduction of TGO 92-compliant labels from August 2016 will further aid consumers in finding and understanding the information on medicine labels;
- The current proposal, if implemented, would restrict sales of oral dose forms of ibuprofen to pharmacy outlets. This restriction is unnecessary and would have a significant impact on consumers, retailers and sponsors with possible unintended consequences such as increased consumption of paracetamol with the attendant public health risk of accidental or deliberate paracetamol overdose.
- In addition limiting schedule 2 pack sizes to 30 tablets seems illogical given paracetamol is available in packs of 96 for relief of symptoms of osteoarthritis and that the safety and tolerability profiles are essentially similar. In fact ibuprofen has a wide therapeutic window and when taken orally, the propensity for toxicity in overdose is low. The consequences of misuse of paracetamol are substantially worse than with ibuprofen.

In summary, there seems to be little foundation for the current proposal to restrict ibuprofen sales to pharmacy and to limit current schedule 2 pack sizes to 30 tablets (5 days supply).

[redacted]

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6 October 2017

Re: Proposed amendment to the Poisons Standard entry for ibuprofen referred to the November 2017 meeting of the Advisory Committee on Medicines Scheduling (ACMS)

Dear Sir/Madam

In reference to the public notice for the November 2017 ACMS meeting, [redacted] appreciates the opportunity to provide comment on the proposed amendment to the scheduling of ibuprofen.

As demonstrated by all of the available evidence, the current scheduling of non-prescription (OTC) ibuprofen remains appropriate because:

1. Considerable OTC experience both within Australia and internationally has been amassed over a number of decades

2. OTC ibuprofen continues to demonstrate a favourable benefit-risk profile. No new safety information has risen to warrant a change in scheduling or access, a position reflected in TGA's recent NSAID review published in 2014

3. Any change in scheduling would be inconsistent with comparable regulatory jurisdictions such as the UK, Canada, the US and New Zealand

4. Restricting the sale of OTC ibuprofen would deny Australian consumers appropriate and timely access to a safe and effective analgesic, thereby limiting their ability to effectively treat or manage sudden symptoms or minor ailments. As such, this would have a negative impact on public health

Ibuprofen 200 mg in small packs (up to 25 dosage units) has been available for **over a decade** in Australia as an unscheduled medicine, and over 20 years as a Schedule 2 medicine. Over this period of time, no new safety information has been identified contributing significantly to the risk of OTC ibuprofen and therefore the overall benefit-risk profile remains favourable. Ibuprofen in small packs does not satisfy the criteria for Schedule 2 classification. Larger packs sizes (up to 100 units) appropriately meet the factors of a Schedule 2 medicine in accordance with the Scheduling Policy Framework with the availability of a pharmacist at the point of sale to support consumers in selecting and using the appropriate medicine.

Scheduling history and regulatory background

Ibuprofen 200 mg or less per dosage unit was first included in Schedule 3 in May 1989 and reclassified to Schedule 2 in May 1995.

[redacted]

In June 2003, the Delegate exempted from scheduling 200 mg or less of ibuprofen in small packs citing[i]:

- The indications for temporary use, low dose (≤1200 mg/day) oral administration of OTC ibuprofen are suitable for self-identification and treatment without professional advice.

- OTC ibuprofen has a comparable safety profile to existing unscheduled analgesic products (aspirin and paracetamol in small pack sizes) indicated for the same use.

- OTC ibuprofen products have been available for general sale in the USA since 1984 and in the UK since 1996 with no significant safety issues arising over that time, and there is considerable OTC marketing experience in Australia as an S2 medicine.

- Ibuprofen has a wide therapeutic index, and the risk of masking a serious disease is very low.

- Appropriate warning statements for GI complications, pregnancy, asthma and use in certain age groups have been included to reduce the risks in sensitive sub-populations. Ibuprofen has a very low to absent potential for abuse.

Therefore, as a non-prescription medicine, ibuprofen has been deemed to be sufficiently safe to allow consumers to self-select with the risk of misadventure effectively managed by the inclusion of precautions and warnings on the medicine label and directions provided on when to seek advice from a pharmacist or doctor.

More recently, the TGA undertook a comprehensive review of cardiovascular safety of non-steroidal anti-inflammatory drugs[ii] that included an assessment of cardiovascular risks that have been described for long-term use of higher, prescription doses of NSAIDs. TGA determined in 2014 that the **current scheduling and availability of OTC NSAIDs are appropriate** and that the addition of stronger label warnings on the labels would be sufficient to alert and inform consumers about the risks associated with excessive use of those products. The review concluded that "*Based on the current evidence, there are no major changes suggested to the availability and warnings on labels for OTC diclofenac, ibuprofen and naproxen. These drugs provide effective pain relief when used according to the label at recommended doses for short durations".* Since that review, there has been no new safety information on OTC ibuprofen to warrant a change in scheduling or access.

It is also relevant to consider the terms of reference[iii] of the Government's Review of Medicines and Medical Devices which note "*a safe and effective regulatory framework for medicines and medical devices should balance safety and market access priorities to the benefit of patients and industry and align with the government's commitment to increase productivity with competitiveness*." The available safety and efficacy data supports that the benefit-risk profile of OTC ibuprofen and its current level of access remains favourable. Given this fact, any proposal to amend the scheduling would be at odds with the Government's stated position on regulation of medicines.

International Regulations

The proposed amendment of scheduling of ibuprofen would be inconsistent with comparable regulatory jurisdictions such as the UK, Canada, the US and New Zealand. Based on the

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clinical evidence, there is no justification for consumers in Australia to be denied similar access to ibuprofen as that afforded to consumers in comparable overseas markets. This would be a retrograde step, resulting in over-regulation of a safe and effective analgesic.

Ibuprofen has been marketed internationally for over 30 years and is available as tablets, chewable tablets, capsules, liquid-filled capsules, topical gels, gel coated tablets, liquids/ suspensions/drops and spray liquids. Ibuprofen has been sold without prescription in the United Kingdom since 1983, in the United States since 1984, and in Canada and Australia since 1989. It is currently approved in 108 countries and marketed in 77.

In the UK and other parts of Europe, ibuprofen has been available without prescription for general sale since 1996 and in the US it has been available from general sales outlets since 1984. Unscheduled ibuprofen became available in Canada in 2000 (where packs of up to 90 dosage units can be accessed via general sales outlets) and in New Zealand in 2004. During the latest 16 year period, it is estimated that 49,618,514,828 standard units of ibuprofen (OTC and Rx) have been distributed (1st quarter of 2002 through 18 February 2017).

As such there is a large body of post-marketing data for ibuprofen 200 mg formulations which demonstrate its well-established safety profile.

Benefit-Risk Analysis

Both pharmacy and grocery outlets play an important role in the Australian healthcare environment and the care continuum, and consumers are entitled to access appropriate OTC analgesics from each. Such availability is supported by the benefit-risk profile of each individual product and the TGA's risk-based approach to regulation.

OTC medicines are a critical component in advancing consumer health because they allow people to treat or manage many health conditions expediently and successfully. They provide easier access to treatment options for common conditions, offering not only convenience but also timely treatment and relief for sudden symptoms or minor ailments.

[redacted]

Any change in scheduling of ibuprofen would leave consumers limited in choice to aspirin and paracetamol in the non-pharmacy retail outlets. Whilst paracetamol is a useful analgesic, when taken in either intentional or unintentional overdose situations it has a high potential for causing hepatotoxicity. Aspirin has a significantly worse GI profile than ibuprofen. Ibuprofen best fits the profile for self-medication and will not cause major complications in overdose situations and has a good safety profile when taken according the labelling.

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[redacted]

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These recent publications, similar to earlier publications which have been reviewed by the TGA and other regulatory authorities, do not indicate an increased risk of CV adverse events with ibuprofen administered at OTC doses and durations. Therefore, the overall benefit risk profile of OTC ibuprofen remains favourable.

Conclusion

In the absence of any new safety data, there is no evidence available to support a change in scheduling of OTC ibuprofen in Australia. As outlined above, there are numerous reasons to maintain the current scheduling of OTC ibuprofen. Considerable OTC experience, both within Australia and internationally, has been amassed over a number of decades. Following a safety review of NSAIDs with a focus on CV risk, the TGA concluded in 2014 that OTC ibuprofen continues to demonstrate a favourable benefit-risk profile. Since that review, there has been no new safety information on OTC ibuprofen to warrant a change in scheduling or

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access. Any change in scheduling would be inconsistent with comparable regulatory jurisdictions such as the UK, Canada, the US and New Zealand. Finally, restricting the sale of OTC ibuprofen would deny Australian consumers convenient and timely access to a safe and effective analgesic, thereby limiting their ability to effectively treat or manage sudden symptoms or minor ailments. As such, this would have a negative impact on public health.

In summary, with no new evidence or data to the contrary, [redacted] the current scheduling of OTC ibuprofen in Australia remains appropriate.

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