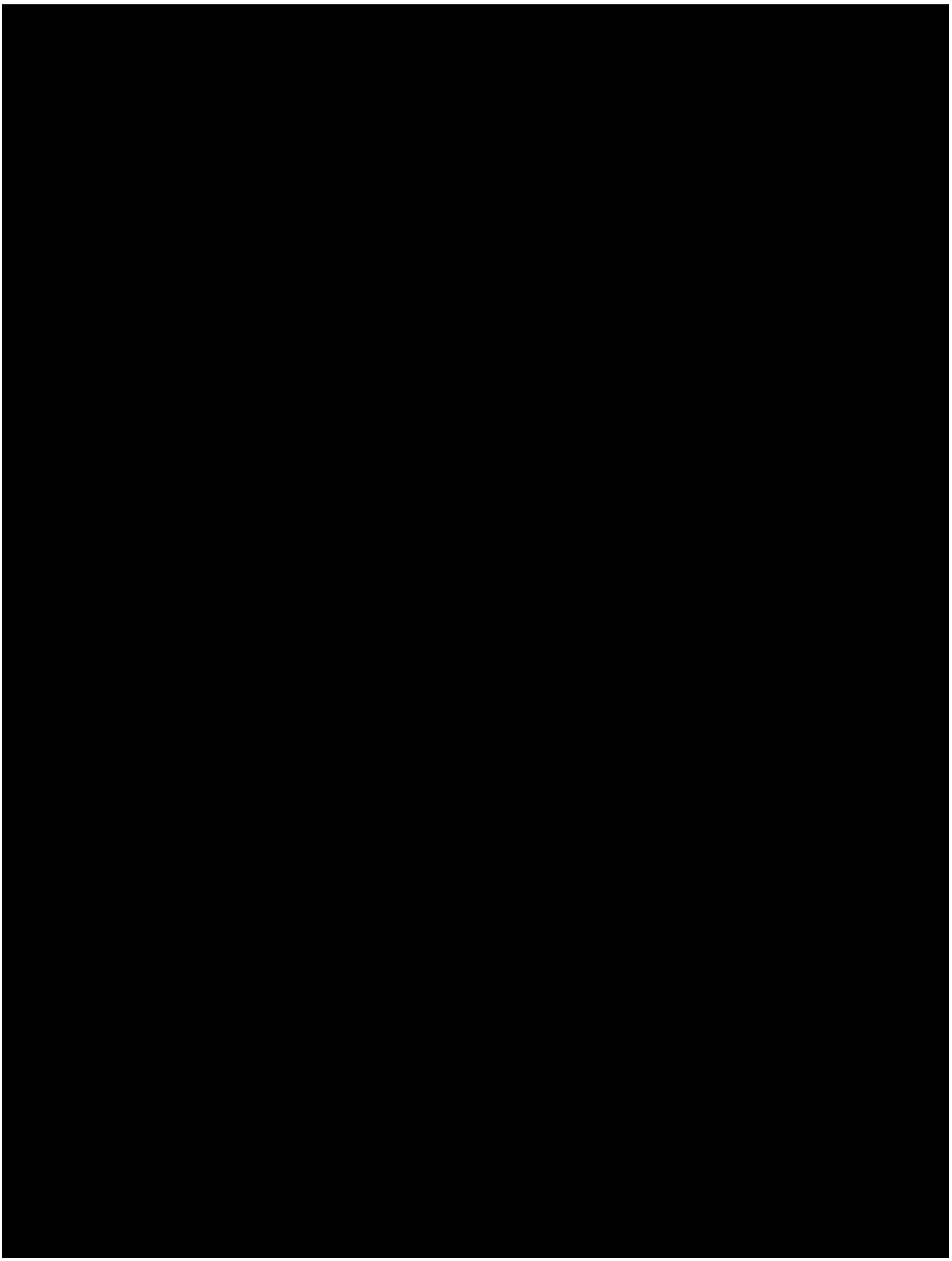
AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

[redacted]

September 2019

Proposed amendments to the Poisons Standard – ACMS and ACCS, November 2019 – TGA consultation

Response from the Australian Commission on Safety and Quality in Health Care



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Summary

The Therapeutic Goods Administration (TGA) proposes amendments to the Poisons Standard which are to be considered by its Advisory Committee on Medicines Scheduling (ACMS) and Advisory Committee on Chemical Scheduling (ACCS) at the November 2019 scheduling meetings. The Commission is only providing a submission on amendments to the scheduling of medicines being considered by ACSM.

The TGA has invited public consultation on amendments that will impact the following medicines:

1.1 Paracetamol in liquid formulations
1.2 Hyoscine butylbromide liquid formulation
1.3 Calcifediol monohydrate (new entry)
1.4 Lidocaine for topical use
1.5 Paracetamol and ibuprofen combination.

The Australian Commission on Safety and Quality in Health Care (the Commission) strongly supports the intent of this important initiative for patient safety.
The Commission supports the proposed scheduling changes for the following three medicines:

1.2 Hyoscine butylbromide liquid formulation
1.3 Calcifediol monohydrate (new entry)
1.4 Lidocaine for topical use.

The Commission does not support the scheduling changes for 1.1 Paracetamol in liquid formulations and 1.5 Paracetamol and ibuprofen combination.

The Commission recommends that ACSM:

- review the intention and implementation of the proposed amendment to Schedule 2 pack size of **paracetamol liquid**

- uphold the 2018 interim decision to retain the Poisons Standard entry in relation to available pack sizes of paracetamol/ibuprofen in combination[7]

Introduction

On 2 September 2019, the TGA published an invitation to comment on Proposed amendments to the Poisons Standard which are to be considered by ACMS and ACCS at the November 2019 scheduling meetings [redacted].

The Commission is only providing a submission on amendments to the scheduling of the five medicines being considered by ACSM.

The Commission supports three (3) proposed amendments:

1.2 Hyoscine butylbromide liquid formulation – Support proposed amendment to the entry for Schedule 2 (Box 2)

1.3 Calcifediol monohydrate – Support proposed new entry for this medicine / chemical entity under Schedule 4 (Box 3)

1.4 Lidocaine for topical use – Support proposed amendment to the entry for Schedule 2 to allow unscheduled access to lidocaine 0.6% topical aqueous spray (Box 4)

The Commission proposes recommendations for two (2) proposed amendments:

1.1 Paracetamol in liquid formulations – refer feedback and recommendations.

1.5 Paracetamol and ibuprofen combination – refer feedback and recommendations.

Context

Medicine scheduling in Australia is an important aspect of medicine legislative control and ensures safe and appropriate access to formulations and pack sizes by patients.

The TGA has proposed scheduling amendments which have been referred to the expert advisory committee. TGA is required to invite public submissions to be made to the expert advisory committee along with the proposed amendments to the Poisons Standard.

The Commission supports this initiative and its potential impact on improving medication safety and delivering safer patient care.

Background

1.1 Paracetamol in liquid formulations

Paracetamol is indicated for temporary relief of pain associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, arthritis, osteoarthritis, rheumatic pain, period pain, fibrositis, neuralgia, sore throat, tennis elbow, and colds and flu. Paracetamol also reduces fever. For paediatric use liquid formulations are available with additional indications for use that are appropriate to the age group: relief of pain associated with teething, earache and/or immunisation.[1] Liquid formulations are also used in situations where oral solid dose formulations are not suitable, for instance, consumers who have swallowing difficulties.

Access to the most effective and safe medicines that are needed in a health system for relief of pain and/or fever underpins the national listing of paracetamol. In addition, paracetamol is considered an essential medicine by the World Health Organisation (WHO) and remains on the WHO Model List of Essential Medicines for both adults (including palliative care) and children.[2,3]

1.2 Hyoscine butylbromide

Hyoscine butylbromide is an anticholinergic and is indicated for the treatment of spasms of the gastrointestinal tract, biliary spasm and renal spasms and as a diagnostic aid in radiology.[4]

1.3 Calcifediol monohydrate

Calcifediol monohydrate is considered a derivative or vitamin D; is available in oral formulations; is not equipotent to vitamin D; and is not included in the Poisons Standard. Its safety profile has been reviewed by the TGA and a 2018 study supports the view that lower dosages than vitamin D are needed, with study findings suggesting oral calcifediol is 3.2-fold more potent that oral cholecalciferol.[5]

1.4 Lidocaine for topical use

Lidocaine is a local anaesthetic and currently included within Schedules 2, 4 and 5. Throat lozenges containing lidocaine are unscheduled and available for general sale without professional advice. Lidocaine preparations (10% or less) are currently listed within Schedule 2 in preparations for topical use (other than eye drops). The exception is dosage units containing 30 mg or less of total local anaesthetic, for instance, lozenges.[6]

1.5 Paracetamol / ibuprofen combination

Paracetamol in combination with ibuprofen has been available since 2014, initially launched as two new analgesic products by [redacted] ([redacted] – paracetamol 500 mg and Ibuprofen 200 mg) and [redacted] ([redacted] – paracetamol 500 mg and ibuprofen 150 mg). In 2016, small pack sizes (up to 12 tablets) of the combination product were down-scheduled to Schedule 2. Until this time both products were classified Schedule 3: Pharmacist Only Medicines under the Poisons Standard available over-the-counter (OTC) in all pack sizes and accompanied by professional advice.

Paracetamol is available in supermarkets in Australia with no restrictions to prevent consumers from purchasing multiple packs (for instance 20 packs paracetamol 500 mg tablets, contains 10 gram paracetamol). Moreover, in pharmacies, under Schedule 2, 100 tablets (totalling 50 gram paracetamol) can be freely purchased without a pharmacist's involvement.

Feedback

Comments and feedback to [redacted] are provided.

1.1 **Paracetamol in liquid formulations**

Schedule 4 and Schedule 2 amended entries (Box 1) are NOT supported.

Amendments are proposed to provide a limit on the amount of paracetamol that can be supplied in the liquid form in Schedule 2. The amended entries aim to minimise the risk of accidental poisoning by limiting the total amount of paracetamol in a pack. However, the pack size of 100 mL containing a maximum concentration of paracetamol 50 mg/mL and with a limit of 50 gram paracetamol is excessive and could still result in accidental poisoning. These proposed amendments may also impact access to other pack sizes available OTC in pharmacies:

- Pack sizes for use in children: 100 mg/mL 5 mL (containing 500 mg paracetamol) and 20 mL (containing 2 gram paracetamol)
- The range of larger volume pack sizes for those who may be elderly or disabled and unable to swallow solid dose formulations.

Schedule 4 - Amend Entry

PARACETAMOL:

a. when combined with aspirin or salicylamide or any derivative of these substances except when separately specified in these Schedules;
b. when combined with ibuprofen in a primary pack containing more than 30 dosage units;
c. in slow release tablets or capsules containing more than 665 mg paracetamol;
d. in non-slow release tablets or capsules containing more than 500 mg paracetamol;
e. in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;
f. in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in Schedule 2;
g. in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;
h. for injection;
i. <u>in liquid preparations for oral use except when in Schedule 2.</u>

Schedule 2 - Amend Entry

PARACETAMOL for therapeutic use:

a. <u>liquid preparations for oral use containing no greater than 50 mg per mL of paracetamol in 100 mL with a maximum of 50 g paracetamol per container;</u>

Box 1: Proposed Schedule 4 and Schedule 2 amendments for paracetamol liquid – refer clauses <u>underlined</u>

1.2 **Hyoscine butylbromide liquid formulation**

Schedule 2 amended entry (Box 2) is supported.

This amendment provides for a set amount of liquid (in undivided oral doses) hyoscine butylbromide per pack to be available within Schedule 2. This aligns with the current scheduling of oral tablet formulation and enhances access without a prescription to a liquid formulation for treatment of abdominal cramping and pain.

Schedule 2 - Amend Entry

HYOSCINE BUTYLBROMIDE as the only therapeutically active substance:

1. in divided preparations for oral use, containing 20 mg or less of hyoscine butylbromide per dosage unit in a pack containing 200 mg or less of hyoscine

   butylbromide; or

2. <u>in undivided preparations for oral use with a recommended single dose not exceeding 20 mg of hyoscine butylbromide in a pack containing 100 mg or less of hyoscine butylbromide.</u>

Box 2: Proposed Schedule 2 amendment for hyoscine butyl bromide to include a liquid dose form and pack size – refer point 2 as <u>underlined</u>.

1.3 **Calcifediol monohydrate**

New entry under Schedule 4 (Box 3) is supported.

This medicine or chemical entity is not specifically scheduled in the current Poisons Standard. It is considered a derivative of vitamin D, and currently covered by the scheduling for vitamin D. Calcifediol is reported to provide the same health benefits as vitamin D, however the potency may be as much as three times greater than vitamin D. The entry has been created to restrict the daily dosage to <10 micrograms per day (unless medically indicated or prescribed).

Schedule 4 - New Entry

CALCIFEDIOL MONOHYDRATE for human internal therapeutic use except in preparations containing 10 micrograms or less of calcifediol monohydrate per recommended daily dose.

Index - New Entry

CALCIFEDIOL MONOHYDRATE

Schedule 4

Box 3: Proposed Schedule 4 amendment to include an entire new entry for calcifediol monohydrate as underlined.

1.4 **Lidocaine for topical use**

Schedule 2 amendment to entry (Box 4) is supported.

This amendment will allow unscheduled access to lidocaine 0.6% topical aqueous spray. Lidocaine throat lozenges are currently available at higher dose limits without access to health professional advice. Lidocaine 0.6% throat spray offers an alternative method of delivery for people who prefer a choice of formulation without having to visit a pharmacy.

Schedule 2 - Amend Entry

LIDOCAINE in preparations for topical use other than eye drops:

a. containing 10 per cent or less of total local anaesthetic substances, **except**:

i. in dermal preparations containing 2 per cent or less of total local anaesthetic substances; or

ii.in aqueous sprays for oromucosal use containing 0.6 per cent or less of total local anaesthetic substances; or

b. in divided preparations containing 200 mg or less of total local anaesthetic substances, **except** in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.

Box 4: Proposed Schedule 2 amendment to include a new entry for lidocaine 'aqueous sprays' containing 0.6% (or less) as underlined.

1.5 **Paracetamol and ibuprofen combination**

Schedule 4, 3 and 2 amendment to entries (Box 5) is NOT supported.

These proposed amendments modify (increase) the pack size limits within each of these Schedules and exempt the pack size of 12 from scheduling. The rationale is based upon applying the sequence of controls on paracetamol/ibuprofen combinations based on pack size with

- 12 dosage units or less as 'exempted from scheduling'
- 13 to 30 dosage units or less as 'Pharmacy Medicine' (Schedule 2)
- 31 to 50 dosage units or less as 'Pharmacist Only Medicine' (Schedule 3), and
- larger pack sizes as 'Prescription Only Medicine' (Schedule 4).

The proposed pack size changes for the combination product are broadly consistent with pack sizes for paracetamol or ibuprofen used separately and available without prescription. .

In 2018, the TGA published the interim decisions NOT to amend the Poisons Standard in relation to available pack sizes of paracetamol combined with ibuprofen.[7] The Commission supports the interim decisions and considers there is no additional clinical evidence to support increasing pack sizes within the various Schedules nor to exempt the smallest pack size to allow general sale in supermarkets. The reduction in scheduling infers a perceived safety around use of these medicines.

In the existing regulation, access to medicines remains supported with larger packs of the combination are already available OTC in pharmacies, accompanied by (Schedule 3) or with access to (Schedule 2) professional advice.

Advertising is available for Schedule 2 medicines and governed by an advertising code.[8] It is likely that manufacturers would use the scheduling exemption to promote the availability of the combination packs without the need to go to a pharmacy in direct-to-consumer advertisements.

Schedule 4 - Amend Entry

PARACETAMOL:

a. when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;

b. in slow release tablets or capsules containing more than 665 mg paracetamol;

c. when combined with ibuprofen in a primary pack containing more than ~~30~~**50**dosage units;

d. in non-slow release tablets or capsules containing more than 500 mg paracetamol;

e. in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;

f. in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in schedule 2;

g. in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;

h. for injection.

Schedule 3 - Amend Entry

PARACETAMOL when combined with ibuprofen in a primary pack containing ~~30~~**50** dosage units or less **except** when included in or expressly excluded from Schedule 2.

Schedule 2 - Amend Entry

PARACETAMOL for therapeutic use:

a. when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than ~~12~~**30** dosage units per pack **except** in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or

Box 5: Proposed Schedule 4 and Schedule 2 amendments to pack sizes and exemption to allow general sale of 12 dosage unit packs of paracetamol and ibuprofen combination products as underlined

Recommendations

1. Paracetamol in liquid formulations

The Commission recommends that ACSM review the intention and implementation of the proposed amendment to Schedule 2 pack size of paracetamol liquid.

The Commission strongly supports amendments to the Poisons Standard that would limit the pack size of paracetamol liquid within Schedule 2.

However, the proposed amendment is confusing and appears to imply the maximum total quantity of paracetamol in a single pack is either 5 gram (100 mL container of 50 mg/mL) or 50 gram.

The proposed amendment could lead to unintended consequences by limiting pack sizes and strengths available within pharmacies or for general sale.

The proposed amendment appears to limit access or even result in elimination of various strengths and presentations of products that are currently available and remain suitable for treatment of fever in young children. For instance, 100 mg/mL paracetamol in 5 mL and 20 mL pack sizes.

The Commission suggests that the Schedule 2 limit for liquid paracetamol be expressed only in terms of the maximum gram content per container, i.e. 5 gram.

Larger volume pack sizes should continue to be available for purchase by adult consumers with swallowing difficulties who rely on liquid medicine formulations. The Commission suggests an entry within Schedule 3 could provide for larger pack sizes. For example, up to 25 gram paracetamol could be purchased OTC with pharmacist advice in schedule 3 Liquid pack sizes over 25 gram could be included in Schedule 4.

2. Paracetamol / ibuprofen combinations pack sizes

The Commission recommends ACSM

- **retain existing scheduling and pack size limits for paracetamol/ibuprofen combination products with continued restriction on general sale.**

In 2018, the TGA published the interim decisions NOT to amend the Poisons Standard in relation to available pack sizes of paracetamol combined with ibuprofen.[7]

The Commission continues to support the sound reasons for the interim decision in 2018 that balanced the risks and benefits of use; the purpose for use; toxicity and other matters related to public protection.

The potential for confusion and double dosing of both paracetamol and ibuprofen in the community is high. In June 2017, NPS MedicineWise published a summary report on ‘dose confusion with paracetamol/ibuprofen combinations’.[9] Since 2016 the NSW Poisons Information Centre had witnessed an increase in calls from consumers worried that they may have “accidentally overdosed” on paracetamol.

The maximum manufacturer dosage recommendation for each medicine is

- Paracetamol 1 gram per dose and 4 gram per day taken in 4 divided doses (or 1 gram every 6 hours)
- Ibuprofen 400 mg per dose and 1200 mg taken in divided doses per day (or 400 mg every 8 hours).

The maximum number of tablets to reach the maximum dose of ibuprofen would be 6 tablets of the combination product [redacted] and 8 tablets for [redacted]. This would be exceeded if a consumer follows their understanding of the directions for the maximum dose of paracetamol per day (4 gram) which has been communicated (and advertised) to consumers over many years through various education campaigns aimed at reducing the risk of overdose.[10]

In Australia, paracetamol poisoning and deaths from overdose remains an issue.[11] A recent article in a pharmacy newsletter, Pharmacy News reported findings from two studies, one reporting that the rate of toxic liver disease attributable to paracetamol misuse is rising by almost 8% year-on-year in Australia since 2004.[12]

The second of the studies reported that almost half of the overdoses involved staggered ingestion. This is potentially a sign of unintentional overdose with consumers taking higher than appropriate doses over a period of time.[13] The study authors [Australasian Management of Acute Liver Failure Investigators team] called for more controls that would reduce both deliberate and unintentional overdose with paracetamol. Allowing combination packs of paracetamol and ibuprofen available for general sale within supermarkets could compound this issue. Indeed, up scheduling of all paracetamol formulations may need to be considered.

The maximum recommended daily adult dose of paracetamol is 4 gram. Single oral doses of paracetamol above 10 grams or 200 mg/kg of bodyweight, whichever is lower, have a reasonable likelihood of causing liver toxicity and irreversible damage. The proposed increases in pack size from 30 to 50 tablets would increase the total amount of paracetamol from 10 gram to 25 gram and ibuprofen from 6 gram to 10 gram.

Ibuprofen should only be used with caution in consumers with coexisting medical conditions such as, asthma, heart conditions, gastrointestinal bleeding risk, or kidney disease. At least 50% of patients have one or more of the listed medical conditions, with heart conditions generally the most common.[14] The percentage of patients with these conditions increases with age and is higher amongst those diagnosed with a musculoskeletal problem.[14]

Ibuprofen can reduce the antiplatelet activity of low-dose of aspirin and potentially reduce or negate its cardio-protective effect if taken routinely. In addition, NSAIDs such as ibuprofen can interact with other medicines. The combination of an ACE inhibitor or an angiotensin II receptor antagonist (A2RA), a diuretic and an NSAID (including a COX-2 selective NSAID), may predispose vulnerable patients to renal failure.[15, 16] Risk factors include advanced age, pre-existing renal impairment and dehydration. There is a risk that consumers with a chronic or musculoskeletal pain will self-medicate with the combination product without health professional advice, especially as there would be no controls on the purchase of multiple packs in supermarkets. In addition, consumers risk exposing themselves to potential interactions between ibuprofen and their prescribed and other medicines.

Ongoing long-term treatment with any analgesic requires medical intervention especially when patients suffer additional conditions and already prescribed medicines that could interact with NSAIDs such as ibuprofen. The Schedule 4 entry for the paracetamol/ibuprofen combination already enables medical practitioners to prescribe larger quantities when appropriate.

Discussion

The Commission is responsible for the development and support of the NSQHS Standards including standards for medicines management. In addition, the Commission consults within its stakeholder groups on the impact on health services of any changes to medication management (including medicines scheduling amendments).

The TGA's proposed amendments to the Poisons Standard were tabled at the Commission's Health Services Medication Expert Advisory Group (September 2019). Feedback was sought from members as major stakeholders on issues relating to medication safety. [redacted]

The Commission supports review of entries within the Poisons Standard to ensure appropriate controls are placed upon pack sizes for individual medicines, as well as medicine combinations such as paracetamol and ibuprofen.

Since 2004, in Australia, the incidence of paracetamol poisoning-related hospital admissions and deaths in Australia has increased.[11] Allowing combination packs of paracetamol and ibuprofen available for general sale within supermarkets, along with additional direct-to-consumer advertising, has potential to compound this issue.

The Commission supports three of the proposed amendments to the Poisons Standard to be considered at the ACMS, in November 2019.

Two (2) of the proposed amendments are **NOT supported** and the Commission recommends that ACSM:

- review the intention and implementation of the proposed amendment to Schedule 2 pack size of **paracetamol liquid**
- uphold the 2018 interim decision to retain the Poisons Standard entry in relation to available pack sizes of paracetamol/ibuprofen in combination[7]

The Commission welcomes further opportunities to provide responses to future TGA consultations, which directly impact medication safety and reduce risk of medication misadventure by patients and their carers.

Appendices

A: Therapeutic Goods Administration. Consultation: Proposed amendments to the Poisons Standard – ACMS and ACCS, November 2019

www.tga.gov.au/consultation-invitation/consultation-proposed-amendments-poisons-standard-acms-and-accs-november-2019

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