Purpose

makes this submission on proposed amendments to the Poisons Standard referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling in November 2016.

comments relate to proposed amendments to:

• melatonin
• paracetamol compounded with caffeine
• vardenafil
• nicotine
• vitamin D
• cetirizine.
Summary of position

Melatonin

is firmly opposed to the proposal to exempt melatonin from scheduling given the lack of comprehensive data on long term use and the safety risks posed by the potential for inappropriate use in an unregulated market.

Paracetamol compounded with caffeine

is firmly opposed to the proposal to exempt paracetamol and caffeine combination products from Schedule 2.

Vardenafil

supports the proposal to create a new Schedule 3 entry for vardenafil but does not support the inclusion of vardenafil in Appendix H.

Nicotine

Although the need for more contemporary regulatory arrangements for electronic nicotine delivery systems is acknowledged, does not support the proposed exemption from scheduling of these preparations for the purpose of tobacco harm reduction as this course of action is not likely to provide the necessary safeguards for public health and consumer safety.

Vitamin D

supports the inclusion of vitamin D in Appendix H.

Cetirizine

does not support the proposal to exempt cetirizine in packs up to 10 days’ supply from Schedule 2 as smaller packs of cetirizine as well as other comparable options with preferred safety profile are readily available.

Comments on specific substances

Melatonin

Proposal to exempt melatonin from scheduling (Schedule 4) in preparations containing 1 mg or less.

Safety and efficacy

Melatonin is a naturally occurring hormone associated with the control of circadian rhythm. As we age, endogenous production of melatonin declines and therefore the incidence of primary insomnia increases with advancing age.
understands that the current classification of melatonin varies across the world whereby it is a ‘prescription only’ medicine in countries such as Australia, New Zealand and the UK but in other countries it can be regulated as a dietary supplement (US) or a natural health product ingredient (Canada).

A product of 2 mg prolonged release formulation (tablet) is registered in Australia with the approved indication of “monotherapy for the short term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over”. The melatonin in this product is not of plant or animal origin. In the target population melatonin was regarded to be safe and well tolerated.²

### Use in children

Melatonin is used in children, for example, to aid sleep in children with autism spectrum disorders particularly where other sleep strategies or behaviour change options may not be providing benefit. In Australia, it is likely that a paediatrician or sleep specialist would be involved in the care of a child requiring melatonin therapy. It is stated that melatonin is safe in children for short term use in doses between 0.5 mg to 6 mg³ and generally well tolerated⁴ even in young children. However, data around long term safety are reported to be lacking and therefore routine use without regular review or annual break in treatment is generally discouraged.⁵,⁶

### Potential concerns

has a number of concerns with regards to the current proposal for exemption from scheduling including the following.

- Melatonin is currently available by prescription only. If a new unscheduled melatonin product was to be approved in Australia firmly believes this would cause confusion to many consumers and further, there is a genuine risk that there could be indiscriminate use (e.g. to ‘get through’ academic exams or unhealthy shift work schedules), long term use through self-medication (e.g. including where initial medical diagnosis and long term oversight is warranted), or inappropriate use (e.g. without first investing in other measures to improve sleep hygiene or practices).

- notes that the approval of melatonin in Australia in 2009 was in the context that it would be for short term use (treatment duration of up to three weeks) given more comprehensive safety data to support longer term use was not available.

- Insomnia impacts on individuals differently (e.g. quality, latency, duration, efficiency). While insomnia may be self-reported or self-diagnosed, any causes may also vary and therefore

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‘solutions’ require careful consideration. Pharmacists have a role in supporting consumers around the management of medicines which may affect sleep quality, lifestyle adjustments, sleep management techniques and strategies. Where there may be a serious underlying condition affecting or causing insomnia pharmacists are well placed to refer the consumer for medical advice.

- There are some parents who advocate the use of “natural medicines” (including homeopathic products) for their children for various conditions including sleeplessness. ■■ believes that these individuals would be particularly vulnerable if melatonin was to be exempted from scheduling.

- The use of melatonin is currently not recommended for women who are (or may become) pregnant or breastfeeding due to lack of direct clinical data.

- As reported in the melatonin AusPAR document, 7 there is some literature which suggests that melatonin may also exert a direct sedative effect.

- ■■ is aware that a similar melatonin reclassification application has recently been listed for consideration by the Medicines Classification Committee in New Zealand. In that application, the proposed form of the product is a “fast dissolving thin polymer film embedded with melatonin that melts and dissolves quickly and completely in oral cavity saliva”.

- Although ■■ is unable to ascertain whether the current Australian rescheduling proposal in any way relates to the New Zealand application, we believe the suggested ease of administration may become a focal point of any product advertising. This may contribute further to the potential for inappropriate use by consumers.

Summary

The availability of melatonin in Australia has been determined by the rationale for use based on the role of melatonin in sleep and circadian rhythm regulation and the age-associated decrease in endogenous levels. This is clearly reflected in the parameters of the approved indication of the currently registered melatonin-containing product.

■■ is not aware of any recent more comprehensive data on the use of melatonin which would demonstrate or help clarify long term safety.

We believe that introducing melatonin into the unregulated market through exemption of scheduling may lead to inappropriate use with considerable safety risks. Therefore ■■ is firmly opposed to this proposal to exempt melatonin from scheduling.

Paracetamol compounded with caffeine

Proposal for combination products containing paracetamol and caffeine to be exempt from Schedule 2 when supplied in primary packs of not more than 10 tablets/capsules or 5 sachets of powders or granules.

understands that Schedule 2 paracetamol and caffeine combination products generally consist of 500 mg of paracetamol and 65 mg of caffeine per dosage unit.

As part of the current range of analgesic medicines, paracetamol and caffeine combination products provide an alternative for consumers seeking relief of pain or to reduce fever. There are a range of minor ailments for which this combination of active ingredients may be appropriate.

believes that the current Schedule 2 classification provides the most appropriate environment for consumers who may require or benefit from supplementary health information or advice, or have the opportunity to have a discussion with the pharmacist.

Caffeine is considered to be safe at recommended doses of the Schedule 2 combination product. Although it is reported that caffeine enhances the effects of paracetamol, the benefits are generally thought to be small. Further, believes it is critical to consider the types of adverse effects that caffeine may cause – some of which are outlined below.

- Caffeine toxicity can occur at doses above 500 mg. However, smaller doses (e.g. 50 mg) may result in adverse outcomes depending on an additive effect of caffeine from other sources including other medicines and dietary intake.
- Unscheduled oral dose caffeine preparations are available for the relief of mental fatigue and drowsiness. These are generally presented as 100 mg caffeine per dosage unit with a maximum daily dose of six tablets. The recommended wording for inclusion in the labelling of caffeine preparations to be used as a stimulating or alerting agent is: 100 mg per dose maximum, which may be repeated at three hourly intervals. Do not exceed 600 mg in 24 hours.
- Vitamin and mineral supplements may also contain caffeine. Generally the quantity of caffeine per dosage unit in these products are in the low range however there are exceptions, for example, Berocca Boost (ARTG ID 218721) contains 72.7 mg of caffeine per tablet and ThermoBooster (for the support of weight management; ARTG ID 224691) contains 37.8 mg of caffeine per tablet. Such levels will contribute substantially to the total caffeine intake often without the person realising the additive effect or potential consequences.
- Dietary intake of caffeine can vary between individuals but can reach significant levels through consumption of food and beverages such as tea, coffee (average of 80 mg caffeine per cup), cola, chocolate and energy drinks (e.g. 250 ml can of Red Bull contains 80 mg of

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Many consumers may not be aware of or associate their dietary caffeine intake with the active ingredients of the medicines they are taking.

has also commented previously regarding the use of words such as “extra” in the brand name of the combination product to differentiate it from single ingredient analgesic products. believes the use of this particular word has the potential to misguide consumers. We believe consumers may display a preference to use these products as first-line therapy when this may not be warranted. Relevant quality use of medicines advice including appropriate first-line therapy choices could not be offered in a non-pharmacy retail environment.

It is also possible that some consumers may choose the combination product with a preference for, or reliance on, the effects of caffeine. In such cases there is considerable risk of paracetamol toxicity through ingestion of multiple tablets even though this may be within a ‘safe’ dose range for caffeine.

Summary

does not believe increasing consumer access to paracetamol and caffeine combination products is warranted given the range of analgesic medicines already available outside of pharmacies. It is of significant concern that the potential for consumers to experience an adverse event or outcome is greatly increased if paracetamol and caffeine combination products are made available where professional intervention, and therefore the opportunity to prevent medication misadventure, is not available.

is firmly opposed to the proposal to exempt combination products containing paracetamol and caffeine from Schedule 2.

Vardenafil

Proposal to create a new Schedule 3 entry for vardenafil in oral preparations containing 10 mg or less per dosage unit in packs of not more than 8 dosage units.

Safety and efficacy

Vardenafil is one of the oral phosphodiesterase type 5 inhibitors currently registered in Australia. Its approved indication is “for the treatment of erectile dysfunction in adult males (inability to achieve or maintain penile erection sufficient for satisfactory sexual performance)”.

Vardenafil has undergone a full evaluation at initial registration in Australia and is not aware of any new information that may alter the clinical safety and efficacy profile of this medicine.

Key considerations

believes the key considerations around whether this rescheduling proposal is acceptable to

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health professionals and safe for consumers will depend heavily on implementation issues including the following.

- The application of clear parameters (e.g. exclusion criteria, off-label use) by pharmacists in the screening and risk assessment step to determine whether it is appropriate to supply the medicine to the consumer.

- Clear criteria for when immediate (or conditional) referral to a medical practitioner is warranted and for these to be clearly highlighted for pharmacists.

- Recommendations on the use of an appropriate consultation area.

- Addressing consumer understanding and expectations in relation to supply or non-supply and appropriate follow up actions.

- Assisting with the management of other comorbidities.

- Appropriate communication with prescribers (e.g. consumer’s GP, other prescribers in the area).

Most of these are the types of issues that would be included for consideration and advice when [redacted] develops suitable resources to support the implementation of a new rescheduling from Schedule 4 to Schedule 3 (see also the next section).

**Resources for pharmacists**

Vardenafil has been available in Australia since 2003 as a Schedule 4 medicine. Pharmacists already possess the appropriate knowledge and competencies relating to the medicinal characteristics and biological profile of the substance. However, some additional information and advice in the context of Schedule 3 supply are likely to be of benefit to pharmacists.

One of the fundamental roles of [redacted] is the development of education and training, clinical practice guidance and implementation support tools for pharmacists in the context of any substance which has been rescheduled from Schedule 4 to Schedule 3. It is paramount that such resources are evidence-based and offer contemporary, realistic and useful guidance to pharmacists to support good decision-making in practice and offer tailored and optimised health care.

Although early planning has already commenced, generally [redacted] will conduct detailed scoping of the optimal range of education, training and practice support tools around the time that the interim scheduling decision is made public. Resources may include, for example: Schedule 3 guidance document, clinical education article [redacted] including continuing professional development self-assessment questions, a national webinar, consumer information leaflet, case studies, best practice documentation templates, and a guide on the application of relevant professional practice standards (e.g. screening and risk assessment).

As advocated previously [redacted] is keen to work with relevant stakeholders to ensure rigorous, consistent and user-friendly professional education and practice support tools can be developed for the pharmacy profession.
Training for pharmacists

Consistent with the current framework for pharmacist supply of Schedule 3 medicines, does not believe specific mandatory training is required for pharmacists to supply vardenafil as a Schedule 3 medicine. It is likely that will make recommendations to pharmacists on education updates and/or training opportunities which would help support the implementation of any new Schedule 3 arrangements.

Appendix H listing

If a new Schedule 3 entry is created for vardenafil, does not support the inclusion of vardenafil in Appendix H at this time given the lack of experience as a Schedule 3 medicine.

Summary

supports the creation of a new Schedule 3 entry for vardenafil as outlined in the proposal. However, does not support the inclusion of vardenafil in Appendix H.

does not believe mandatory training of pharmacists is required but will aim to issue appropriate recommendations around any education or training updates.

Nicotine

Proposal to exempt nicotine from Schedule 7 at concentrations of 3.6% or less for self-administration with an electronic nicotine delivery system ('personal vaporiser' or 'electronic cigarette') for the purpose of tobacco harm reduction.

The use of electronic nicotine delivery systems is increasing worldwide. The regulatory arrangements in different countries appear to vary, possibly due to the evolving nature of this market as well as the availability of evidence on the comparative risks and benefits being, at times, not consistent or not readily available. Discussions around the most appropriate regulatory arrangements for Australia into the future are complicated by fundamental dilemmas, for example, that tobacco which is more harmful to the user than electronic nicotine delivery systems can be obtained legally.

In 2015 the National Health and Medical Research Council (NHMRC) concluded\(^\text{13}\) that there is insufficient current evidence on "whether e-cigarettes are a ‘safe alternative’ to conventional tobacco cigarettes" and that further research is needed. The NHMRC also reported there is insufficient evidence on "whether e-cigarettes can benefit smokers in quitting" although we note that the current rescheduling proposal relates to the purpose of “tobacco harm reduction”, not “smoking cessation”.

Options for the regulation of electronic cigarettes are also currently under consideration and public consultation in New Zealand.

has a number of concerns with regards to the current rescheduling proposal.

- It would appear that an e-cigarette containing 3.6% of nicotine is marketed by some sources as “extra strength” with a suggestion that it may ‘suit’ a person who smokes two and a half packs or more per day of tobacco cigarettes. If we regard 3.6% to be the higher end of the available concentration range, it would appear to mean that the proposed exemption could capture the full range of nicotine concentrations used in the electronic delivery systems. does not support this given the uncertainty of evidence base around the impact that the use of these delivery systems may have on the individuals directly as well as those who experience secondhand exposure.

- Exemption from scheduling may mean there will be less control over standards and quality control of preparations, labelling and packaging considerations and the application of warning statements.

- It is not clear what data or evidence is available on the extent of tobacco harm reduction likely to be achieved through the use of electronic nicotine delivery systems. If a scheduling exemption is granted, there would be even less chance of obtaining this type of data to help inform future policy decisions.

- An exemption to scheduling may result in heavy marketing of these products. With easier accessibility, would echo the concerns expressed by the NHMRC that wider use of e-cigarettes may pose a greater risk to the community including the possibility that smoking may, once again, become socially acceptable. is also concerned that flavoured e-cigarettes, with or without nicotine content, could appeal to adolescents leading to rapid uptake of tobacco smoking.

In summary, believes there is an urgent need to consider the implementation of more contemporary regulatory arrangements for electronic nicotine delivery systems. However, does not support the proposed exemption from scheduling of these preparations for the purpose of tobacco harm reduction. We believe that such a course of action will not provide the necessary safeguards for public health and consumer safety.

Vitamin D

Proposal to include in vitamin D in Appendix H.

A Schedule 3 entry of vitamin D was created in 2013 to include preparations containing 175 micrograms (7000 IU) or less per recommended single weekly dose (except in preparations containing 25 micrograms or less per recommended daily dose). There was also a decision to not recommend inclusion of vitamin D in Appendix H.

understands from published information that the reasons for not recommending Appendix H listing were as follows.

- Off-label use could occur and could be inadvertently promoted through the Appendix H listing.

- Existing public health campaigns around vitamin D supplementation.
In the context of the original Schedule 3 decision, it was noted that a once-weekly dose was likely to be favourable in terms of enhancing compliance. This has been shown, for example, in a study which investigated rates of adherence to osteoporosis treatment in clinical practice. Greater than 80% compliance to recommended dosing of several medicines was measured and reported to be significantly higher for weekly dosing of alendronate when compared to daily dosing regimens of alendronate and calcium plus vitamin D supplements.\(^\text{14}\)

A separate systematic review and meta-analysis of studies investigating the effect of dosing frequency on medication adherence rates, again conducted mostly in individuals with osteoporosis, also found improvement in adherence for weekly dosing compared to daily dosing.\(^\text{15}\) This publication also refers to other studies, most indicating that reducing dosing improves adherence and patients prefer a less frequent dosing schedule.

Given the Schedule 3 supply of vitamin D will involve pharmacist oversight, \(\Box\) believes the possibility of off-label use would be minimal. Although a weekly dosing regimen could be regarded to be more unusual than daily dosing, pharmacist intervention and advice is likely to enhance adherence and minimise incorrect dosing. If a consumer did inadvertently take a daily dose of the 175 microgram product, \(\Box\) is aware that the delegate has previously noted the risk of toxicity to be minimal.

So far as any branded advertising is concerned, \(\Box\) believes the usual advertising rules and regulations will apply and that it would not be likely that off-label use could be inadvertently promoted as a consequence of an Appendix H listing. Although there may be a risk that some consumers would initiate self-medication as a result of seeing a branded advertisement, lower dose vitamin D products are already readily available to consumers and any request for the higher dose Schedule 3 product would be handled through pharmacist intervention.

Low vitamin D levels is a public health issue and relevant to certain groups of the Australian population. While there are existing public health campaigns to address vitamin D supplementation \(\Box\) does not believe the current proposal is contrary to the objectives of those efforts.

In summary, \(\Box\) supports the inclusion of vitamin D in Appendix H.

**Cetirizine**

*Proposal to exempt from Schedule 2 when in preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over, in a maximum pack size of 10 days’ supply labelled with a recommended daily dose not exceeding 10 mg.*

\(\Box\) notes that allergic rhinitis is classified according to pattern of symptoms (intermittent or persistent) and severity (mild or moderate-to-severe) rather than the previously used terms of


seasonal and perennial.  It is reported that seasonal allergic rhinitis is one of the two most common respiratory conditions affecting an estimated 3.7 million Australians.

The goals of treatment are to reduce symptoms and to improve daily functioning and quality of life. Optimal management of allergic rhinitis can also have other benefits such as reducing the risk of developing asthma or obstructive sleep apnoea.

A range of OTC medicines is available for the management of symptoms and include intranasal corticosteroids, oral and intranasal antihistamines, and topical and oral decongestants. Oral antihistamines can provide rapid relief of symptoms such as sneezing, itching and rhinorrhoea and often (but not always) a preference is shown for less sedating antihistamines. Treatment guidelines however generally recommend intranasal corticosteroids as first line therapy for adults and children although maximal effect requires regular use.

A number of antihistamines including cetirizine in small pack sizes are already available to consumers from a general sale outlet believes this range of products already provides consumers with the benefit of choice and ease of accessibility through a non-pharmacy setting if they so choose.

From a best practice and consumer safety perspective, does not believe the availability of cetirizine in a general retail setting should be expanded. A five day supply pack should be adequate in providing for the general goals of treatment outlined above. We do not believe there is substantial public health benefit in widening the scheduling exemption for cetirizine.

The safety profile of cetirizine is different to other medicines in the same therapeutic class such as loratadine. For example, cetirizine is required to carry a sedation warning i.e. it is listed in Appendix K of the Poisons Standard and accordingly requires to be labelled with cautionary advisory label 1. Cetirizine is most likely of the less sedating antihistamines to cause sedation.

Further, the use of cetirizine in pregnancy and breastfeeding is not recommended. In pregnancy, a sedating antihistamine is preferred; if a less sedating antihistamine is required, loratadine is preferred. In breastfeeding, loratadine or short-acting sedating antihistamines are preferred.

has previously noted that when a health professional such as a pharmacist guides allergic rhinitis management the consumer experiences better outcomes than those who set their own

goals for treating the disease.\textsuperscript{25} Consistent with this, strongly favours arrangements which promote the opportunity for consumers to discuss their allergic rhinitis management with a pharmacist.

The support of pharmacists is important for those who self-manage effectively with OTC medicines or non-pharmacological measures and is also beneficial in assisting those who have an allergic rhinitis treatment plan\textsuperscript{26} developed through a medical or nurse practitioner. Providing information, advice and education, and assisting and monitoring tailored treatments are important areas that pharmacists have a core role in supporting individuals.

In summary, does not support the proposal to widen the Schedule 2 exemption criteria for cetirizine as there are other options readily available and also in the best interests of consumer safety.

Submitted by:

1 September 2016
