The Pharmacy Guild of Australia

PROPOSED AMENDMENTS TO POISONS STANDARD

ACMS and Joint ACMS-ACCS Meeting November 2022

Comments by The Pharmacy Guild of Australia to the proposed amendments to the Poisons Standard

1. **Ivermectin**
2. **Brimonidine**
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5. **Melatonin**
6. **Green tea extract**

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IVERMECTIN

Proposal

The application is proposing to delete the Appendix D entry for ivermectin. This would remove the current restrictions on the prescribing and use of ivermectin for oral administration for human use, allowing prescribing without restrictions on prescriber speciality and potential for off-label indications such as the prevention and treatment of COVID-19.

Scheduling considerations

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

Ivermectin belongs to the anthelmintics group of medicines. It is indicated for the treatment of parasitic infections including onchocerciasis, strongyloidiasis and crusted scabies, as well as papulopustular rosacea.[1] The Australian Medicines Handbook also lists other intestinal nematode infections, cutaneous larva migrans and lymphatic filariasis as accepted indications.

In Australia, the precise prevalence of parasitic infections treated with ivermectin is relatively unknown, making it difficult to determine the extent of use of ivermectin. For instance, the prevalence of strongyloidiasis is estimated to be between 35-60% in Indigenous Australian communities, however it is difficult to detect and not routinely tested for.[2] Similarly, whilst scabies is considered common across Australia, crusted scabies is considered a rare but highly infections variant.[3] Review of Pharmaceutical Benefit Scheme data would provide further insight into the use of ivermectin for permitted indications.

The COVID-19 pandemic led to some medicines being repurposed for the prevention and treatment of COVID-19. There were suggestions that ivermectin had the potential to be used for this indication due to its ability to inhibit the replication of viruses in vitro. An updated Cochrane systematic literature review assessing the efficacy and safety of ivermectin for the prevention of infection with SARS-CoV-2 (post exposure) and treatment of COVID-19 was published in June 2022. The review '*found no evidence to support the use of ivermectin for treating COVID-19 or preventing SARS-CoV-2 infection'.*[4]

The current Appendix D entry enables ivermectin to be used for the purpose of clinical trials and does not act as a barrier for further research on the use of ivermectin for COVID-19 prevention and treatment. The Guild believes that it is appropriate to retain the current Appendix D entry until there is sufficient and definitive evidence that ivermectin is effective for the prevention or treatment of COVID-19.

Any other matters necessary to protect public health

Vaccination is the mainstay for prevention of vaccine-preventable diseases such as COVID-19. In Australia, consumers are fortunate to have free access to COVID-19 vaccines through the National COVID-19 vaccination rollout. COVID-19 vaccination protects against severe illness and death from COVID-19; helps prevent complications such as long COVID; and reduces the burden on the health system by preventing hospitalisations.[5] Vaccination is not 100% effective at preventing infection and means access to treatments for COVID-19 is also required.

[1] https://amhonline.amh.net.au/chapters/anti-infectives/anthelmintics/other-anthelmintics/ivermectin
[2] https://theconversation.com/strongyloidiasis-is-a-deadly-worm-infecting-many-australians-yet-hardly-anybody-has-heard-of-it-81687
[3] https://www.racgp.org.au/afp/2017/may/scabies-a-clinical-update
[4] https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD015017.pub3/full
[5] https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/about-rollout#benefits-of-vaccination

The Therapeutic Goods Administration has granted provisional registration to many treatments for use in COVID-19 positive patients. These treatments have been determined to meet the safety, efficacy and quality standards required for use in Australia.[6] The treatments that have been granted provisional registration enable patients access to safe and effective treatment of COVID-19 regardless of whether they are being managed in the community setting by primary care providers or in hospital.

The Guild believes that it is important to retain the current Appendix D entry for ivermectin to ensure patients continue to utilise vaccination for the prevention of COVID-19 infection and access COVID-19 treatments that are safe and effective.

Summary

The Guild opposes the proposed amendment to remove ivermectin from Appendix D. Studies conducted on the use of ivermectin for the prevention and treatment of COVID-19 have so far failed to conclude that it is effective for this indication. As a matter of public safety, the Guild believes that the current restrictions remain appropriate to ensure individuals receive safe and effective treatment for COVID-19.

[6] https://www.tga.gov.au/products/covid-19/covid-19-treatments/covid-19-treatments-provisional-registrations

BRIMONIDINE

Proposal

The application is proposing an amendment to the Poisons Standard to create a Schedule 2 entry for brimonidine 0.025% in ophthalmic preparations for treatment of eye redness and minor irritation in adults aged 18 years and older.

Scheduling considerations

The risks and benefits of the use of a substance

Risks

In Australia, brimonidine in ophthalmic preparations is only available in higher concentrations than the 0.025% proposed by this application.

The Australian Medicines Handbook (AMH) states that brimonidine is contraindicated in children aged less than 2 years, and that serious adverse effects such as CNS depression are more likely in children than adults. It also recommends avoiding use close to childbirth and whilst breastfeeding due to theoretical risk of CNS depression and apnoea in the neonate. Use in severe cardiovascular disease is listed as a precaution as the condition may worsen. [7]

The adverse effects of brimonidine (ophthalmic) in the AMH include fatigue, drowsiness, dizziness, bradycardia, hypotension and uveitis.[8] Clinical studies on brimonidine 0.025% have observed no clinically significant systemic adverse effects or ocular allergic conjunctivitis.[9]

Benefits

Brimonidine is a selective alpha-2 adrenergic agonist used as an ophthalmic decongestant. When applied topically to the eye brimonidine acts on receptors to constrict the blood vessels on the conjunctiva. Vasoconstriction of conjunctival blood vessels results in rapid reduction of ocular redness.[10]

Other substances currently marketed in Australia as ophthalmic decongestants are either selective alpha-1 adrenergic agonist or mixed alpha-1/alpha-2 adrenergic agonists. Issues associated with alpha-1 adrenergic agonists include a loss of effectiveness with continued use and rebound redness upon discontinuation of treatment. These issues have not been observed or were rarely reported in clinical trials of brimonidine 0.025%, therefore offering a benefit of this substance over currently available ophthalmic decongestants.[11]

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

Brimonidine is available in ophthalmic preparations containing at least 0.15% brimonidine for the treatment of glaucoma and ocular hypertension. It is also available in a topical preparation for the treatment of facial erythema due to rosacea.[12,13] Products containing brimonidine 0.025% are not

[7] https://amhonline.amh.net.au/chapters/eye-drugs/drugs-glaucoma/alpha2-agonists/brimonidine-eye
[8] ibid
[9] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7399465/
[10] ibid
[11] ibid
[12] https://amhonline.amh.net.au/chapters/eye-drugs/drugs-glaucoma/alpha2-agonists/brimonidine-eye
[13] https://amhonline.amh.net.au/chapters/dermatological-drugs/drugs-rosacea/brimonidine-skin

currently available in Australia, although there are products available in the US and Canada for the relief of red eye that contain 0.025% brimonidine.[14]

Conjunctivitis, or red eye, is inflammation of the conjunctiva.[15] It is considered a common condition and can be caused by infectious and non-infectious factors. [16,17] Common causes of non-infectious conjunctivitis include tiredness, allergies, dry eyes, and chemical or physical irritants (e.g. exposure to smoke or wearing contact lenses).[18,19] The inflammatory process associated with conjunctivitis causes vasodilation of blood vessels on the surface of the eye, causing redness. Ophthalmic decongestants, such as brimonidine, reduce eye redness through vasoconstriction of blood vessels and are recommended for short-term symptomatic relief of non-infectious conjunctivitis.[20]

Anecdotal evidence suggests that the use of ophthalmic decongestants for relief of red eye is relatively common in the community. Overuse of the ophthalmic decongestants currently available leads to rebound redness and perpetuates use. As rebound redness has not been experienced in clinical trials of brimonidine 0.025%, prolonged use and possibly the extent of use will hopefully be reduced.

Summary

The Guild supports the proposed amendment to the Poisons Standard for brimonidine. This amendment will allow access to low dose (0.025%) brimonidine for the relief of red eye. Low dose brimonidine is generally well tolerated and does not cause the same issues of rebound redness and loss of effectiveness seen with the ophthalmic decongestants currently available in Australia. On balance, the Guild believes the benefits of access outweigh the risks.

[14] https://www.lumifydrops.com/professional

[15] https://tgldcdp.tg.org.au/viewTopic?etgAccess=true&guidelinePage=Antibiotic&topicfile=conjunctivitis&guidelinename=Antibiotic&sectionId=toc_d1e47#toc_d1e47

[16] https://www.healthdirect.gov.au/conjunctivitis

[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5443986/

[18] https://www.aao.org/eye-health/treatments/redness-relieving-eye-drops

[19] https://www.allergy.org.au/patients/allergic-rhinitis-hay-fever-and-sinusitis/allergic-conjunctivitis

[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5443986/

FEXOFENADINE

Proposal

The application is proposing to amend the Poisons Standard entry for fexofenadine 180mg to increase the pack size that can be sold in general retail from 5 dosage units to 10 dosage units.

The Guild notes that one of the reasons for the applicant's proposal is that larger pack sizes would be more convenient for seasonal allergic rhinitis sufferers who reside in "*parts of Australia where the distance or duration of travel to a pharmacy during their opening hours may not be convenient."*. Community pharmacies are well distributed across Australia, with 97% of people in capital cities having access to at least one pharmacy within a 2.5 km radius and 66% of people in the rest of Australia having access to a pharmacy within a 2.5 km radius.[21] Additionally, many community pharmacies are open extended hours, on weekends and public holidays. The Guild believes that given the distribution of community pharmacies across Australia, the current restriction of 5 dosage units allows enough time for consumers to access a pharmacy for a packet with more dosage units if required.

Scheduling considerations

The risks and benefits of the use of a substance

Use in pregnancy

The Australian Medicines Handbook states that fexofenadine is safe to use in pregnancy although there is more experience with older sedating antihistamines.[22] The Royal Women's Hospital factsheet '*Medicines in pregnancy'* recommends sedating antihistamines over less-sedating antihistamines.[23]

Fexofenadine has a pregnancy category rating of B2[2] and fexofenadine in medicines for oral use must be accompanied by the following advisory statement: "*If you are pregnant or breastfeeding, check with your doctor or pharmacist before using this medicine."* It is important to note that pregnancy category B indicates that human data is lacking or inadequate for these substances and is therefore based on animal studies.*[24]* In contrast, sedating antihistamines are generally designated pregnancy category A, indicating that they have been taken by a large number of pregnant women or women of childbearing age without evidence of any increased frequency of malformations or harmful effects on the foetus.[25]

The Guild argues adherence to these advisory guidelines is less likely to occur if fexofenadine is purchased in general retail where there is no ready access to professional advice. While labelling may provide useful guidance for woman who are pregnant or breastfeeding, studies suggest not all consumers read information provided with the medicine. A survey of 1000 people conducted in Northern Ireland identified only 80% of participants always or often read the instructions on non-prescription medicine packages and that 3.4% rarely or never read the information. Combined with participants that only sometimes read the manufacturer's information, 10% of people could be at risk of misusing these medicines.[26]

Given this proposal would increase the quantity of tablets that could be sold in general retail, this exacerbates the current risk on non-adherence to important advisory statements.

[21] Pharmacy Guild of Australia 2020.
[22] https://amhonline.amh.net.au/chapters/allergy-anaphylaxis/antihistamines/less-sedating-antihistamines?menu=vertical
[23] https://thewomens.r.worldssl.net/images/uploads/fact-sheets/Medicines-in-pregnancy-220804.pdf
[24] https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy
[25] ibid
[26] M Wazaify, E Shields, CM Hughes et al; Societal perspectives on OTC medicines; Family Practice 2005 22:170-176

Pro-arrhythmic potential

A study conducted in Europe investigated the pro-arrhythmic potential of antihistamines by combining safety reports of the FDA Adverse Event Reporting System (FAERS) with drug utilisation data from 13 European Countries. The study found five agents, which included fexofenadine had strong signals for torsadogenicity and recommends regulators and clinicians should consider risk-minimisation activities.[27]

The Guild believes that a further relaxing of the scheduling exemption for fexofenadine would increase the risk of medicine misadventure for consumers that have a pre-existing heart condition.

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

Currently the indication for fexofenadine that is exempt from scheduling is treatment of seasonal allergic rhinitis in adults and children 12 years of age and over. However, fexofenadine is also indicated for chronic urticaria, and increasing the amount of fexofenadine available in general retail may lead to consumers using fexofenadine products for conditions other than allergic rhinitis such as dermatitis, soap allergies or severe reactions to substances or insect bites. When medicines are sold outside pharmacy, there is no access to health professional advice regarding diagnosis nor the appropriateness of particular treatments.

This could result in a greater number of consumers self-medicating for undiagnosed conditions other than the product indications (allergic rhinitis) over a longer period without contact with a health professional. This risk is exacerbated by the lack of restrictions on the number of packs that can be purchased in a single transaction in general retail.

Consumer Health literacy

The Health Literacy Survey (HLS) conducted by the Australia Bureau of Statistics (ABS) in 2018, identified that only 39 percent of people find it always easy to understand health information and 8 percent find it difficult to understand health information.[28] One of the indicators used in the HLS to assess understanding of health information was the ability to read and understand all the information on medical labels. It has been established that individuals with low health literacy are more likely to have worse health outcomes and poorer understanding of medication instructions leading to non-adherence and improper use.[29]

Consequently, it is the view of the Guild that consumers should always receive advice on the correct and proper use of medicines, and this is best achieved by consumers having access to professional advice from pharmacy staff. This is particularly important for the most vulnerable consumer groups, particularly children, the elderly, those from low socio-economic and/or culturally and linguistically diverse backgrounds as well as those with chronic or multiple disease conditions. Facilitating access to professional advice for the prescribing and supply of medicines is the best way to maintain safe and cost-effective access to medicines.

The toxicity of a substance

The key feature of toxicity in overdose of less-sedating antihistamines is prolongation of the QT interval with associated risk of torsades de pointes. As mentioned previously given there are usually no restrictions on the number of packs that can be purchased by customers from general retail, this increases this risk of toxicity occurring.

[27] Poluzzi, E., Raschi, E., Godman, B., Koci, A., Moretti, U., Kalaba, M., ... & De Ponti, F. (2015). Pro-arrhythmic potential of oral antihistamines (H1): combining adverse event reports with drug utilization data across Europe. *PloS one*, *10*(3), e0119551

[28] https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-health-survey-health-literacy/latest-release#articles

[29] ibid

Any other matters necessary to protect public health

Co-morbidity with other conditions

Allergic rhinitis often coexists with asthma and atopic dermatitis.[30] People who suffer from allergic rhinitis have a higher chance of developing asthma, with approximately three out of four people with asthma also having allergic rhinitis.[31] Guidelines indicate it is important to recognise and treat allergic rhinitis as part of ongoing management of asthma as the condition contributes to frequent symptoms and is associated with worse asthma control in children and adults.[32] This is less likely to occur if consumers are purchasing these products from general retail where there is no access to health professional advice.

Summary

The Guild opposes the proposed amendment to the Poisons Standard in relation to fexofenadine. Fexofenadine may not be appropriate for use in all individuals and the ability for consumers to seek advice from a health professional is important to support the safe use of medicines. On balance, we believe that the risks of increasing access to packets containing more dosage units outweighs the patient benefit.

[30] Allergic rhinitis and conjunctivitis - Therapeutic Guidelines online

[31] National Asthma Council Australia. https://www.nationalasthma.org.au/living-with-asthma/resources/patients-carers/brochures/hay-fever-allergic-rhinitis-and-your-asthma

[32] ibid

IBUPROFEN

Proposal

The application is proposing to amend the Poisons Standard to reschedule from Schedule 3 to Schedule 2, modified release ibuprofen in divided preparations containing 300mg or less of ibuprofen. The pack size would be restricted to not more than 12 dosage units and would be required to be labelled with a recommended daily dose of 1200mg or less.

Scheduling considerations

The risks and benefits of the use of a substance

Benefits

Ibuprofen is indicated for the relief of acute and/or chronic pain states in which there is an inflammatory component. The Guild does not refute the benefits of ibuprofen as an analgesic for the treatment of these pain states. However, the risks associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) require careful consideration in any potential decision to include modified release ibuprofen in Schedule 2 of Poisons Standard.

Risks

Ibuprofen is a non-selective NSAID. The risk of adverse effects associated with the use of ibuprofen that are of greatest concern are gastrointestinal (GI) adverse effects such as GI ulceration and bleeding, renal adverse effects such as NSAID-induced acute kidney injury, and an increased risk of cardiovascular adverse effects such as myocardial infarction and stroke. These can occur even in healthy individuals[33] and are a reminder that ibuprofen use can cause harm. Additionally, immediate adverse effects such as NSAID-induced asthma, may be prolonged by modified release formulations due to the extended clearance time. The importance of pharmacist assessment of existing health conditions is paramount to the safe use of modified release ibuprofen.

Non-selective NSAIDs are associated with a higher risk of gastrointestinal (GI) adverse effects when compared to selective NSAIDs. Whilst ibuprofen has a lower risk of GI adverse effects when compared to other non-selective NSAIDs, when used at full dose this advantage is lost.[34] The recommended maximum daily dose for modified release ibuprofen is 1200mg daily, with a 12 hourly dosing frequency.[35] The proposal refers to 300mg modified release preparations; the instructions for use for these preparations are two tablets every 12 hours.[36] The Guild is concerned that patients may inadvertently take more than the recommended maximum daily dose due to the many different ibuprofen products currently available as Schedule 2 medicines, the consequence of which may be very serious given the potential adverse effects.

The consultation paper states that there are 230 non-prescription medicines containing ibuprofen. As a product that is readily available in pharmacies and grocery stores, consumers are likely to be familiar with ibuprofen in a strength of 200mg per tablet; they may be less familiar with the 400mg tablets that have been down-scheduled from Schedule 3 to Schedule 2. The recommended dosing frequency of 200mg

[33] https://amhonline.amh.net.au/chapters/rheumatological-drugs/drugs-other-musculoskeletal-conditions/nsaids?menu=vertical#nsaids-comparative

[34] https://amhonline.amh.net.au/chapters/rheumatological-drugs/drugs-other-musculoskeletal-conditions/nsaids?menu=vertical#nsaids-comparative

[35] https://www.mimsonline.com.au/Search/FullPI.aspx?ModuleName=Product%20Info&searchKeyword=ibuprofen&PreviousPage=~/Search/QuickSearch.aspx&SearchType=&ID=129970001_2#Overdosage14867

[36] https://www.nurofen.com.au/products/adult/nurofen-12-hour-pain-and-inflammation-relief-ibuprofen-300mg/

and 400mg immediate release ibuprofen tablets is three times a day. Making 300mg modified release ibuprofen tablets more readily available is likely to add to confusion and lead to potential overdose, where people who would usually take immediate release ibuprofen three times a day may take modified release ibuprofen at the same frequency. This has a potential to cause adverse effects as outlined above.

Drug interactions and precautions

TGA approved Product Information lists many interactions and precautions for people considering using ibuprofen. These include chronic conditions that are relatively prevalent in the Australian community such as asthma, cardiovascular disease including hypertension, diabetes, gastrointestinal disorders, depression and medicines that are used to treat these conditions. The potential drug interactions with ibuprofen are well documented and occur via a number of pathways, including through hepatic metabolism mediated through the cytochrome P450 (CYP450) pathways, the effects on renal function through the renin-angiotensin system including the risk of renal impairment, the anti-platelet effects and many others.

Renal function can be affected by many medicines, including antihypertensive used to reduce blood pressure. To understand the potential risk of renal impairment due to concurrent ibuprofen and antihypertensive use, it is important to highlight to what extent people use antihypertensives. The *PBS Expenditure and Prescriptions Report* for 2020-21 showed 8 antihypertensive medicines (sartans, ACE inhibitors, diuretics) in the top 50 PBS drugs by prescription volume.[37] These 8 medicines accounted for over 20 million prescriptions per annum, indicating that there are a lot of people using these medicines, many of whom will have other risk factors as well. Ibuprofen should be used with caution and by consulting with a health professional, such as in the community pharmacy setting.

The Guild considers pharmacist intervention essential to identifying and managing the known adverse effects, drug interactions and contraindications for use associated with modified release ibuprofen, to ensure any potential risks to patient safety are mitigated.

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

The TGA approved indications for registered products containing 300mg modified release ibuprofen are the temporary relief of persistent pain and/or inflammation likely to last more than 6 hours associated with sinus pain, toothache, dental procedures, backache, muscular aches and pains, osteoarthritis, rheumatic pain, period pain, fibrositis, neuralgia, sore throat, tennis elbow, and colds and flu.[38,39]

Whilst the Guild agrees that ibuprofen is an effective analgesic for pain that has an inflammatory component, we note that one approved indication, osteoarthritis, is a chronic disease most commonly affecting older people who are at greater risk of potential harm from NSAIDs.[40] Patients with osteoarthritis are also more likely to have comorbidities such as hypertension and diabetes,[41] which can be negatively impacted by NSAIDs use. Availability of 300mg modified release ibuprofen as a Schedule 2 medicine may lead to patients with osteoarthritis believing that this medicine is inherently safe and continuing to use it long-term. This misperception of safety may also be perpetuated by the fact that modified release paracetamol is Schedule 3, therefore the ready availability of modified release ibuprofen as a Schedule 2 medicine must signify that it is safer.

[37] https://www.pbs.gov.au/info/statistics/expenditure-prescriptions/pbs-expenditure-and-prescriptions-report-30-june-2021
[38] https://www.tga.gov.au/resources/artg/335682
[39] https://www.tga.gov.au/resources/artg/335681
[40] https://tgldcdp.tg.org.au/viewTopic?topicfile=osteoarthritis&guidelineName=Rheumatology&topicNavigation=navigateTopic#toc_d1e360
[41] ibid

Additionally, ‘persistent pain’ and ‘chronic pain’ have become interchangeable terms to describe pain that lasts for more than three months.[42,43] Given the indication for modified release ibuprofen is temporary relief of persistent pain and/or inflammation that is likely to last for more than 6 hours, it is highly likely that patients suffering from persistent pain will continue to use this product long term without review. The Guild believes that maintaining the current scheduling is appropriate to ensure patients are receiving effective treatment for pain to support positive health outcomes.

The toxicity of a substance

There are many significant drug interactions and physiological adverse effects associated with ibuprofen use, that make it potentially a very toxic substance if not used with caution and as directed by a health professional.

The dosage, formulation, labelling, packaging and presentation of a substance

The Guild does not support the assertion that labelling is adequate to prevent the potential confusion and harms associated with the proposed scheduling change.

The Guild does not agree that the quality use of medicines for 300mg modified release ibuprofen can be achieved by labelling, packaging and/or provision of information alone. Results from the Health Literacy Survey conducted by the Australian Bureau of Statistics found that only just over one in three people (39%) found it always easy to understand health information such as having the ability to read and understand all the information on medical labels. The results also found that 8% of people find it difficult to understand health information.[44]

The dosage of ibuprofen in this proposed scheduling change is 300mg, in comparison to 200mg and 400mg dosages already available as Schedule 2 medicines. Given the large number of non-prescription medicines containing ibuprofen, it is conceivable that patients could accidently select a product containing 300mg modified release ibuprofen when their true intention is to select a product containing 200mg or 400mg immediate release ibuprofen. This could lead to a patient taking a higher than recommended dose as a result of re-dosing at the incorrect dosing interval.

Additionally, modified release ibuprofen is a formulation that is unfamiliar to patients; other Schedule 2 analgesics are immediate release formulations. The Guild believes the need for pharmacist intervention remains for modified release ibuprofen to ensure patients know how to use it in a safe and effective manner, and that it is therefore more consistent with the scheduling factors for pharmacist only medicines (Schedule 3) and should continue to be included in Schedule 3 of the Poisons Standard.

The potential for abuse of a substance

There is low potential for abuse of ibuprofen, however the Guild has outline under ‘risks’ the potential for unintended misuse due to the myriad of ibuprofen-containing products on the market.

Summary

The Guild opposes the proposed scheduling change to ibuprofen. The risks associated with the use of ibuprofen can be serious and include gastrointestinal, cardiovascular and renal adverse effects. The

[42] https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/Living-with-persistent-pain
[43] https://www.verywellhealth.com/persistent-pain-297140
[44] https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-health-survey-health-literacy/latest-release

reasons for the proposed change do not warrant the increased risk associated with the potential for confusion and misuse created by an additional strength of ibuprofen being more readily available. Furthermore, the current range of commercially available ibuprofen formulations adequately serves the needs of people with swallowing difficulty or for those seeking the convenience of a small preparation. This includes liquid preparations, gel capsules, small, coated tablets in a range of brands.

There is no evidence in practice, or in the proposal put forward by the applicant, of a public benefit of making available up to 12 tablets of 400mg ibuprofen. As all other ibuprofen containing products, these medicines have a large potential for harm and should be sold under direct supervision of a pharmacist.

The Guild is concerned that making modified release ibuprofen a Schedule 2 medicines will lead to use as a first line treatment by consumers that are at risk of harm from NSAIDs, particularly in the current climate where many paracetamol products are unavailable, and most others are undergoing review. The Guild believe Schedule 3 remains the appropriate schedule for modified release ibuprofen to support the quality use of medicines and patient safety.

MELATONIN

Proposal

The application is proposing amendment to the Poisons Standard to reschedule immediate release melatonin from Schedule 4 to Schedule 3 for the treatment of jet lag. It would apply to preparations containing 5mg or less of melatonin, in packs containing no more than 10 dosage units, for adults aged 18 years and over. The application is also proposing inclusion in Appendix H to allow these products to be advertised.

Scheduling considerations

The risks and benefits of the use of a substance

Risks

The Australian Medicines Handbook lists back pain and arthralgia as common adverse effects, and weakness as an infrequent adverse effect.[45] The most common adverse effects reported in literature are mild and related to fatigue, mood, psychomotor and neurocognitive performance, including drowsiness, dizziness, weakness and confusion.[46,47]

The safety profile of melatonin has been widely established by research, particularly for doses below 10mg, with evidence demonstrating it has favourable efficacy and tolerability.[48] Occasional short-term use is generally considered safe.[49]

Benefits

Jet lag is caused by rapidly crossing multiple time zones, which leads to a disruption of the body's circadian rhythms. The circadian rhythms relate to the bodily processes that occur over a 24-hour period such as temperature control, hormone production, digestion, heart rate, blood pressure and brain states.[50,51] Symptoms of jet lag are a result of misalignment of these bodily processes with the time zone at a persons final destination and can include fatigue, daytime sleepiness, anxiety, confusion, irritability, memory loss, constipation or diarrhoea, nausea, indigestion, dehydration, sweating, headache and dizziness.[52,53]

Melatonin is a hormone that regulates the circadian rhythm and can be used to accelerate circadian rhythm alignment with a new time zone, the benefit being alleviation of symptoms of jet lag and therefore increased daytime alertness and reduced sleep deprivation.[54]

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

The Australian Medicines Handbook lists the indications for available modified-release melatonin products as short-term use as monotherapy in primary insomnia with poor sleep quality, and treatment of insomnia in autism spectrum disorder or Smith-Magenis syndrome where sleep hygiene measures are

[45] https://amhonline.amh.net.au/chapters/psychotropic-drugs/drugs-anxiety-sleep-disorders/other-drugs-anxiety-sleep-disorders/melatonin
[46] https://www.sciencedirect.com/science/article/abs/pii/S0965229918309373
[47] https://apcz.umk.pl/JEHS/article/view/JEHS.2020.10.05.018/25695
[48] https://www.sciencedirect.com/science/article/abs/pii/S0965229918309373
[49] https://apcz.umk.pl/JEHS/article/view/JEHS.2020.10.05.018/25695
[50] https://www.betterhealth.vic.gov.au/health/healthyliving/jet-lag
[51] https://nigms.nih.gov/education/fact-sheets/Pages/circadian-rhythms.aspx
[52] https://apcz.umk.pl/JEHS/article/view/JEHS.2020.10.05.018/25695
[53] https://www.betterhealth.vic.gov.au/health/healthyliving/jet-lag
[54] https://apcz.umk.pl/JEHS/article/view/JEHS.2020.10.05.018/25695

insufficient.[55] Additional indications published in the Australian Therapeutic Guidelines include jet lag, delayed sleep-wake phase disorder and sleep-wake disturbance in shift workers.[56]

The proposed amendment to the Poisons Standard would enable Schedule 3 supply of immediate-release melatonin for jet lag. The proposed indication is consistent with the recommendations of the Australian Therapeutic Guidelines which states that immediate-release melatonin has evidence of benefit to prevent or reduce jet lag in adults; a dose of between 0.5mg to 5mg taken on the plane at the bedtime of the final destination and continued for 3 subsequent nights is recommended.[57] Jet lag usually resolves within a week, and only necessitates short term use of melatonin.[58]

In Australia, there are currently no commercially available melatonin products for the treatment of jet lag. Immediate release melatonin products not registered in Australia can be accessed by the Special Access Scheme or from a compounding pharmacy.[59] For this reason it is difficult to determine the extent of use of melatonin for this indication, although use would likely become more prevalent if a Schedule 3 immediate release melatonin product were available and international travel returns to pre-COVID-19 levels.

The dosage, formulation, labelling, packaging and presentation of a substance

Melatonin in modified-release tablets containing 2mg or less is currently included in the *Therapeutic Goods (Medicines Advisory Statements) Specification 2022*. Some of these warnings will be applicable to melatonin in immediate release tablets for short-term treatment of jet lag, whilst others such as the current age restriction and duration of use will need to be modified.

Summary

The Guild supports the proposed amendment for melatonin. This application is proposing to down-schedule immediate release melatonin in preparations containing 5mg or less of the substance for the treatment of jet lag. Supply for this indication is consistent with the Australian Therapeutic Guidelines for jet lag and would be restricted to adults 18 years or over. The Guild considers Schedule 3 to be the appropriate schedule to achieve quality use of the medicine for the defined indication.

[55] https://amhonline.amh.net.au/chapters/psychotropic-drugs/drugs-anxiety-sleep-disorders/other-drugs-anxiety-sleep-disorders/melatonin
[56] https://tgldcdp.tg.org.au/searchAction?appendedinputbuttons=melatonin
[57] https://tgldcdp.tg.org.au/viewTopic?etgAccess=true&guidelinePage=Psychotropic&topicfile=jet-lag&guidelinename=Psychotropic&sectionId=toc_d1e69#toc_d1e69
[58] https://link.springer.com/chapter/10.1007/978-3-030-43803-6_13
[59] https://tgldcdp.tg.org.au/viewTopic?etgAccess=true&guidelinePage=Psychotropic&topicfile=jet-lag&guidelinename=Psychotropic&sectionId=toc_d1e69#toc_d1e69

GREEN TEA EXTRACT

Proposal

The application is proposing amendment to the Poisons Standard to create a Schedule 2 entry for green tea extract. Green tea extract is currently unscheduled and products will only become Schedule 2 if they fail to include proposed warnings about the potential for green tea extract to cause liver damage and the signs and symptoms that consumers need to monitor for.

The Guild notes that there are few entries in the Poisons Standard that include detailed warning statements as is being proposed by this application. We also note that there is no intention to include this warning in the Required Advisory Statements for Medicine Labels, which would be a more logical location, particularly given most medicines containing green tea extract currently active on the ARTG are listed medicines. Given this is quite unorthodox, the Guild believes the Poisons Standard may not be the appropriate mechanism.

Scheduling considerations

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

Green tea is produced from the leaves of the Camellia sinensis tree. It contains a high number of polyphenolic compounds that have been attributed for producing antioxidant, anti-inflammatory, anti-microbial and anti-carcinogenic activity.[60] For this reason, green tea and green tea extract (GTE) are often used for cancer prevention, cardiovascular risk reduction, diabetes risk reduction, and weight loss; evidence is inconsistent to support the use of green tea and GTE for many of these indications.[61]

Green tea has a long history of consumption as a beverage, particularly in Southeast Asian countries to which the Camellia sinensis tree is native. The use of GTE is a more recent development and is considered to be one of the most common herbal supplements ingested worldwide.[62]

The toxicity of a substance

Catechins are a type of polyphenolic compound found in green tea, and the most abundant catechin in green tea is (-)-epigallocatechin gallate (EGCG).[63] Due to the processes utilised for the manufacture of GTE, the concentration of catechins in GTE is much higher than traditional green tea.[64]

There have been case reports of acute liver injury following consumption of GTE.[65,66] A systematic review of published toxicology and human intervention studies looking at the potential hazards associated with green tea and preparations such as GTE, recommended that a safe intake level of 338mg EGCG/day for adults could be considered for GTE ingested as a concentrated solid bolus dose.[67] The concentration of GTE, and therefore catechins, can vary greatly between products putting patients at risk of exceeding a safe intake level.

[60] https://www.intechopen.com/chapters/78081
[61] https://apf.psa.org.au/complementary-medicines/complementary-medicines/monographs
[62] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3746392/
[63] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3679539/
[64] https://www.sciencedirect.com/science/article/pii/S2214750019306596
[65] https://www.ncbi.nlm.nih.gov/books/NBK547925/
[66] https://www.sciencedirect.com/science/article/pii/S2214750019306596
[67] https://www.sciencedirect.com/science/article/pii/S0273230018300928

The Guild believes that it is appropriate for products containing GTE to provide a warning to patients on the potential to cause liver damage and signs and symptoms that patients should be aware of.

Summary

The Guild has no objection to the proposed inclusion of green tea extract in the Poisons Standard. There is some evidence that consumption of products containing GTE can cause hepatoxicity. The proposed amendment aims to ensure that products containing green tea extract are either appropriately labelled or accessed in a setting where a healthcare professional has oversight and can provide advice to consumers.