Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists

21 May 2020

Therapeutic Goods Administration
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To whom it may concern

RE: ASCEPT Submission to TGA related to the proposed down-scheduling of cannabidiol to S3 (Pharmacist Only Medicine).

Thank you for the opportunity to provide comment on the Submission to TGA related to the proposed down-scheduling of cannabidiol to S3 (Pharmacist Only Medicine).

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).

Overall position: **ASCEPT does not support the down-scheduling cannabidiol to S3** and provides the following discussion to support this position.

Following the completion of the Therapeutic Goods Administration's (TGA) Report: Safety of low dose cannabidiol , the 'Delegate of the Secretary has proposed to down-schedule low dose CBD.'

Basing a down-scheduling decision for an experimental medicine on only limited case report and clinical trial evidence outlined in the TGA review Safety of low dose cannabidiol is not in the best interests of patient care from a public health perspective. The report specifies that:

- '… CBD has not been widely used in clinical practice and the evidence for which conditions it is effective has not been thoroughly characterised.'
- 'There was a paucity of high quality published trials (meta-analyses and RCTs) with the majority of the literature for analysis being lower quality explorative studies or case series with no placebo control. Thus, no clear conclusions can be drawn on efficacy of CBD at low doses as larger phase III and conclusive efficacy trials have not been conducted.'
- 'There is limited clinical safety data in the form of meta-analysis or higher quality clinical studies in relation to adverse effects at the lower range of 1 mg/kg/day and less (up to a maximum of ~ 60 mg/day).'

The proposal to down-schedule cannabidiol to Schedule 3 (Pharmacist Only Medicine) does not provide a sufficient safety net for an experimental medicine and sets a precedent for down-scheduling of other experimental medicines in this manner. Our experience with codeine as a Schedule 3 medicine (culminating in up-scheduling to Schedule 4)[1] is indicative that Pharmacist Only medicines do not always provide the necessary safeguards in terms of limiting quantities sold or ensuring adequate checks in terms of drug-drug and drug-disease state interactions. There are also no safeguards in place to prevent patients from obtaining multiple supplies of cannabidiol from different pharmacies in order to achieve higher doses.

Applicant's reasons for down-scheduling

The benefit/risk ratio is such that cannabidiol (CBD) formulations in which 98% or greater of the cannabinoid content is CBD and where the upper limit to THC content is 0.2% (by dry weight), should not be regulated as an unapproved medicine through its inclusion on Schedule 4 of the SUSMP, but instead, regulated as listed, assessed-listed or registered medicines (depending on the level of therapeutic claim) under the Australian Register of Therapeutic Goods (ARTG).

ASCEPT does *not* endorse down-scheduling of cannabidiol from Schedule 4 to a listed, assessed-listed or registered medicine (depending on the level of therapeutic claim) under the ARTG.

Rationale for not endorsing the down-scheduling of cannabidiol includes:

- Cannabis is an experimental drug and its inclusion in schedule 4 facilitates experimental use. Further down-scheduling of cannabinoids is inappropriate at this time until adequate clinical trial data is provided proving safety and efficacy.
- The majority of scientific literature pertaining to clinical indications for which cannabidiol may be considered utilises doses higher than the low dose (≤ 60 mg/day) proposed. This pseudoscientific approach promotes use of a sub-therapeutic dose when the majority of scientific literature pertains to higher doses, where adverse effects are frequently reported.
- The statement made by the applicant that 'clear evidence of benefits, good safety profile and low risk' is not supported by current scientific literature. There is clinical trial and case report evidence of cannabidiol adverse events and drug-drug interactions. There is limited evidence of safety and effectiveness across the dosage range spectrum, including low doses. The U.S. Food and Drug Administration (FDA) product information for Epidiolex (cannabidiol) details a wide range of adverse events and drug-drug interactions. There is a high likelihood that there are additionally a number of drug interactions as yet uncharacterised.
- Potential for pharmacokinetic drug-drug interactions with cannabidiol and potential for adverse effects.
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- Potential for harm, including serious adverse effects that would pose a significant risk to public health.[2,3]
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- Down-scheduling of cannabidiol would obliterate any potential for monitoring adverse effects.
- 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.
    - All cannabidiol preparations currently available in Australia are not registered on the ARTG. It is critically important to note that the Database of Adverse Event Notifications (DAEN) public dashboard does not include adverse event reports related to unregistered cannabidiol products and/or cannabidiol products used in clinical trial contexts. Hence, the misperception that there have been no adverse events related to cannabidiol in Australia is inaccurate.
    - The FDA Adverse Events Reporting System (FAERS) public dashboard notes that there were 3,189 adverse event reports with cannabidiol in 2019 alone, of these 1,111 cases were classed as serious cases and 96 deaths were reported.[2] The Canada Vigilance Adverse Reaction Online Database notes 23 adverse event reports with cannabidiol.[3]
- If cannabidiol is down-scheduled this equates to:
    - Inadequate capture of usage or outcome data
    - Lack of prescriber checks
    - Use by vulnerable patient populations e.g. paediatric (purchased by individuals > 18 years without divulging intent of paediatric administration), older (this is particularly of concern with carer administration to vulnerable, cognitively impaired patients without consent), pregnant and oncology patients.
    - Potential for a wide and incompletely characterised spectrum of adverse effects and drug-drug interactions
    - Limited prescriber knowledge or relative contraindications, drug interactions
    - No limitations on prescribing for inappropriate indications
- Consideration of these risks to patient safety are particularly imperative, given the limited evidence to date.

Manufacturers and suppliers have a significant fiduciary interest in the down-scheduling of cannabidiol and increased profits,[5] rather than improvement in the health of Australians, is likely to be the only benefit of the down-scheduling process.

- **Given its clear evidence of benefits, good safety profile and low risk, it should be regulated as a complementary medicine in the same way that other plant medicines (herbal medicines) are regulated in Australia.**

  As detailed above, there is not clear evidence of benefits, good safety profile and low risk.

  Due to current limited clinical trial evidence of safety and effectiveness, cannabidiol is not intended to be used as a first line treatment strategy. Down scheduling of cannabidiol is likely to fuel current public misperceptions of safety and efficacy and has the potential for promoting inappropriate use, delaying more evidence-based treatment.

  Patients are often reluctant to discuss complementary medicine use with their medical practitioner[4], further increasing the risk of drug-drug interactions and undiagnosed adverse effects.

- **The potential benefits of removing plant-derived CBD from the Poisons Standard and instead regulating it as other herbal medicines and complementary medicines are regulated (listed, assess-listed or registered on the ARTG) is that this will substantially increase its access and reduce costs to the consumer.**

  There are multiple suppliers of unapproved cannabidiol products in Australia and the cost of cannabidiol containing preparations has decreased since 2018.[5] The cost of cannabidiol products is based on the quantity of cannabidiol a product contains. There is no evidence to substantiate the claim that down-scheduling of cannabidiol products will increase access (based on affordability) or reduce costs, particularly as pharmacy mark-ups can vary substantially. Increased access by down-scheduling to Schedule 3 will come at a significant public health safety risk.

- **Regulation of CBD as a complementary medicine will allow its prescription by other qualified healthcare practitioners such as western herbal medicine practitioners and registered Chinese herbal medicine practitioners, consistent with their scope of practice, and further increase access to patients.**

  Western herbal medicine practitioners and Chinese herbal medicine practitioner consultations are not subsidised under Medicare. The costs of these privately funded consultations may be an additional cost barrier to access. It is critically important that following initiation of a cannabidiol containing product that a patient is appropriately monitored in follow up appointments for therapeutic and adverse effects.

  Cannabis medicines, particularly cannabidiol has variable and in many cases limited clinical trial evidence for a wide spectrum of clinical indications for which it is being used, including treatment resistant paediatric epilepsy, febrile infection-related epilepsy syndrome (FIRES), schizophrenia, bipolar disorder, Huntington's disease, Parkinson's disease, post-traumatic stress disorder, Crohn's disease and anxiety. The notion that many of the possible low dose indications detailed in the TGA review Safety of low dose cannabidiol (such as chronic pain, anxiety and insomnia) do not require medical supervision is of concern. The scope of practice of Western herbal medicine practitioners and Chinese herbal medicine practitioners is limited and specialist

medical practitioner involvement is necessary for many of the clinical indications for which cannabidiol may have some therapeutic benefit.

Due to clear evidence of pharmacokinetic and pharmacodynamic drug interactions, it is important to consider that a medical professional is best placed to assess potential risks and benefits for patients. Compared to medical professionals, complementary medicine practitioners have limited training in pharmacokinetic and pharmacodynamic drug interactions. Due to high script volumes and understaffing prevalent in the community pharmacy industry, pharmacists have limited time to perform a thorough drug interaction check and undertake comprehensive patient counselling regarding safety considerations.

- **This amendment would allow the same level of access to CBD products as is enjoyed in many western countries including the US and countries within Europe where hemp-derived CBD products may be purchased over the counter or online.**

International researchers have highlighted that with increased availability to cannabinoid products, such as cannabidiol there is a decline in incentive to perform further research into safety and effectiveness.[6]

With increased access there is potential for misuse and inappropriate use of cannabidiol. For example, although a person aged over 18 years may purchase the proposed Schedule 3 cannabidiol this does not prevent them from intentional administration to or unintentional ingestion by paediatric patients under their care.

The article Cogan PS. On healthcare by popular appeal: critical assessment of benefit and risk in cannabidiol based dietary supplements. Expert Rev Clin Pharmacol. 2019; 12(6):501-511. notes that 'Available data regarding the efficacy of cannabidiol for the treatment of any specific condition are equivocal at best and may be explained, at least in part, by pharmacokinetic interactions and non-specific effects. This calls into question expectations of therapeutic utility of cannabidiol for any given indication. Available data on adverse events associated with cannabidiol, its demonstrated pharmacokinetic interactions with other drugs, and a lack of experience with its arbitrary dosing place consumers at undue risk.' The expert opinion is provided that 'Ongoing lack of meaningful regulation of cannabinoid supplements continues to put consumers at undue risk without clear evidence of therapeutic value.'

Concerns about potential drug-CBD interactions can be handled effectively through limiting the amount of CBD able to be sold in a month's supply and the inclusion of appropriate warning labels.

Cannabidiol doses that have been assessed in the majority of research studies are higher than the proposed low dose.[7] Limitations on the amount of cannabidiol sold per unit does not preclude patients from purchasing cannabidiol from multiple pharmacies to achieve higher doses. There is a lack of clinical trial evidence to support the notion that a low dose prevents cannabidiol drug interactions. There is also the high possibility that even with appropriate labelled warnings these products would likely be used by vulnerable patient populations, such as paediatric, pregnant, those with complex co-morbidities and polypharmacy and older patients as evidenced by prescribing patterns.

It is suggested that the Schedule 4 entry for CBD be reworded to explicitly include (future) synthetic or semi-synthetic formulations.

The TGA review Safety of low dose cannabidiol details additional concerns related to synthetic and semi-synthetic preparations

References

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[redacted] Please find our feedback attached to the email and if you require any further information contact [redacted]

Kind regards

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