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 may receive submissions from the public on a proposed amendment to the Poisons Standard where there has been an invitation to the public for submissions on the proposal in accordance with the Therapeutic Goods Regulations 1990. These submissions may contain personal information of the individual making the submissions and others.

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.

[redacted]

AUSTRALIAN MEDICAL ASSOCIATION

[redacted]

AMA submission to ACMS re orphenadrine downscheduling proposal

The AMA strongly opposes the proposal to create a new Schedule 3 entry to allow low dose/small packs of orphenadrine compounded with paracetamol to be available over the counter without a prescription from a medical practitioner.

The Advisory Committee on Medicines Scheduling (ACMS) will be well aware that orphenadrine is potentially very toxic in overdose. It also has significant abuse potential and is responsible for the majority of anticholinergic deaths in countries where this has been studied.

Orphenadrine is not a high volume prescription item, and given that those who would benefit from it have conditions which should require medical management, there is no rationale for a proposal to downschedule.

The AMA reiterates, as it has in previous submissions to the ACMS, that without having any details of the proposal, the rationale and its objectives, it is difficult to frame an informed and relevant submission.

In the absence of any other information the AMA can only rely on the currently available published evidence pointing to risks of abuse, overdose and death.

Contact

[redacted]

September 2017

Submission to Advisory Committee on Chemicals Scheduling(ACCS), Advisory Committee on Medicine Scheduling(ACMS) and the joint ACCS-ACMS on proposed amendment to the Poisons Standard (Medicines)

In **support of: Deleting the exemptions in the Schedule 2 entry for ibuprofen that currently allow general sale of up to 25 dosage units of 200 mg ibuprofen**

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CONTENTS OF SUBMISSION

1. Executive Summary of submission supporting deletion of the exemptions in the Schedule 2 entry for ibuprofen that currently allow general sale of up to 25 dosage units of 200 mg ibuprofen

1.1 It is evident that the decision taken by the then NDPSC in 2003 included overseas data that was not applicable to the assessment of the Australian proposal to consider allowing consumer self-selection of non-scheduled medication products in general store outlets.

In addition, the Committee drew on assumed precedents of safety in use, which, in our view, were unable to be substantiated. Also, it was stated that "the evaluator acknowledged that the PAIN study excluded patients with contraindications"- i.e. the very patients most at risk from self-selection of non-scheduled medication products in general store outlets.

1.2 Patterns of medication management since 2003, in particular the relatively new and increasing pattern of use of combination tablets containing an ACE inhibitor or ARB plus a diuretic for hypertension, has resulted in an increased potential risk of "triple whammy" renal adverse medication events. In addition, there is greater use of antithrombotic drugs to reduce the risk of stroke in atrial fibrillation; the co-administration of these drugs with NSAIDs can result in major bleeding events.

This especially poses a risk for consumers who self-select the NSAID treatment and choose to purchase these products from a general store, without the benefit of health professional screening and advice.

1.3 Perhaps most importantly, much more information is now available on the risks associated with NSAID use, particularly related to cardiovascular events. These reports highlight the fact that individual NSAIDs have different cardiovascular safety issues that need to be considered when choosing appropriate treatment, and that these considerations are also relevant for healthy individuals.

This underlines the importance of the need for appropriate counselling for NSAID therapy in the general population, including counselling and professional advice for OTC sales of NSAIDs.

1.4 With the change in scheduling of codeine-based analgesic combination choices from 2018, it is important that guidance and counselling from a pharmacist be readily available for the likely additional increased cohort of consumers who will turn to NSAID products with or without paracetamol.

If ibuprofen remains available for sale outside pharmacies, it is likely that some consumers will turn to self-selection from a general store, without professional advice.

For all these reasons relating to providing optimum opportunities for individualised patient advice on risks versus benefits of NSAID products, we are in favour of ibuprofen sales being again restricted to supply only within pharmacies, where up-to-date professional advice and counselling is available.

2. Background to the 2003 NDPSC decision and rationale for this submission

Summary of background to the 2003 decision allowing general sale of small-sized packs of ibuprofen 200 mg

Ibuprofen was first listed in Schedule 4 of the SUSDP at the February 1973 meeting. Subsequently, at the May 1989 meeting, ibuprofen was included in Schedule 3, in packs of 24 or less tablets or capsule for the relief of dysmenorrhoea or of pain associated with inflammation.

The Schedule 3 entry was amended at various meetings until the May 1995 meeting, when a new Schedule 2 entry was proposed.

At the May and August 1998 meetings, the Committee considered exempting ibuprofen from scheduling in divided dosage units containing 200mg or less of ibuprofen per unit in pack sizes of 24 or less. It decided that there should be no change to the scheduling due to the safety concerns associated with the wider availability of another NSAID for use as an analgesic. Ibuprofen is currently available for oral use in Schedules 2 and 4 of the SUSDP.

At the October 2002 meeting the NDPSC exempted ibuprofen for external use from scheduling on the basis of the available safety data.

At the 38th Meeting of the then NDPSC, it was decided to exempt pack sizes of 24 ibuprofen from scheduling, thereby allowing consumers to self-select these products at grocery and other general sales outlets, without the option of professional advice.

(NDPSC Meeting 38 17-19 June 2003 -Item 14.1.2 and Reasons pp 107-114 and Appendix 1 and Submissions against proposal Appendix 1 pp 179-181).

Reasons given for the Decision by the NDPSC to exempt small packs of ibuprofen from scheduling

It appears that there were two persuasive factors in operation for the NDPSC decision to allow the sale of small pack sizes of ibuprofen tablets in non-pharmacy outlets, exempt from Poisons Scheduling:

I. The "PAIN" studies of 1999 & 2003, namely:

- Moore N et.al. The PAIN STUDY. Paracetamol, Aspirin and Ibuprofen New Tolerability Study. Clin Drug Invest, 1999;18:89-98, and
- Moore N et al, Risk factors for adverse events in analgesic drug users: results from the PAIN study. Pharmacoepidemiology and Drug Safety, 2003;12:1-10.

II. Ibuprofen 200mg tablets had been available in small packs without prescription for general sale in the USA and UK since 1984 and 1996, respectively, which the NDPSC stated had been "without any increase in the incidence of adverse effects".

3. Comment on the justification by NDPSC in 2003 allowing general sale of small-sized packs of ibuprofen 200 mg

3.1 Inapplicability of the PAIN studies to the Australian situation

The PAIN studies of 1999 and 2003 were not applicable to the Australian non-prescription products sales environment, and in our view were clearly not a relevant precedent for supporting self-selection of an analgesic by consumers in a general store environment, for the following reasons:

- In Australia, the NDPSC decision was made in respect to consumer self-selection of analgesics at general stores **without any professional input whatever**. However, both PAIN study reports analysed data on **analgesics obtained by consumers, not by self-selection, but at a general practitioner consultation.** As stated in the 1999 PAIN study report method, the study was "a blinded, multicentre study in general practice of up to 7 days of aspirin, paracetamol (both up to 3g daily) or ibuprofen (up to 1.2g daily), administered for common painful conditions, using patient-generated data **with physician assistance**".

- As stated by NDPSC in their reasons for the decision, the evaluator acknowledged that the PAIN study **excluded patients with contraindications** – the very patients most at risk from NSAIDs.

3.2 A statement was made by the NDPSC Committee that "Ibuprofen 200mg tablets have been available in small packs without prescription for general sale in the USA and UK since 1984 and 1996, respectively, which the NDPSC stated had been without any increase in the incidence of adverse effects".

How would an increase in the incidence of adverse effects been detected? In our view, in the absence of robust outcome data, there can be no justification in introducing the idea of 'precedents', whether with or without any purported increase in the incidence of adverse effects', in the review of products for which an exemption from scheduling is being considered.

Each application must be considered on its own merits with regards to the use and safety profile of the medicine concerned.

Indeed, it is self-evident that there are no established quality assurance processes for the supply through grocery and other general sales outlets of products that are exempt from scheduling. To our knowledge, there has been no such systematic monitoring or reporting carried out in Australia.

Clearly, it is unknown how many, if any, potential problems there have been in the community from the use of these 'precedents' due to their unrestricted access. It is even unlikely that if consumers presented to a hospital emergency department with a NSAID-induced adverse event following a purchase from a general store that it would be recognised and recorded as such an event.

Furthermore, we have no direct knowledge as to whether or to what extent, consumers read the warnings and cautions on the labels of proprietary medicine products, although various studies have indicated that a large proportion do not read these warnings and cautions (eg. Hoy MG & Levenshus AB. A mixed methods approach to assessing actual readership on branded drug websites. Journal of Risk Research 27th. August, 2016).

With medications obtained through a pharmacy, professional guidance and explanation of cautions is readily available. **This is becoming increasingly important in the evolving pattern of fixed 2 and 3 component combined presentations of various prescription medications for a variety of conditions.** Obviously, this may present **an increased risk of severe drug interactions** for people using NSAID medications, as will be explained shortly.

4. Changes in drug usage patterns and risk factors for NSAID use since 2003 supporting the need to have ibuprofen sold only within pharmacies

Firstly, the use of antithrombotic therapy for stroke prevention in atrial fibrillation has increased markedly over the past decade, especially with the availability of the direct oral anticoagulants (DOACs) - which include a direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban and apixaban). NSAIDs should not be taken with these drugs because of the increased risk of bleeds, including major gastrointestinal and intracranial haemorrhage (e.g. Di Nisio M et al. Risk of major bleeding in patients with venous thromboembolism treated with rivaroxaban or with heparin and vitamin K antagonists. Thromb Haemost 2016;115(2):424-32; Mavrakanas TA et al. Direct oral anticoagulants: efficacy and safety in patient subgroups. Swiss Med Wkly 2015;145:w14081).

What has also changed substantially since 2003 is that there is now abundant evidence of the risk of ibuprofen and other NSAIDs/COX-2-selective inhibitors (admittedly dose-related) for both cardiac arrest and stroke risk, including in “healthy” individuals.

Some references to this, including relevant brief summaries of key points in each case are as follows:

- Fosbol, E. L., et al. (2010). "Cardiovascular safety of non-steroidal anti inflammatory drugs among healthy individuals." Expert Opin Drug Saf 9(6): 893-903
  CONCLUSION: Individual NSAIDs have different cardiovascular safety that needs to be considered when choosing appropriate treatment. In particular, rofecoxib and diclofenac were associated with increased cardiovascular mortality and morbidity and should be used with caution in most individuals. This notion is also valid for healthy individuals and underlines the importance of critical use of NSAID therapy in the general population and also **that over-the over-the counter retail sale of NSAIDs should be reassessed.**

- Weinstein, R. B., et al. (2017).Drug Saf. 2017 Aug 5.doi: 10.1007/s40264-017-0581-7. Channeling in the Use of Nonprescription Paracetamol and Ibuprofen in an Electronic Medical Records Database: Evidence and Implications.

INTRODUCTION: Over-the-counter analgesics such as paracetamol and ibuprofen are among the most widely used, and having a good understanding of their safety profile is important to public health. Prior observational studies estimating the risks associated with paracetamol use acknowledge the inherent limitations of these studies. One threat to the validity of observational studies is channeling bias, i.e. the notion that patients are systematically exposed to one drug or the other, based on current and past comorbidities, in a manner that affects estimated relative risk.
RESULTS: The proportions of prior MI, GI bleeding, renal disease, and stroke were significantly higher in those prescribed any paracetamol versus ibuprofen alone, after adjusting for sex and age. We were not able to adequately remove selection bias using a selected set of covariates for propensity score adjustment; however, when we fit the propensity score model using a substantially larger number of covariates, evidence of residual bias was attenuated.

The above paper is particularly relevant to the PAIN studies; the safety of a drug can not be evaluated if patients at risk of adverse events are intentionally excluded.

- Thone, K., et al. "Non-Steroidal Anti-Inflammatory Drug Use and the Risk of Acute Myocardial Infarction in the General German Population: A Nested Case-Control Study." Drugs Real World Outcomes. 2017;4:127-137
  "Diclofenac and ibuprofen, the most frequently used NSAIDs, were associated with a 40-50% increased relative risk of AMI, even for low cumulative NSAID amounts."

- Bally, M., et al. "Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta- analysis of individual patient data." BMJ 2017; 357 doi: https://doi.org/10.1136/bmj.j1909
  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.

- Sondergaard, K. B., 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." Eur Heart J Cardiovasc Pharmacother 2017:3:100-107.
  The results were driven by an increased risk of cardiac arrest in ibuprofen and diclofenac users. Use of diclofenac (odds ratio [OR], 1.50 [95% confidence interval (CI) 1.23-1.82]) and ibuprofen [OR, 1.31 (95% CI 1.14-1.51)] was associated with a significantly increased risk of cardiac arrest.

- Semergen. 2017 Sep 4. pii: S1138-3593(17)30226-5. doi: 10.1016/j.semerg.2017.07.004.
  A moderate risk was observed for ibuprofen. It increases the risk of acute coronary syndrome within 5 years of having a cardiovascular event, especially in the 2nd year (OR 1.63; 95% CI 1.42-1.87). It also increases the risk of stroke (HR 1.23; 95% IC 1.10-1.38).

- Varas-Lorenzo, C., et al. "Myocardial infarction and individual nonsteroidal anti-inflammatory drugs meta-analysis of observational studies." Pharmacoepidemiol Drug Saf 2013;**22**: 559-570.
  CONCLUSIONS: Most frequently NSAIDs used in clinical practice, except naproxen, are associated with an increased risk of AMI at high doses or in persons with diagnosed coronary heart disease. For diclofenac and rofecoxib, the risk was increased at low and high doses.

- Trelle, S., et al. "Cardiovascular safety of non-steroidal anti-inflammatory drugs: Network meta analysis." BMJ 2011;342: c7086.
  CONCLUSIONS: Although uncertainty remains, little evidence exists to suggest that any of the investigated drugs are safe in cardiovascular terms. Naproxen seemed least harmful. Cardiovascular risk needs to be taken into account when prescribing any non-steroidal anti-inflammatory drug.

- Kontogiorgis, C., et al. "Use of Non-Selective Non-Steroidal Anti-Inflammatory Drugs in relation to Cardiovascular Events. A Systematic Pharmacoepidemiological Review." Curr Vasc Pharmacol 2016;14:502-513.
  RESULTS: The best safety profile related to MI was found for naproxen, while the worst safety profile with excessively increased risk for stroke, MI and major bleeding, was for diclofenac. **Naproxen showed higher risk for major bleeding than ibuprofen and the risk for stroke was slightly higher than ibuprofen.**
  Regarding heart failure, ibuprofen presented the highest risk while the highest risk for AF was attributed to the current use of diclofenac. There are few data related to mefenamic acid, which showed a strong association with increased risk or stroke and a moderately increased risk for MI.

- Lavonas E et al. “Comparative risks of non-prescription analgesics: a structured topic review and research priorities”. Expert Opinion on Drug Safety, 2012; 11:1, 33-44, DOI: 10.1517/14740338.2012.629782
  - In addition, non-prescription medication use is not captured in data systems commonly used for medication safety research”.
  - Viewed from a policy perspective, harm that occurs when non-prescription doses are exceeded must also be considered. More than 20% of non-prescription ibuprofen and naproxen users exceed the label dose
  - One recent prospective cohort study of patients previously hospitalized for heart failure found an absolute increase in risk of death of 1.9/1000 person-years (95% CI: 1 - 2.8) on ibuprofen therapy (Ref.cited: Gislason GH, Rasmussen JN, Abildstrom SZ, et al. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs in chronic heart failure. Arch Intern Med 2009;169:141-9).

- Hamilton K et.al. High risk use of OTC NSAIDs and ASA in family medicine: A retrospective chart review. International Journal of Risk & Safety in Medicine 27 (2015) 191–199
  BACKGROUND: Complications associated with the use of NSAIDs, antiplatelet agents, and anticoagulants are among the top causes of preventable drug-related ER visits,

hospitalizations and death. Although over-the-counter (OTC) NSAIDs and ASA also contribute to this preventable risk, it is unclear how well these medications are documented in primary care records.
METHODS: A retrospective electronic and paper chart review was conducted to evaluate the prevalence of 13 evidence-based high-risk prescriptions and the contribution of OTC NSAIDs and ASA to these potentially inappropriate prescriptions (PIPs).
RESULTS: Of the 148 patients included in the review, ASA was taken by 117 patients (79%) while OTC NSAIDs were taken by 36 (24%). OTC NSAIDs were never documented within the "medication" section of the electronic record, whereas ASA was documented in 65 (56%) cases. Eighty percent (118/148) taking either OTC NSAIDs or ASA were identified as having at least one PIP.
CONCLUSION: **OTC NSAIDs and ASA are widely available and are commonly taken without the knowledge of the prescriber. These medications contribute to the overall risk of bleeding.** Review and documentation of OTC NSAIDs and ASA use should be part of all relevant patient encounters when prescribing NSAIDs, antiplatelets and anticoagulants

- Cavagna L et.al. Overuse of Prescription and OTC Non-Steroidal Anti-Inflammatory Drugs in Patients With Rheumatoid Arthritis And Osteoarthritis. International Journal of Immunopathology and Pharmacology 2013; Vol. 26, No. 1,279-281
  Non-steroidal anti-inflammatory drugs (NSAIDs) have been demonstrated to have significant cardiovascular and gastrointestinal toxicity; high dose of intake and concomitant use of multiple compounds or corticosteroids are factors that increase the risk of NSAID toxicity. In this paper we described our experience on NSAIDs misuse (both prescribing and OTC formulations), particularly relevant in the setting of rheumatoid arthritis and osteoarthritis. We also evaluated causes underlying NSAIDs misuse (e.g, not satisfactory pain control, other painful conditions, etc).
  Summary Comments:
  Overall analysis reveals: **a) NSAID overuse is common in both RA and OA; b) it involves both prescription and OTC drugs; and c) very importantly, conditions other than disease-related pain may lead to additional NSAID consumption as the result of physician prescription or self-medication. These findings indicate that physicians do not always take into account the pharmaceutical background of patients and patients are not completely aware of risks associated with NSAID use, despite having been previously informed, or perhaps are not familiar with other medications in the family of NSAIDs.** Based on these patterns of misuse revealed by this study and others, clinicians must enhance their own habits of medication reconciliation in regard to multiple NSAIDs and concomitant glucocorticoid use as well as their approach to patient education in order to emphasize safe NSAID use and hopefully reduce the risk of NSAID-related side-effects.

- MacDonald TM et al. The safety of drugs for OTC use: what evidence is required for an NSAID switch? Pharmacoepidemiology and drug safety 2002; 11: 577–584
  The safety of OTC products in actual conditions of use is crucial for their wide distribution, since the circumstances of their use may be different from the prescription-only setting. **A group of experts met in Geneva, Switzerland, with the aim of exploring the criteria required to show safety equivalence of OTC medications,**

with specific reference to low-dose non-steroidal anti-inflammatory drugs (NSAIDs) used for analgesia. It was agreed that an acceptable surrogate marker for safety as the primary endpoint in a study designed to show that a new NSAID was not inferior to a current NSAID would be any adverse event leading the patient to consult a physician. A sample size of 10 000 patients in each arm of a two-arm study would be sufficient to show non-inferiority with acceptable relative risk equal to 1.2 with at least 90% power for an event rate of 5%. An example of a possible pharmacy-based randomized study design to demonstrate safety equivalence of OTC analgesics is given.
The study population would be all patients entering the study pharmacies with the intent of purchasing analgesics.

- Arfe A et.al. Non-steroidal anti-inflammatory drugs and risk of heart failure in four European countries: nested case-control study.
  BMJ 2016; 354 doi: https://doi.org/10.1136/bmj.i4857 (Published 28 September 2016)
  A recent, multi-centre, nested case-control European Study comprehensively covering the issue of cardiovascular risks of NSAIDs, with relevant references, and strengths and limitations of the Study as below:

  Summary:
  Risk of admission for heart failure increased for seven traditional NSAIDs (diclofenac, **ibuprofen**, indomethacin, ketorolac, naproxen, nimesulide, and piroxicam) and two COX 2 inhibitors (etoricoxib and rofecoxib).

  Results: Risk of admission for heart failure increased for seven traditional NSAIDs (diclofenac, **ibuprofen**, indomethacin, ketorolac, naproxen, nimesulide, and piroxicam) and two COX 2 inhibitors (etoricoxib and rofecoxib)

  Strengths and limitations of study:

  "Our findings, which focused only on prescription NSAIDs, might apply to NSAIDs obtained over the counter as well. Although over-the-counter NSAIDs are probably typically used at lower doses, by younger people, and for shorter durations than prescribed NSAIDs, they are sometimes available at the same doses than those prescribed and may be inappropriately overused. Therefore, our findings could have large scale consequences in public health and further research needs to assess the safety of over-the-counter NSAIDs under the conditions they are typically used".

Relevant background references quoted in this Study:

1. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med 2001;345:433-42.doi:10.1056/NEJM200108093450607 pmid:11496855.
2. Fries JF. Selective cyclooxygenase inhibition: promise for future NSAID therapy?Scand J Rheumatol Suppl 1996;102:1.doi:10.3109/03009749609097224 pmid:8628977.
3. Bombardier C, Laine L, Reicin A, et al. VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520-8, 2, 1528.doi:10.1056/NEJM200011233432103 pmid:11087881.
4. Amer M, Bead VR, Bathon J, Blumenthal RS, Edwards DN. Use of nonsteroidal anti-inflammatory drugs in patients with cardiovascular disease: a cautionary tale. Cardiol Rev 2010;18:204-12. doi:10.1097/CRD.0b013e3181ce1521 pmid:20539104.
5. Bresalier RS, Sandler RS, Quan H, et al. Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092-1102. doi:10.1056/NEJMoa050493.

6. Solomon SD, McMurray JJ, Pfeffer MA, et al. Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071-80.doi:10.1056/NEJMoa050405 pmid:15713944.
7. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials.BMJ 2006;332:1302-8. doi:10.1136/bmj.332.7553.1302 pmid:16740558.
8. García Rodríguez LA, Tacconelli S, Patrignani P. Role of dose potency in the prediction of risk of myocardial infarction associated with nonsteroidal anti-inflammatory drugs in the general population. J Am Coll Cardiol 2008;52:1628-36.doi:10.1016/j.jacc.2008.08.041 pmid:18992652.
9. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med 2011;8:e1001098. doi:10.1371/journal.pmed.1001098 pmid:21980265.
10. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086. doi:10.1136/bmj.c7086 pmid:21224324.
11. Bhala N, Emberson J, Merhi A, et al. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769-79. doi:10.1016/S0140-6736(13)60900-9 pmid:23726390.
12. Fabule J, Adebajo A. Comparative evaluation of cardiovascular outcomes in patients with osteoarthritis and rheumatoid arthritis on recommended doses of nonsteroidal anti-inflammatory drugs. Ther Adv Musculoskelet Dis 2014;6:111-30.doi:10.1177/1759720X14541668 pmid:25342992.
13. Scott PA, Kingsley GH, Scott DL. Non-steroidal anti-inflammatory drugs and cardiac failure: meta-analyses of observational studies and randomised controlled trials. Eur J Heart Fail 2008;10:1102-7.doi:10.1016/j.ejheart.2008.07.013 pmid:18760966.
14. García Rodríguez LA, Hernández-Díaz S. Nonsteroidal antiinflammatory drugs as a trigger of clinical heart failure.Epidemiology 2003;14:240-6. doi:10.1097/01.EDE.0000034633.74133.C3.

5. Increased potential for adverse effects, including a "triple whammy" renal outcome, due to the advent of fixed-dose antihypertensive combination tablets

5.2 Background - The "Triple Whammy Effect"

In 2003 and again in 2006, the then ADRAC issued warnings about the severe adverse health outcomes including renal failure, that can and did arise in patients who were prescribed an ACE inhibitor or ARB medication with a diuretic, and then also took an NSAID product - the "triple whammy effect", resulting from reduced renal blood flow.

- Anon: ACE Inhibitor, diuretic and NSAID: a dangerous combination. Adverse Drug Reactions Bulletin 2003;22(4):14-15.

- Anon. Beware the triple whammy. Adverse Drug Reactions Bulletin 2006;25(5):18.

- This concern has also been endorsed by various other medical experts e.g. MJA Insight "Call to extend NSAID warnings". 2014;37(6).

5.3 Changes to combined product availability and potential increase in risk of the triple whammy outcomes in consumers

In the years since 2003, the availability and use of various combination products for cardiovascular conditions, containing both a diuretic with an ACE inhibitor or ARB in the one tablet, has proliferated.

Indeed, this type of combined tablet has, in recent years, become a frequently

prescribed type of antihypertensive medication oral medication in Australia, thereby increasing the potential population cohort at risk of renal complications from inadvertent concurrent use of an NSAID product.

5.4 Two studies dealing with acute kidney damage associated with use of NSAIDs

- With specific reference to potential renal damage with use of Ibuprofen, a paper published in the Medical Journal of Australia dealt with life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis (RTA). This paper noted that, although RTA usually occurs with excessive doses, it can occur at doses below the maximum recommended. (Ng JL et al. Life-threatening hypokalaemia associated with ibuprofen-induced renal tubular acidosis. MJA 2011;194:313-316.)
  Summary:
  Renal tubular acidosis is an underreported complication of ibuprofen misuse, and can result in life-threatening hypokalaemia. We describe four patients who presented with profound hypokalaemia and muscle weakness associated with excessive ibuprofen ingestion. Ibuprofen cessation and supportive management resulted in complete biochemical resolution within a few days. These cases remind practitioners about potential complications of unmonitored use of over-the-counter analgesics, including those with potential for misuse due to their codeine content.
  Conclusion:
  In conclusion, profound hypokalaemia due to RTA is a potentially fatal complication of ibuprofen use. Although it usually occurs with excessive doses, it can occur at doses below the maximum recommended. Therefore, ibuprofen toxicity should be considered in the differential diagnosis of patients presenting with severe hypokalaemia or hypokalaemic paralysis.

- Lipworth L et.al. High prevalence of non-steroidal anti-inflammatory drug use among acute kidney injury survivors in the southern community cohort study. BMC Nephrology 2016 **17**:189 https://doi.org/10.1186/s12882-016-0411-7
  Background: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used and have been linked to acute kidney injury (AKI), chronic kidney disease (CKD) and cardiovascular disease (CVD). Patients who survive an AKI episode are at risk for future adverse kidney and cardiovascular outcomes. The objective of our study was to examine the prevalence and predictors of NSAID use among AKI survivors.
  Methods: The Southern Community Cohort Study is a prospective study of low-income adults aged 40–79 in the southeastern US. Through linkage with Centers for Medicare and Medicaid Services, 826 participants with an AKI diagnosis (ICD-9 584.5-584.9) at any age prior to cohort enrollment were identified. At baseline, data were collected on regular use of prescription and over-the-counter NSAIDs, as well as demographic, medical and other characteristics. Additional comorbidities were ascertained via linkage with CMS or the US Renal Data System.

Conclusion

In summary, regular NSAID use is common (20%) among socioeconomically disadvantaged AKI survivors.

The high prevalence of an avoidable risk factor in a group at high risk for both kidney and cardiovascular events is concerning and underscores the need to better understand the association between NSAID use in this population and future adverse events and in whom the risks are highest, as well as the reasons for use and effective strategies to improve education and awareness among physicians, patients and caregivers.

5.5 Discussion about this issue:

- NPS MedicineWise Radar 10 November, 2010.
  New fixed-dose antihypertensive combination tablets including the first triple therapy were listed on the Pharmaceutical Benefits Scheme (PBS) on 1 November 2010). https://www.nps.org.au/radar/articles/new-dual-and-triple-antihypertensive-combinations-pbs-listed-be-aware-of-potential-confusion
- NPS MedicineWise "What you need to know about fixed-dose combinations 16 October 2013. Summary ". https://www.nps.org.au/medical-info/clinical-topics/news/what-you-need-to-know-about-fixed-dose-combinations#r21
  At its meeting in February 2013 the PBAC's Drug Utilisation Sub-Committee (DUSC) expressed concern about emerging trends with fixed-dose combination (FDC) products, including a higher proportion of patients starting on FDCs before trialling individual components, and increased use of FDCs without a comparable decline in the prescribing of individual components. The benefits of FDC products have been promoted by sponsors as improved adherence, convenience and reduced cost to the consumer. While there is evidence to support adherence benefits of FDC products, there are risks and disadvantages associated with their use. It may be difficult to identify the ingredient responsible for an adverse effect, and dose adjustment is not always possible. Furthermore, it is well established that adverse renal effects resulting in, albeit temporary, renal failure can also arise in people with existing renal compromise, as well as otherwise healthy people with temporary fluid compromise from vomiting or diarrhoea, when using NSAID products even for a short time. (1),(2),(3):

1. Batagol RP. New TGA warning label for use of NSAIDs in fluid-depleted children. Med J Aust 2014; 201 (7): 381-382,

2. Call to extend NSAID warnings MJA Insight. Issue 37/6 October 2014.

3. ABC The Health Report 30/10/2006. "Kidney Health Australia warns of 'triple whammy' risks"
   According to Kidney Health Australia around one in ten Australian adults who take certain medications for high blood pressure could be at risk of a potentially fatal interaction known as the 'triple whammy' because they are

using non-steroidal anti-inflammatory drugs (NSAIDS) such as ibuprofen at the same time.
At: http://www.abc.net.au/radionational/programs/healthreport/kidney-health-australia-warns-of-triple-whammy/3359284

6. Imminent schedule change, and implications, of codeine moving from 'over-the-counter (OTC)' to prescription-only (S4)

With codeine-containing analgesics moving from non-prescription availability (OTC) to the prescription-only medication (S4) schedule in early 2018, we are already seeing new combinations of ibuprofen with paracetamol marketed and promoted to replace codeine/ibuprofen and codeine/paracetamol combinations.

It is not unreasonable to expect that more consumers will be using non-prescription NSAID products, and require pharmacist counselling. This presents the added potential risk that, if Ibuprofen remains available from general stores, consumers may turn to the "easy option" of self-selecting ibuprofen products in general store outlets, as an alternative option if these remain available for purchase at general stores, without the benefit of professional advice and screening.

7. Summary

Therefore, for all the reasons documented in these comments, relating to providing optimum opportunities for patient advice on risks versus benefits of NSAID products, we are in favour of ibuprofen sales being again restricted to supply-only within pharmacies, where up-to-date professional advice and counselling is available.

We feel this is particularly important for ensuring selection of the safest and most appropriate selection of non-prescription pain relief products by the consumer, given the changes in prescription medication pack presentation and recent studies relating to cardiovascular risk factors of NSAIDs.

In addition, there are the likely increased potential health hazards in the near future, as some at-risk consumers seek out non-prescription options after codeine products becomes prescription-only, if the current option of self-selection without professional assistance and counselling in non-pharmacy outlets is allowed to remain available to them.

[redacted]

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

Dear Sir or Madam,

Notice inviting public submissions under Reg 42ZCZK of the *Therapeutic Goods Regulations* 1990. Scheduling proposals to be considered at the ACCS, ACMS and ACCS/ACMS Meetings, November 2017

We refer to the notice inviting public comment under Regulation 42ZCZK of the *Therapeutic Goods Regulations* and would like to provide comment on six of the scheduling proposals that will be referred to the November 2017 meetings of the ACCS, ACMS and ACCS/ACMS.

[redacted]

[redacted] appreciates the opportunity to provide public comment in relation to ACCS, ACMS and ACCS/ACMS agenda scheduling proposals. We wish to address relevant matters under section 52E of the *Therapeutic Goods Act* 1989. Please find below our comments in relation to the scheduling proposal for ibuprofen:

- to up-schedule ibuprofen to pharmacy (S2) and restrict pack sizes available S2 to 30 dosage units.

[redacted] Comment

[redacted] notes that ibuprofen in pack sizes of 24 and below have been sold in grocery channels since 2003. The Medicines Scheduling Committee considered a proposal to up-schedule ibuprofen and restrict sale to pharmacy only in 2014/15 and this was rejected on the grounds that there was insufficient evidence to make a change to the scheduling. *"The TGA concluded that the current scheduling and availability of OTC NSAIDs are*

appropriate and that the addition of stronger label warnings 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" (16 Nov 2015). We are also aware that changes to labelling of these products is underway with the aim of these changes to assist consumers to purchase and use ibuprofen, and other medicines, safely.

To the best of our knowledge there have not been any safety alerts or concerns raised in the intervening time to warrant a further review or a change in the current scheduling of ibuprofen. Indeed in many other markets including NZ and some countries in Europe ibuprofen is available for sale in grocery stores. If the current proposal was supported it would limit choice of analgesics in the grocery environment and therefore result in inconvenience to the consumers by additional shopping trips etc. Consumers have been used to purchasing ibuprofen products for every day pain in grocery for many years. Importantly limiting options and accessibility may not result in optimum outcomes/treatment options.

In the current proposal there is no indication provided to support the requested change making it very difficult to respond to this proposal in an informative and considered way. Indeed we question if this is just the start of a broader plan to remove medicines generally from grocery and may create more of a monopoly and potentially add to the debate on pharmacy ownership.

[redacted]

In conclusion, [redacted] does not support the proposal to up-schedule ibuprofen and deny consumer access in grocery.

[redacted]

[redacted]

[redacted]

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

Email to: Medicines.Scheduling@tga.gov.au and to:
chemicals.scheduling@health.gov.au

Dear Sir or Madam,

Notice inviting public submissions under Reg 42ZCZK of the *Therapeutic Goods Regulations* 1990. Scheduling proposals to be considered at the ACCS, ACMS and ACCS/ACMS Meetings, November 2017

We refer to the notice inviting public comment under Regulation 42ZCZK of the *Therapeutic Goods Regulations* and would like to provide comment on six of the scheduling proposals that will be referred to the November 2017 meetings of the ACCS, ACMS and ACCS/ACMS.

[redacted]

[redacted] appreciates the opportunity to provide public comment in relation to ACCS, ACMS and ACCS/ACMS agenda scheduling proposals. We wish to address relevant matters under section 52E of the *Therapeutic Goods Act* 1989. Please find below our comments in relation to the scheduling proposal for ibuprofen:

- to up-schedule ibuprofen to pharmacy (S2) and restrict pack sizes available S2 to 30 dosage units.

[redacted] notes that ibuprofen in pack sizes of 24 and below have been sold in grocery channels since 2003. The Medicines Scheduling Committee considered a proposal to up-schedule ibuprofen and restrict sale to pharmacy only in 2014/15 and this was rejected on the grounds that there was insufficient evidence to make a change to the scheduling. *"The TGA concluded that the current scheduling and availability of OTC NSAIDs are appropriate and that the*

addition of stronger label warnings 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" (16 Nov 2015). We are also aware that changes to labelling of these products is underway with the aim of these changes to assist consumers to purchase and use ibuprofen, and other medicines, safely.

To the best of our knowledge there have not been any safety alerts or concerns raised in the intervening time to warrant a further review or a change in the current scheduling of ibuprofen. Indeed in many other markets including NZ and some countries in Europe ibuprofen is available for sale in non-pharmacy stores. Consumers have been used to purchasing ibuprofen products for every day pain for many years. If the current proposal was supported it would limit choice of analgesics in the non-pharmacy environment and with limiting options and accessibility it may not result in optimum outcomes/treatment options.

In the current proposal there is no indication provided to support the requested change making it very difficult to respond to this proposal in an informative and considered way. However if this proposal went ahead, it would have a detrimental effect [redacted]. This proposal would also reduce the consumer's ability to choose the appropriate medication when needed and pharmacies are closed.

In conclusion, [redacted] do not support the proposal to up-schedule ibuprofen and deny consumer access outside of the pharmacy channel.

Regards,

[redacted]

[redacted]

[redacted]

29th September 2017

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601
medicines.Scheduling@tga.gov.au
Cc
chemicals.scheduling@health.gov.au

[redacted] submission re: proposal to up-schedule ibuprofen to pharmacy (S2) and restrict pack sizes available S2 to 30 dosage units

To whom it may concern,

[redacted] we make the following comments in relation to scheduling proposals under section 52Eof the Therapeutic Goods Act 1989, specifically in relation to the scheduling proposal for ibuprofen.

[redacted] is concerned about the proposal to up-schedule ibuprofen to pharmacy (S2) and restrict pack sizes available S2 to 30 dosage units.

Our experience tells us that such a change will have negative impacts on the convenience industry in terms of reduced sales, shifts in consumer purchasing behaviour to the major supermarkets, the erosion of consumer choice and customer inconvenience, all the while failing to deliver any health benefits to the community.

Ibuprofen in pack sizes of 24 and below have been sold in various retail channels, including the convenience channel, since 2003. These products are an important contributor to the range of medicinals available for purchase in convenience stores, a category which grew by 18.9% in sales to $44 million in our channel in 2016, [redacted].

While this only represents about 0.5% of total sales, medicinals such as ibuprofen play an important role in the convenience store offering and are often attached to additional purchases by customers.

Consumers can buy these products from convenience stores at times when pharmacies are closed, providing them greater convenience and choice, and our industry believes we should remain able to provide this convenient service to customers in their time of need.

[redacted] understands that the Medicines Scheduling Committee considered a proposal to up-schedule ibuprofen in 2014/15, and this was rejected on the grounds that there was insufficient evidence to make a change to the scheduling.

"The TGA concluded that the current scheduling and availability of OTC NSAIDs are appropriate and that the addition of stronger label warnings 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" (16 Nov 2015).

[redacted] is not aware of any safety alerts or concerns raised in the intervening time to warrant a further review or a change in the current scheduling of ibuprofen.

Nor are we aware of any out of the ordinary purchases of ibuprofen products and we see no reason why shopper behaviour would be any different should ibuprofen be restricted in a way that drives consumers to make their purchasers from pharmacies.

There appears no evidential basis on which to change the current scheduling of ibuprofen.

Finally, it is worth noting that increased regulation on certain retail products invariably impacts small businesses such as convenience stores to a significantly greater degree than the major supermarkets, which can often benefit from channel shift away from smaller retailers due to price impacts. The major supermarkets are typically able to offset higher costs for regulated products against their many other product categories.

Thank you for your consideration of our comments and please don't hesitate to contact me for any further information.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4 October 2017

Medicines Scheduling Secretariat
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606
Australia

RE: Consultation: Proposed amendments to the Poisons Standard – ACCS, ACMS and Joint ACCS/ACMS meetings, November 2017
Comments on the request for changes to the scheduling of Ibuprofen

Dear Sir/Madam,

We note that the following request has been made to amend the scheduling of ibuprofen:

- Amend the Schedule 2 entry for ibuprofen to restrict no more than 30 dosage units when in divided preparations containing 200mg or less 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 200mg; and
- Amend the Schedule 3 entry for ibuprofen to allow up to 100 dosage units containing 200mg or less of ibuprofen in a primary pack.

[redacted] does not agree with this proposal to amend the current Poison Standard with respect to ibuprofen. The decision to allow the general sale of ibuprofen 200mg in pack sizes of < 25 was made in 2003 and was based on the following reasons:

- 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.

Fifteen years after the original decision to allow the general sale of ibuprofen for short term use, the reasons for this decision remain valid and there is little evidence to support a change to a more restrictive situation. Ibuprofen products have an excellent safety record and profile, while the labelling of products is supported by safety warnings (RASML) that are updated as required or when potential safety concerns are identified.

[redacted]

Ibuprofen scheduling in Australia is in-line with all major international countries (including New Zealand) and the supports the current schedule. Having medicines accessible to patients is also a key factor in determining scheduling and changing the schedule will make it difficult for consumers to readily access pain relief products for short term use, especially in country areas. The access to ibuprofen is similar to that of other products used for short term pain relief such as paracetamol and aspirin. We believe that the current schedule is appropriate and the evidence does not support or warrant any changes to the scheduling of ibuprofen.

Should you require further information please do not hesitate to contact me at the contact details listed below.

Yours sincerely,

[redacted]ednesday, 4 October 2017

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

Dear Sir or Madam,

Re: Public Submission – under Reg. 42ZCZK of the Therapeutic Goods Regulations 1990. ACMS meeting, November 2017.

[redacted] refers to the pre-November 2017 Scheduling meeting notice and we wish to comment specifically on the application to reschedule ibuprofen. [redacted] and [redacted] which contain [redacted] respectively.

The scheduling item is as follows:

- 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.

[redacted] **does not supports this rescheduling item for ibuprofen.**

There is insufficient detail provided in the agenda to allow key stakeholders to prepare and submit adequate submissions or address any particular issue that has been raised in any application to change the schedules of the Poisons Act.

Ibuprofen has demonstrated safe use worldwide for many years as an OTC medicine (inclusive of exempt status) at its approved dosing, with no safety signals that justify up-scheduling.

Ibuprofen is a well-established OTC Non-Steroidal Anti-inflammatory medicine that was included as a Schedule 4 medicine in Australia in 1973. It was then down scheduled to Schedule 3 medicine in 1989 and then in 1995 it was down-schedule 2 when in divided preparations for oral use containing 200mg or less of ibuprofen per dosage unit. It was then further down scheduled to exempt status at the June 2003 NDPSC meeting when in pack sizes containing 25 or less dosage units, when ibuprofen is the only therapeutically active constituent other than an effervescent agent and when labelled with a maximum recommended daily dose of 1200 mg of ibuprofen.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted] has been available [redacted] since 2012 and as an unscheduled product since 2013. When considering the Adverse Events reporting in Australia over the last 5 years, it is very clear that this combination has a sound safety profile with no evidence to suggest that up-scheduling should be considered, let alone warranted.

[redacted] has been available as a [redacted] and again there has been no evidence to suggest that further up-scheduling is warranted

[redacted]

Overall [redacted] believe that the evidence demonstrates that the current scheduling for ibuprofen remains accurate. Ibuprofen is considered safe and effective when used in accordance to the registered dosing. The OTC and unscheduled scheduling remains justified as the benefits outweigh the risks in line with section 52E (1) of the Therapeutic Goods Act 1989.

Yours faithfully,

[redacted]

6 October 2017

Australian Government
Department of Health
Therapeutic Goods Administration

Email: medicines.scheduling@health.gov.au

Dear Sir / Madam

Proposed Amendments to the Poisons Standard – ACCS, ACMS and Joint ACCS/ACMS meetings

Coles appreciates the opportunity to provide comment about the scheduling proposals in relation to Ibuprofen.

Coles is a major Australian retailer with more than 800 supermarkets and over 700 convenience outlets nationally. Each week more than 21 million customers visit our stores nationally.

Coles has been offering for sale products containing Ibuprofen in packs of 24 or less since 2003. Currently Coles provides customers with the choice to purchase 16 products that contain Ibuprofen for everyday pain relief.

At Coles, the customer is central to everything that we do. Our key objective is to make shopping easier for our customers and to provide them with the products that they tell us that they want to buy.

It is well established that many households are confronted with increased living costs and family budgets are under pressure. At Coles we are seeing a shift toward value products and this trend is prevalent across our store network.

The proposal to limit the availability of products containing Ibuprofen to pharmacies only, will have a direct impact on our customers by both restricting their access to the product and through increased prices. For example, [redacted] the generic brand [redacted] retails at $2.99 for a 24 tablet pack whilst Coles' brand retails for $1.65 for the same pack size. By shopping at the pharmacy, consumers are paying 80 percent more for this product.

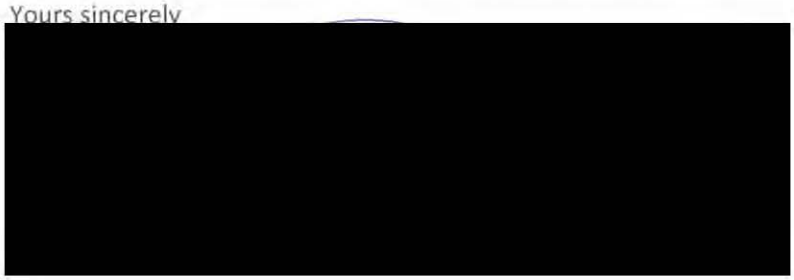
Coles' vast store network combined with competitive pricing for branded and proprietary products means that customers are able to quickly access the products they want to buy, at affordable prices.

[redacted]

[redacted]

Coles does not support the proposed change to limit the availability of Ibuprofen because it will only serve to inconvenience our customers and to increase their cost of living.

Yours sincerely



[redacted]

Ref: 17134

6 October 2017

TGA Scheduling Committee
Po Box 100
Woden ACT 2601

Dear TGA Scheduling Committee

Re: Ibuprofen Up-scheduling Proposal

Background:
Perrigo Australia requests the reclassification of ibuprofen not to proceed on the basis that it is unnecessary, ineffective, disadvantages community access to effective pain relief, and the long-established product safety has not fundamentally changed regardless of recent publicity regarding the potential for cardiac issues.

Introduction:
Ibuprofen as an NSAID (Non-Steroidal Anti-Inflammatory Drug) is a COX 1 & COX 2 inhibitor, inhibiting prostaglandin synthesis, fever; swelling; inflammation; and pain transmission. NSAIDs have been shown to be more effective than paracetamol for some types of pain and in many acute pain settings they provide analgesia equal to the usual starting doses of opioids (1). Ibuprofen is one of the oldest OTC NSAID on the market with a long safety history of OTC use at dosages up to 1200 mg per day versus an even longer history as prescription medicine at dosages up to 2400 mg per day (1, 2). Compared to other NSAIDs, such as naproxen and ketoprofen, ibuprofen is considered to have the best benefit-risk profile (1).

Discussion:
Recently there has been concern raised by a Danish study, which found the use of NSAIDs is associated with persistently increased coronary risk regardless of time elapsed after first-time myocardial infarction (MI) (3). Together with the previous findings of other studies, the results have been interpreted to support the opinion that NSAIDs have no apparent safe treatment window among patients with myocardial infarction (MI) (4). However the study noted

> *"During our study period, the only NSAID that was available over the counter in Denmark was ibuprofen (since November 1, 2001), but the low only in low dosage (200 mg) and with maximum purchase of 100 tablets. Such NSAID use having major effects in this study is therefore unlikely"*. The study authors have considered the influence of consumer driven use of 200 mg ibuprofen

[redacted]

and having no major effect on the study, thereby they considered this is not a factor in increased risk of reoccurring MI.

Therefore in the opinion of the Danish study authors 200 mg OTC ibuprofen does not present an increased risk.

Up scheduling general sale ibuprofen to a pharmacy only medicine will not provide any significant additional health care professional supervision, with interaction typically provided by a pharmacy assistant, and will only result in reduce access to general pain relief to consumers.

Where a consumer has a past history of myocardial infarction they will already be under the supervision of a doctor. Therefore education of consumers by doctors and pharmacists of the potential increased risk of myocardial infarction would be more effective than making ibuprofen a pharmacy only medicine.

A change to move ibuprofen from non-scheduled to schedule 2 is counter to the recent ACMS advice to the delegate to down schedule ibuprofen 600 mg in a modified release dosage form, each containing 600 mg of ibuprofen from schedule 4 to schedule 3 and the inclusion in schedule H. (6)

Although paracetamol is an effective pain reliever, ranked below ibuprofen for efficacy (1), it has no anti-inflammatory action, meaning that the up-scheduling of ibuprofen, from general sales to pharmacy only, will result in the loss of public convenience for the emergency access to anti-inflammatory treatment of bruises, muscle aches and toothaches. Waiting for the pharmacy to open will be the only option and consumers, will have lost a diagnostic tool useful to healthcare professionals that if symptoms persist there may be something more to the pain, fever, or inflammation than at first anticipated, adding unnecessary treatment delay.

Up-scheduling is a decision that should be made based on improved safety versus the negative impact on reduced availability of a medicine. The cardiac risks of NSAIDs is not new information. The Danish study is more correctly described as new detail to an already well-known and well established safety profile, the significance of which only applies to a small sector of the public likely to be already monitored by healthcare professionals. Up-scheduling will in no measure reduce the public risk to those without MI risk or to those with MI risk already being monitored by healthcare professionals. The small minority with no known MI risk or healthcare professional interaction, will not benefit from reduced convenience as they will continue to remain unaware and simply access what they want during opening hours, with or without healthcare professional interaction. Better labelling and better education by healthcare professionals to at risk patients would be the far

[redacted]

more effective measure than unnecessary and ineffective up-scheduling, which adds no extra safety, and only reduces access to a valuable pain-reliever resource with unique anti-inflammatory properties not seen in paracetamol, while having a greater safety profile than general sales available Aspirin (1).

Conclusion:

In our company's opinion there has been no new information to significantly change the already well-established and well-known safety profile of ibuprofen nor is there well-publicised evidence of general sales versus pharmacy only consumption of ibuprofen leading to increased hospital admissions or deaths. Whereas better education of at risk patients and improved product labelling are far more obviously effective measures with a greater impact than reduced convenience and impeded access.

References:

1. Moore ND. In search of an ideal analgesic for common acute pain. Acute Pain. 2009;11(3):129-37
2. TGA Brufen Tablets and Syrup Product Information https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2009-PI-00035-3&d=20170927161146224483
3. Anne-Marie Schjerning Olsen, Emil L Fosbol, Jesper Lindhardsen et al; Long-Term Cardiovascular Risk of NSAID Use According to Time Passed After First-Time Myocardial Infarction: A Nationwide Cohort Study; Circulation; published online 10 September 2012. https://www.tga.gov.au/sites/default/files/scheduling-submissions-1206-2.pdf
4. Heart Foundation - Australian Heart Disease Statistics 2015
5. https://www.heartfoundation.org.au/images/uploads/publications/RES-115-Aust_heart_disease_statstics_2015_WEB.PDF
6. Therapeutic Goods Administration Scheduling delegate's final decisions, June 2017 https://www.tga.gov.au/book-page/14-ibuprofen-0

If I can provide any further information, please do not hesitate to contact me.

Regards

[redacted]

Tony Pal
Pharmacovigilance and Professional Relations Pharmacist

Perrigo Australia [redacted]

[redacted]

Dr Michael A Downes MB ChB FACEM
Emergency Physician and Clinical Toxicologist
President (acting) TAPNA Inc.
[redacted]

Joint Advisory Committees on Chemicals and Medicines Scheduling (Joint ACCS-ACMS) Therapeutic Goods Administration
Comments on the proposed amendments to the Poisons Standard

06/10/2017

Dear Sir,

TAPNA Inc. is a collaboration of health professionals from Poisons information centres and clinical toxicology units within Australia and New Zealand.
On behalf of our association I would like to submit a response with regard to two proposed amendments based on clinical expertise and experience.

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

TAPNA Inc. supports the continued inclusion of cathinones, MDMC and alpha-PVP in schedule 9. The poisons information centres and clinical toxicology units around Australia 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. There is no place for these agents therapeutically, and so inclusion in Schedule 4D would be of no value. Deaths have occurred due to alpha-PVP toxicity[1]

1. Sellors et al https://www.ncbi.nlm.nih.gov/pubmed/25390268

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.

TAPNA Inc. oppose 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. Orphenadrine is over represented in deaths when compared to other antimuscarinics or antipsycotics[1].
(71.5 deaths per million prescriptions compared to 0-6.1 deaths per million prescriptions for other anticholinergics)
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.
Clinical Toxicology units have experienced an increase in presentations with orphenadrine ingestion in recent years as the management of chronic pain turns it's focus onto alternatives to opioids.

The attached pdf details a poster presentation at the 2016 Asia Pacific Association of Medical Toxicology scientific meeting in Singapore, outlining presentations with orphenadrine toxicity to the Hunter Area Toxicology Service. The spectrum of toxicity produced by what is a relatively small number of cases, is of concern.

1. Buckley and McManus https://www.ncbi.nlm.nih.gov/pubmed/9828983

Yours sincerely

[redacted]

Michael A Downes

Orphenadrine ingestion : A case series

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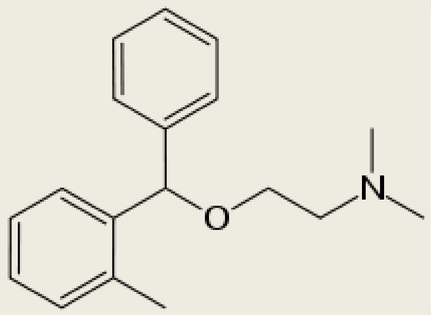

Objectives:

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 it's antispasmodic effects. This study aimed to describe orphenadrine ingestions presenting to a regional toxicology service.

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 Quantified**

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 unquantified in three cases, one of which was supratherapeutic use rather than 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 of 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 unquantified 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 60 hours.

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.

[redacted]

6 October 2017

medicines.scheduling@tga.gov.au

RE: Proposed amendments to the Poisons Standard - ACMS meeting, November 2017

The Society of Hospital Pharmacists of Australia (SHPA) is the national professional organisation for over 4,400 pharmacists, pharmacists in training, pharmacy technicians and associates working across Australia's health system. SHPA is the only professional pharmacy organisation with a strong base of members practicing in public and private hospitals and other health service facilities.

SHPA is committed to facilitating the safe and effective use of medicines, which is the core business of pharmacists, especially in hospitals. SHPA believes that any changes to the scheduling of medicines should be driven and underpinned by the principles of consumer safety and quality use of medicines.

SHPA has the following comments to make with respect to proposed amendments to the Poisons Standard.

Cardarine (GW501516), Stenabolic (SR9009) and other synthetic REV-ERB agonists

SHPA does not support the proposed Schedule 4 Prescription Only entry for cardarine (GW501516), Stenabolic (SR9009) and other synthetic REV-ERB agonists. SHPA understands that these medicines are used to alter gene expression and can be used as a physical performance enhancer. Clinical evidence of purported health outcomes such as reduced obesity and diabetes through altering gene expression is scant, of low quality and only produced in mice subjects[1]. Human studies of this medicine have not been published. Thus, SHPA believe it is not appropriate for this medicine to receive a Schedule 4 entry.

SHPA has no remarks on the simultaneous application for a Schedule 9 Prohibited Substance entry for these medicines.

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

SHPA does not support proposed Schedule 4 Prescription Only for methylone (MDMC) and alpha-pyrrolidinovalerophenone (alpha-PVP), noting that that they are synthetic psychostimulants associated with overdoses, suicides and illicit use. SHPA notes that in New South Wales, alpha-PVP was explicitly banned in 2013 after synthetic psychostimulants were determined to be the cause of death in a teenager[2].

SHPA does not support amending the Schedule 9 Prohibited Substance entries for cathinones, methylone (MDMC) and alpha-pyrrolidinovalerophenone (alpha-PVP), and believe these to be appropriate. SHPA notes that cathinones are illegal in many other countries such as the United States of America, the United Kingdom, Sweden and New Zealand.

Clotrimazole

SHPA does not support the proposal to downschedule clotrimazole for vaginal thrush from Schedule 3 Pharmacist Only to Schedule 2 Pharmacy Medicine, which would allow for patients to self-select topical antifungal treatments for vaginal candida infection.

It is imperative that patients presenting with vaginal disorders are consulted by a pharmacist to ensure that the diagnosis and treatment is appropriate and/or necessary, and to ensure referrals to doctors are made when appropriate. Trigger points for referrals to physicians are diabetic patients, patients under 16 and over 60 years of age, pregnant women, and patients taking immunosuppressants.[3] A consultation with a pharmacist is also important to rule out common differential diagnoses such as bacterial vaginosis which requires treatment with antibiotics.

Orphenadrine

SHPA does not support the downscheduling of orphenadrine from Schedule 4 Prescription Only to Schedule 3 Pharmacist Only. Orphenadrine has very limited role in pain management,[4,5] poor efficacy and patients rapidly develop tolerance to this medicine. An SHPA member reported providing care to a patient who had overdosed on orphenadrine resulting in ischaemic bowel and the formation of a stoma.

Ibuprofen

SHPA supports the proposals to

- Delete the exemptions for ibuprofen in Schedule 2 Pharmacy Medicine which allow it to be sold in supermarkets
- Restrict the pack size of ibuprofen 200mg in Schedule 2 Pharmacy Medicine to 30 dosage units, down from 100 dosage units

These proposals would reduce the incidence of self-selection of ibuprofen to treat pain or muscular inflammation, and allow for patients to appropriately receive counselling and guidance from pharmacists when accessing treatment in a pharmacy setting. Two comprehensive review of NSAIDs conducted by the TGA in recent years acknowledged the cardiovascular, hepatotoxicity and pregnancy risks associated with these medicines[6,7]. Thus, it is appropriate that access to these medicines are restricted [redacted]

[redacted] please do not hesitate to contact [redacted].

Yours sincerely,

[redacted]

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[redacted]

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5 October 2017

Joint Advisory Committees on Chemicals and Medicines Scheduling (Joint ACCS-ACMS)
Therapeutic Goods Administration

Comments on the proposed amendments to the Poisons Standard

The NSW Poisons Information Centre (NSWPIC) provides a phone-based advice service on suspected poisonings to the public and health professionals calling from NSW, TAS and ACT on a near full-time basis and a shared after-hours service to the remainder of Australia. This results in approximately half of Australia's poisons-related calls being received by our centre. Our staff consists of pharmacists, poisons information specialists, emergency physicians, clinical toxicologists and pharmacologists.

We would like to submit a response based on the following four proposed amendments based on our clinical expertise, experience and Australian poisoning databases.

Helium

To create new entries in Schedules 6 and 7 and Appendices E and F for helium with cut-offs. The proposal also requires helium gas to be in pressurised gas canisters or cylinders containing an aversive when being sold to or hired by consumers intended for household or domestic use.

The NSWPIC supports the proposed amendment to the Poisons Standard to include Helium in Schedules 6 and 7. Data from the National Coronial Information System (NCIS) shows an increase in deaths with helium listed as a cause of death. All of these deaths were intentional suicides in individuals ranging in age from 16yrs to 94yrs. Availability of helium for purchase online in large quantities makes this an attractive, easy, relatively inexpensive and very efficient method of suicide. Websites supporting euthanasia run workshops and sell adaptors online to facilitate the use of helium for asphyxiation, eg https://exitinternational.net/product/n-flow-control/. The NSWPIC has received two calls regarding use of helium in deliberate self-poisonings. Inclusion of an aversive in canisters of helium being sold or hired to consumers should make exposure to excessive quantities of helium more difficult and unpleasant.

Table 1. NCIS intentional self-poisoning deaths with helium listed as a cause of death as at 26/9/17.

Year	Number of closed cases
2001	1
2002	2
2003	4
2004	4
2005	7
2006	9
2007	10
2008	15
2009	11
2010	25
2011	19
2012	29
2013	17
2014	29
2015*	17
2016*	9
2017* (to 26/9/17)	2

* Case closure rates as of 3/10/17 are 84.8% 2015, 55.5% 2016, 19.6% 2017