[redacted]

PROPOSED AMENDMENTS TO POISONS STANDARD

ACMS Meeting November 2018

Comments by The Pharmacy Guild of Australia to the proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling

1. **Nabiximols**
2. **Racetams and nootripics**

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[redacted]

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[redacted]

NABIXIMOLS

- Down-schedule nabiximols from Schedule 8 to Schedule 4 (with revised wording) and delete the Appendix D, Item 1 entry.

Overview

Nabiximols as present in the product [redacted] are registered on the ARTG for *"symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy*".

This product is currently listed as a Schedule 8 medicine but we agree it would be more appropriately classified under Schedule 4 as it does not require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.

The risks and benefits of the use of a substance

Risks

The following 'Precautions" are noted in the TGA-approved PI for [redacted]:

- Mild or moderated dizziness is commonly reported most frequently in the first few weeks of treatment.
- Alterations in pulse rate and blood pressure have been observed following initial dosing and fainting episodes have been observed.
- Psychiatric adverse events including disorientation (4.1% vs 0.8%), depression (2.9% vs 2.0%), euphoric mood (2.2% vs 0.9%), and dissociation (1.7% vs 0.1%) occurred more frequently in patients given [redacted] than in those given placebo in clinical trials.
- Approximately 10% more patients given [redacted] experienced a psychiatric adverse event than those given placebo (17.6% vs 7.8%).
- Serious psychiatric adverse events including transient psychosis occurred in 4/41 healthy volunteers given 18 actuations of [redacted] twice daily.
- There is a risk of an increase in incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait.
- [redacted] may produce undesirable effects such as dizziness and somnolence which may impair judgement and performance of skilled tasks.

Under "Adverse Effects" the following are noted:

- The most commonly reported adverse reactions in the first four weeks of exposure were dizziness, which occurs mainly during the initial titration period, and fatigue.

Benefits

An observational post-marketing safety registry (which contains data from 941 patients with 2,213.98 patient-years of exposure) of patients in the UK, Germany and Switzerland who have been prescribed [redacted] oromucosal spray[1] reported the following:

- Within this cohort, 60% were reported as continuing treatment, while 83% were reported as benefiting from the treatment.
- Thirty-two percent of patients stopped treatment, with approximately one third citing lack of effectiveness and one quarter citing AEs.

[1] https://www.dovepress.com/an-observational-postmarketing-safety-registry-of-patients-in-the-uk-g-peer-reviewed-article-TCRM

- Psychiatric AEs of clinical significance were reported in 6% of the patients, 6% reported falls requiring medical attention, and suicidality was reported in 2%.
- Driving ability was reported to have worsened in 2% of patients, but improved in 7%.
- AEs were more common during the first month of treatment. The most common treatment-related AEs included dizziness (2.3%) and fatigue (1.7%).

The risks and benefits of the nabiximols would suggest that Schedule 4 is an appropriate classification as abuse, misuse, physical or psychological dependence did not appear to present the most comment adverse effect or risk.

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

We note that the TGA-approved PI for [redacted] states that the product is for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

According to MS.org.au[2] multiple sclerosis affects approximately 25,000 Australians and only a proportion of those patients would be prescribed a trial of this medicine and respond.

We note that the PI states that:

> *"Patients being considered for treatment with [redacted] should be assessed by a neurologist or rehabilitation physician. Patients who then commence a trial of [redacted] should be reassessed by a neurologist or rehabilitation physician after 4 weeks of treatment. Patients who do not show a clinically significant improvement in spasticity on reassessment should not continue [redacted]".*

We note that the product is not listed on the Pharmaceutical Benefits Scheme and would only be accessed by patients with multiple sclerosis willing to pay privately.

Given that the product is not widely used and only then for a subset of a particular patient population we do not believe that it requires restriction of manufacture, supply, distribution or possession.

The toxicity of a substance

We note from the TGA approved PI:

> *The [redacted] clinical program has so far involved over 1500 patients with MS in placebo controlled trials and long-term open label studies in which some patients used up to 48 sprays per day.*
>
> *The most commonly reported adverse reactions in the first four weeks of exposure were dizziness, which occurs mainly during the initial titration period, and fatigue. These reactions are usually mild to moderate and resolve within a few days even if treatment is continued. When the recommended dose titration schedule was used, the incidence of dizziness and fatigue in the first four weeks was much reduced.*

It would appear that the most common side effects from this product is dizziness and fatigue which would appear to resolve in the first 4 weeks.

[2] https://www.ms.org.au/what-is-multiple-sclerosis.aspx

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

The particular formulation of this product requires refrigeration which is difficult as most jurisdictions require Schedule 8 medicines to be stored in a Controlled Drugs safe.

We note that in NSW there is a new storage requirement for Schedule 8 medicines that require refrigeration for retail (community) pharmacies, pharmacies in a public hospital, or pharmacies in a private hospital[3].

> The requirements are:
>
> 1.
>
> a. The refrigerator containing the S8 medicine, which is in a room or enclosure to which the public does not have access, such as the dispensary, must be securely attached to the premises, and kept securely locked when not in immediate use, or
> b. The refrigerator containing the S8 medicine must be kept in a separate room, cupboard or other receptacle which is securely attached to the premises, and which is kept securely locked when not in immediate use.
>
> 2. The S8 medicine may be stored with other medicines, but not with food or other goods.
>
> 3. The refrigerator containing the S8 medicine may be accessed **only** by a pharmacist. This means, any other medicine in the refrigerator where an S8 medicine is stored may be accessed **only** by a pharmacist.
>
> 4. Any key or other device, or any code or combination required to access or unlock the refrigerator, room, cupboard or other receptacle must be kept, and be accessible, only by a pharmacist.
>
> When the above requirements are followed an S8 medicine requiring refrigeration does not have to be stored in a safe which is fixed to the building, as per clause 76, nor required to be stored separate from all other goods (other than cash or documents), as per clause 73(1), of the Poisons and Therapeutic Goods Regulation 2008.

We note that these requirements while well-intentioned are still onerous for community pharmacy. For a product such as [redacted] that meets all the SPFs for Schedule 4, it would appear unnecessary to make an exemption for refrigerated Schedule 8s when these products are more suited to Schedule 4.

The potential for abuse of a substance

The PI states the following:

> **Abuse potential**
> In a study designed to identify its abuse potential, [redacted] at a dose of 4 sprays taken at one time, did not differ significantly from placebo. At 8 sprays there was a moderate effect, significantly different from placebo, and the results were more marked at 16 sprays. [redacted] taken at the maximum recommended doses of up to twelve sprays per day sprays has moderate potential for abuse. Patients with a history of substance abuse may abuse [redacted] and if [redacted] is being considered for these patients close monitoring is recommended.

[3] https://www.health.nsw.gov.au/pharmaceutical/Pages/refrigeration-s8s.aspx

As stated above the product only has “moderate potential for abuse” and therefore would be appropriate for classification under Schedule 4.

We note that an observational post marketing safety registry[4] which contains data from 941 patients with 2,213.98 patient-years of exposure showed that there were no signals to indicate abuse, diversion or dependence.

We also note that no abuse, addiction or misuse hints were detected in the *“Efficacy and safety of cannabinoid oromucosal spray for multiple sclerosis spasticity”*[5] study the aim of which was to describe [redacted] effectiveness and adverse events profile in a large population of Italian patients with MS in the daily practice setting.

Summary

We believe that nabiximols are appropriate under the Scheduling Policy Framework and the criteria under Section 52(e) for inclusion in Schedule 4 as they do not require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.

2. RACETAMS AND NOOTROPICS

A new Schedule 4 group entry for racetams is proposed, in addition to new specific Schedule 4 entries for a number of specific racetams.

Summary

We agree that due to the potential use and adverse events the proposal is appropriate to make these medicines prescription only.

[4] https://www.dovepress.com/an-observational-postmarketing-safety-registry-of-patients-in-the-uk-g-peer-reviewed-article-TCRM
[5] https://www.ncbi.nlm.nih.gov/pubmed/27160523