To: The TGA Delegate:
COMMENTS ON INTERIM DECISION 5/2/18
Scheduling of Ibuprofen

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We wish to provide the following comments for your consideration, regarding the Interim Decision to reject a proposal to reverse the 2003 TGA Decision to exempt from the requirements of the Poisons Schedules, sales of small packs of Ibuprofen products in general stores.

1. **Lack of cautionary labelling and detailed warning for patients with medical conditions necessitating professional guidance when choosing analgesic products (e.g. the risks of dehydration and fluid depletion on the safety of ibuprofen products sold in general stores)**

In the Interim Decision, under main points opposed, It is stated that:
"*For consumers, OTC medicine labels provide the single most important source of information. Australian medicines that contain ibuprofen must be labelled in accordance with the Required Advisory Statements for Medicine Labelling (RASML), which contains detailed mandatory warning statements in language that consumers are able to understand and act upon".*
In the Reasons Statement the Delegate also stated: *"Cardiovascular disease and other complications of NSAID use (gastrointestinal, blood pressure, renal impairment); confusion in elderly is covered by RASML statement*".

Our comment is that it needs to be re-emphasised that, whilst we have a cautionary warning on paediatric liquid formulations of Ibuprofen, we do not have a warning on packs of Ibuprofen products in general stores, about the overall renal risks of NSAIDs in adults who are temporarily or otherwise at risk of renal failure caused by dehydration or fluid depletion.

Furthermore, it has been established that this potential risk is present in situations of both acute and chronic consumption of NSAIDs, *even in otherwise healthy, fluid-depleted people taking a short course of a NSAID product.*

This situation was noted in comments by a medical practitioner on the 2014 MJA Insight article referred to in our Public Submission (https://www.doctorportal.com.au/mjainsight/2014/37/call-extend-nsaid-warnings/.

The relevant comments were as follows:
"The importance of good fluid intake while taking NSAIDs is often underestimated, and not included in warnings of side effects, while there is a lot of emphasis on gastric side effects. NSAIDs are often taken during illness, and also by athletes and sports people, with dehydration possible in both groups, so emphasis on fluid intake is most important".

Also *"The use of NSAIDs is common in footballers, athletes etc with the potential for dehydration during exercise.. There was a tennis player some years ago who developed acute renal failure after five sets of tennis on a hot day with minimal hydration. She had been swallowing diclofenac daily. I always emphasise the need for copious fluid intake in these situations".*

2. **Lack of adequate and clear information on potential drug interactions (e.g. with antithrombotics in patients with atrial fibrillation; with ACE inhibitors in patients with hypertension) within the cautionary labelling, coupled with lack of access to professional advice**

The RASML includes this statement: Unless advised by your doctor or pharmacist, do not use with products containing ibuprofen, aspirin or other anti-inflammatory medicines or *with medicines that you are taking regularly*.
The final part is not a "detailed mandatory warning statement in language that consumers are able to understand and act upon." Does it mean that they should not take ibuprofen if they are taking any medicines regularly? e.g. oral contraceptives? What medicines in particular? The input of a health professional with a knowledge of significant drug interactions is needed. At a minimum, a list of medicines with clinically important interactions with ibuprofen should be listed. These medicines are commonly used and the current labelling and open availability of the ibuprofen products place many consumers at substantial risk (e.g. of gastrointestinal haemorrhage with antithrombotics or acute renal failure with ACE inhibitors), even with few doses of ibuprofen.

Furthermore, the following review from New Zealand also found that "**The risk of AKI in patients taking NSAIDs and other potentially nephrotoxic medicines is greatest at the start of treatment; therefore, even short courses of NSAIDs should be avoided, if possible, in patients at increased risk**".
Non-steroidal anti-inflammatory drugs (NSAIDs): Making safer treatment choices (https://bpac.org.nz/bpj/2013/october/nsaids.aspx)
The review referred to the following study:
Lapi F, Azoulay L, Yin H, et al. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ. 2013;346:e8525

As warned by the then ADRAC Committee in 2003 and 2006, and also by Kidney Health Australia in 2006, the specific potential risks with ACE inhibitors/ARBs can occur acutely, as

a “triple whammy” episode in patients who are concurrently taking a combined antihypertensive ACE inhibitor/ARB with diuretic medication products who then purchase Ibuprofen.
Specific warnings of this are not covered by the RASML labelling for Ibuprofen sold in general stores.
Furthermore, in this context, it is important to emphasise that the availability of the combination tablet/capsule products containing an ACE inhibitor/ARB with a diuretic (i.e. 2/3 of the “triple whammy” risk), were not available when scheduling exemption was given to allow Ibuprofen products to be sold in general stores in 2003.

Similarly, the widespread management of chronic atrial fibrillation with antithrombotic medications to reduce the risk of ischaemic stroke is a relatively new phenomenon, with some of the newer agents coming onto the market after the decision to allow general stores to sell Ibuprofen products. Specific warnings of the interaction of Ibuprofen with these medications are also not covered by current RASML labelling for Ibuprofen sold in general stores.
All of this underlines the importance of access to professional guidance from primary health providers such as pharmacists when consumers are purchasing Ibuprofen.

In this context, we refer to reference 37 (under Footnote) in the Delegate’s reasons document.
The abstract of this reference is as follows, with the conclusion in bold:
AGING AND THE FREQUENCY OF NSAID-RELEVANT COEXISTING MEDICAL CONDITIONS IN THE PRIMARY CARE SETTING
L. Bloom M. Blacketer K. Boyle A. Myers R. Weinstein
Innovation in Aging, Volume 1, Issue suppl_1, 1 July 2017, Pages 875,https://doi.org/10.1093/geroni/igx004.3143Published:30 June 2017
Abstract
The second most common reason adults seek care from primary care providers (PCP) is musculoskeletal and connective tissue conditions; the most common medicines discussed at these visits are analgesics. Primary care providers can help promote the safe use of over-the-counter (OTC) analgesics, especially in the aging population, by identifying all coexisting medical conditions including those that increase the risk of NSAID associated complications. Data from 3 large healthcare claims databases (Truven Health) were analysed to identify NSAID-relevant coexisting medical conditions of interest among adults ⩾18 years with a PCP visit in 2013 and with at least one year of enrolment prior to their first PCP visit. The databases were representative of privately insured, Medicaid, and employer-based supplemental Medicare insurance populations. For this analysis, NSAID-relevant coexisting medical conditions of interest were asthma, CV risk (e.g., prior MI, coronary artery disease, congestive heart failure, hypertension, stroke), GI risk (e.g., history of gastrointestinal bleed, peptic ulcer disease, alcohol use, exposure to anticoagulants or steroids), and renal insufficiency. Hepatic cirrhosis was not included.
Conclusion: 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 conditions. This frequency of at least one NSAID-relevant coexisting medical conditions increased with age in each population. These data reinforce the critical role PCPs can play in

identifying aging patients with NSAID-relevant coexisting medical conditions and in turn providing them guidance on appropriate choice and use of OTC analgesics

In summary, all of these situations of potential adverse health risks in situations of consumer self-selection of NSAID products in general stores, where no professional advice is available, are not consistent with the well-established principle of optimum risk-benefit management in community health. In our view, the availability of a NSAID product in general stores, where no professional advice is available and the labelling information is minimal, is not consistent with providing optimum risk-benefit management.

3. **New information on cardiovascular risks associated with ibuprofen use, including short-term use**

Under "Points Opposed" (to removing Ibuprofen from general stores), it states:
"Safety reviews of NSAIDs, including ibuprofen; these reviews have stated that there is minimal cardiovascular risk associated with ibuprofen when used at recommended OTC doses and duration.
Since the reviews were published there has been no evidence of any significant public health concern that could have altered the risk vs benefit profile of ibuprofen, to warrant a departure from the current scheduling arrangements:"
The Committee stated: "*There are no new safety concerns. The evidence of potential CV risk associated with OTC doses of ibuprofen is not substantiated (Bally M* et al., *BMJ 2017)"*.
The Delegate *stated "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)."*

These statements are not in accordance with the growing literature on this topic or what was actually reported by Bally. In fact, the 2017 Bally study showed an adjusted odds ratio of 1.48 (increased risk by 48%) of an AMI with ibuprofen in "any dose for 1-7 days" for risk of AMI (see table 2 of that paper). Use of even low doses (<1200mg daily) for greater than one month increased the AMI risk by 32%. Similarly, the Danish study we cited (Sondergaard KB 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;3:100-07) recently found that short-term treatment with non-selective NSAIDs, particularly ibuprofen and diclofenac, was associated with an increased early risk of cardiac arrest (by about 30%).

4. **Suggestion of possibility of increased consumption of paracetamol if ibuprofen unavailable in general stores**

Finally, since in the discussion of Ibuprofen there is a prevailing understanding that the current RASML labelling is sufficiently informative to advise on potential adverse effects arising from self-selecting a medication from a general store, there appears to be a logical inconsistency, under "points opposed", to suggest that "*limiting options and accessibility (of Ibuprofen) will not deliver any health benefits to the community. It may result in possible public health consequences such as those arising from increased consumption of paracetamol".*
In fact Paracetamol label warnings are simple and informative, advising*:" Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless*

advised to by a doctor. Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor".
Furthermore, although paracetamol does have a relatively narrow therapeutic index, especially for children and infants, within the recommended the dose range for adults the drug is recommended in almost all national and international guidelines as a preferred analgesic option to ibuprofen or other NSAIDs. Apart from the potential for liver damage at excessive dose level consumption, paracetamol is not regarded as a medication which has anywhere near the range of precautions, safety issues and drug interactions as the NSAID group of medications.
Therefore, if it is assumed that the RASML warnings are sufficient to alert consumers of safety issues for various medications, then this ought to apply equally to paracetamol as it is claimed to do for Ibuprofen.

5. **Suggestion of "significant impact on consumer choice and convenience, reduce competition and increase cost to consumers."**

"Finally, under "Points opposed", the Committee stated:" The proposed changes to the scheduling will have a significant impact on consumer choice and convenience, reduce competition and increase cost to consumers.
The evidence base for this statement is unclear. In fact, we note that, throughout Australia, there is a wide range of community pharmacies which are open for extended evening and public holiday hours, and that the recent expansion of discount pharmacy groups has resulted in a very competitive environment regarding price and availability of non-prescription medications. Surely, public safety is a more important issue.

6. **Summary and Conclusions**

There has been a raft of developments in evidence and knowledge of the safety of ibuprofen since the 2003 legislative exemption to allow small packs of Ibuprofen products to be sold in general stores, and not restricted to pharmacies.
The absence of cautionary RASML cautionary labelling about the risks of fluid depletion, the unclear labelling regarding concomitant drug therapy and lack of warning of potential renal "triple whammy" (with ACE inhibitors/ARBs) or haemorrhagic (with antithrombotic drugs) outcomes with the use of ibuprofen (even in small doses for a short period) and the changes in availability of new single and combined ingredients in some cardiovascular medications since 2003, in addition to new studies indicating potentially increased cardiovascular risks with NSAIDs in any dose, all highlight the importance of making professional advice available for the purchaser of ibuprofen medications.

We therefore believe it is time to withdraw the 2003 legislative exemption to allow small packs of Ibuprofen products to be sold in general stores, and not restricted to pharmacies.

Furthermore, it is noted that throughout Australia, there is a wide range of community pharmacies which are open for extended evening and public holiday hours.