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26 September 2018

Therapeutic Goods Administration

RE: ASCEPT Feedback to the proposed amendments to the Poisons Standard - ACMS #25 on proposed Nabiximols down-scheduling from Schedule 8 to Schedule 4

The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) thank you for the opportunity to provide comment on the proposed amendments to the Poisons Standard.

ASCEPT is the leading professional body in Australasia for clinical pharmacology policy and practice and its members' expertise encompasses experimental and clinical pharmacology and toxicology (including: clinical trial and regulatory issues, pharmacovigilance and quality use of medicines). ASCEPT members serve on most Commonwealth and State committees concerned with medicines regulation or quality use of medicines.

Scheduling of cannabis medicines is currently determined by the amount of tetrahydrocannabinol (THC) a product contains. If a product contains cannabidiol and less than 2% of other cannabinoids found in cannabis (i.e. THC), it is currently scheduled as an S4 (Prescription Only) medicine.

Nabiximols is the only registered cannabis medicine in Australia (for the sole indication of spasticity secondary to multiple sclerosis). There are numerous unregistered cannabis medicines which are compliant with the Therapeutic Goods Order (TGO) 93 (Standard for Medicinal Cannabis). These unregistered products are subject to the same scheduling criteria as nabiximols. The proposed down-scheduling of [redacted] (nabiximols) would set a precedent for the down-scheduling of other cannabis medicines, with resultant negative implications for public health.

The Therapeutic Goods Administration (TGA) has advised that a Special Access Scheme (SAS) application is not required for the prescription of nabiximols for "off-label" indications. There are state specific differences in the regulatory requirements for the prescription of nabiximols. In New South Wales (NSW) an Application for Authority to Prescribe and Supply a Cannabis Product for Human Therapeutic Use to Pharmaceutical Services Branch must be submitted to NSW Health. For an unregistered cannabis medicine, the preferred application process is via the TGA SAS Category B pathway.

International perspectives

In the United States, at a federal level marijuana (cannabis) is classified as a Schedule 1 drug under the Controlled Substances Act, (title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970), which pertains to "substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse".[1] The use of schedule 1 drugs are prohibited for any purpose.[2] "However, several states have either passed laws that remove state restrictions on the medical use of marijuana and its derivatives or are considering doing so."[3]

The U.S. Food and Drug Administration (FDA)[3] has approved a small number of cannabis medicines for limited indications, including:

- [redacted] (cannabidiol) for the "treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older."
- [redacted] and [redacted] (dronabinol, a synthetic delta-9- tetrahydrocannabinol (THC)) for the "treatment of anorexia associated with weight loss in AIDS patients."
- [redacted] (nabilone, which is a synthetic cannabinoid with a chemical structure similar to THC) for the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments

Abuhasira et al.[2] provides an overview of regulations pertaining to the medical use of cannabis and cannabinoid containing products in Europe describing that "to date, no marketing authorization has been granted for medicines derived from cannabis following evaluation by European Medicines Agency (EMA), nor did the EMA authorize cannabinoid-based medicines. The only decisions the EMA authorized regarding cannabis and its products include rare diseases (orphan) designations and pediatric investigation plans." However, "many European countries authorized the use of some cannabinoid-based medicines, by the noncentralized route."

Rationale for *not* endorsing the down-scheduling of nabiximols includes:

- Potential for harm, including serious adverse effects (including those potentially not previously elucidated) that would pose a significant risk to public health.
- As nabiximols contains the psychoactive cannabinoid THC, there is potential for misuse, abuse, illegal use or diversion, particularly in light of the illicit market for street cannabis. The applicant's assertion of lack of spontaneous reporting of such is by no means indicative of its absence.
- Further research is needed investigating incidence of cannabis dependency with supra-therapeutic use. Chye et al.[4] notes that "despite a general community perception of harmlessness, a subset of regular cannabis users—over 13 million—are dependent on cannabis (Degenhardt *et al*. 2013; United Nations Office on Drugs and Crime 2016). In addition, almost 50 percent of substance users seeking treatment are cannabis dependent (United Nations Office on Drugs and Crime 2016). Cannabis dependence represents a significant burden on the individual and society but has been poorly defined neurobiologically compared with heavy, non-dependent use." Furthermore, "individuals with cannabis dependence report diminished control over use and compulsive use despite associated negative consequences to their functioning and mental health (American Psychiatric Association 2013; van der Pol *et al*. 2013a). Relative to non-dependent users, they also experience greater mental health issues (i.e. mood, anxiety and conduct disorder) (van der Pol *et al*. 2013a) and impaired cognitive functioning in the domains of learning, working memory and cognitive flexibility."
- Down-scheduling of nabiximols would obliterate potential for monitoring adverse effects, given the subsequent absence of TGA or state health approval mandating outcome reporting for ongoing prescription.
- The applicant's statement that "*nabiximols is currently available as a prescription medicine in 26 other countries with scheduling that is similar to Schedule 4 in Australia. This level of control has not led to abuse, diversion, dependence or use for illegal purposes of nabiximols*" is questionable. There are unique regulatory structures underlying the scheduling of cannabis in other countries. There is also a paucity of longitudinal outcome data related to potential for abuse, diversion, dependence or use for illegal purposes.
- There are inherent limitations of post-marketing reporting in the global safety database, as this is reliant upon spontaneous reporting. Reliance upon data derived via spontaneous reporting is likely to under-report any potential public health risk signals.
- Nabiximols product information outlines a number of important interactions, including the following:
  - CYP 3A4 inhibition, at clinically relevant concentrations
  - Potential induction of CYP1A2, CYP2B6, CYP3A4
  - UGT1A9 and UGT2B7 inhibition
  - Inhibition of gastrointestinal p-glycoprotein cannot be excluded
  - Additive central nervous system depressant effects with concurrent use with sedatives, hypnotics and alcohol
  - Additive muscle relaxant effects risk and subsequent potential falls risk

There is a high likelihood that there are a number of drug interactions which may as yet be uncharacterised. As such, we would question the notion that the risk profile of nabiximols is considered to be well defined.

- Down-scheduling of nabiximols to S4, with no federal or state application for authority to prescribe and supply a cannabis product for human therapeutic use facilitating monitoring of potential abuse or misuse, would result in:
  - Inadequate capture of usage and outcome data
  - No prescriber or patient suitability checks
  - Potential for serious (e.g. cardiac, respiratory, central nervous system) adverse effects
  - Prescribing by practitioners with limited/inadequate knowledge of appropriate indications, absolute and relative contraindications and drug interactions
  - Potentially, additional patient pressure on practitioners to prescribe

Consideration of these risks to patient safety are particularly imperative, given the limited evidence to date. There does not appear to be a strong patient-centred rationale for the down-scheduling of nabiximols that would offset the potential risks.

Submission prepared in consultation with ASCEPT expert members. Please do not hesitate to contact the ASCEPT [redacted] at [redacted] for any further information.

Yours sincerely,

[redacted]

References

1.United States Drug Enforcement Administration. Drug Scheduling. Available at: https://www.dea.gov/drug-scheduling (cited 14/9/18)

2.Abuhasira R et al. Medical use of **cannabis** and cannabinoids containing products -Regulations in Europe and North America. European Journal of Internal Medicine. 2018;49:2-6.

3.FDA U.S. Food & Drug Administration. FDA and Marijuana: Questions and Answers. Available at: https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421168.htm (cited 14/9/18)

4.Chye et al. Alteration to hippocampal volume and shape confined to cannabis dependence: a multi-site study. Addiction Biology. 2018. doi: 10.1111/adb.12652.