Therapeutic Goods Administration
Symonston ACT 2609

Re.: Proposed amendment to the Poisons Standard - cannabidiol

To Whom it May Concern,

We are writing in response to the current consultations regarding proposed amendments to the scheduling of cannabidiol (CBD).

After careful consideration of the two proposals and the relevant literature, we have formed the view that CBD has a benign safety profile that does not justify access restrictions by way of scheduling, when it is used orally at low doses (approximately up to 1mg/kg/day).

In the TGA's proposal for the down-scheduling of low-dose CBD to Schedule 3, concerns about drug interactions are cited as the main reason a pharmacist should sanction the dispensation. We do not agree that the current evidence for drug interactions involving CBD warrants scheduling.

While the clinical evidence for drug interactions involving CBD is limited, the WHO Expert Committee on Drug Dependence in their 2017 Pre-Review Report on CBD noted that there is "… potential for CBD to be associated with drug interactions through inhibition of some cytochrome P450 enzymes, but it is not yet clear whether these effects occur at physiological concentrations." [1]

Qian et al. (2019) reviewed the potential for interactions between cannabis products and drugs and cited four CBD drug interaction studies, all of which involved the CBD pharmaceutical drug Epidiolex® [2]. These studies, some of which included children and did provide evidence for pharmacokinetic drug interaction potential, administered CBD in high daily doses, in the range 5-50 mg/kg/day.

We are not aware of reports of drug interactions with low dose CBD (i.e. in the range 1 mg/kg/day) [redacted] likely to occur to a clinically relevant degree. We note that [redacted] s St John's Wort (*Hypericum perforatum*) have quite extensive [redacted] ns [3], the risks of which are effectively managed by way of a mandatory label warnings rather than scheduling. We believe any concerns about a possible risk of drug interactions with CBD could successfully be managed in the same way.

In summary, **we support the de-scheduling of low dose CBD for oral use**.

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Scheduling of CBD for topical use

We note that both current proposals for changes to the scheduling of CBD address oral use only. There is an emerging body of literature on the therapeutic use of topical CBD (briefly reviewed in Appendix 1), and we would urge the TGA to include this mode of administration in the deliberations about the potential down-scheduling of CBD.

As detailed below, we believe topical CBD is associated with lower risks than oral CBD, and we suggest that CBD for low-dose, topical use does not warrant scheduling.

Safety of topical CBD

The TGA has recently reviewed the safety of low dose CBD [4]. This review concluded that CBD "presents a good safety and tolerability profile at the low dose range of under 60 mg/day" (for adults) and identified that there are "potential conditions for low dose cannabidiol that would not require oversight by a medical practitioner". Further, the review noted that low-dose CBD (i.e. less than or equal to 1 mg/kg/day) "has possible utility in the management of chronic and generalised pain of broad aetiologies through both systemic and localised administration and in anxiety and insomnia."

The TGA safety review focused on CBD for oral administration and only made brief reference to one study where CBD was applied topically [5]. Further, the review concluded that although low-dose CBD appears to have an acceptable safety and tolerability profile, there is a high potential for cytochrome-P450- based drug interactions, although the likelihood of this occurring with low-dose CBD is currently unknown.

A recent systematic review of CBD trials in adults, not included in the TGA safety review, found that most studies reported no adverse events from acute CBD administration and mild to moderate adverse effect with chronic administration [6]. Only one of the 25 clinical trials included in this systematic review involved topical application of CBD [7].

Safety information from published human studies with topical CBD is briefly reviewed below.

A placebo-controlled trial that administered a transdermal synthetic CBD gel to more than 200 adults with knee osteoarthritis at two different doses for twelve weeks reported the CBD gel to be [redacted] most frequently reported adverse events were application site

Palmieri et al. (2019) reported a retrospective study of 20 patients with psoriasis, atopic dermatitis and resulting outcome scars in which a CBD-enriched ointment was applied to lesioned skin areas twice daily for a period of three months [7]. Treatment significantly improved a range of skin parameters and the Psoriasis Area and Severity Index score. No irritant or allergic reactions were documented, and the topical administration of the ointment was deemed safe.

Topical CBD was successfully used to treat severe, opioid-resistant pain in 25 patients with systemic sclerosis over two months, with no significant side-effects reported [5].

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Nitecka-Buchta et al. (2019) conducted a randomised, placebo-controlled trial of a topical CBD-formulation in myofascial pain caused by temporomandibular disorders [9]. Thirty patients applied the topical CBD-formulation twice daily for 14 days. No adverse effects were recorded.

A Phase 1 study of a novel acne treatment, a 5% synthetic CBD formulation (BTX 1503), applied twice daily in 20 healthy volunteers found that it was well tolerated [10]. Preliminary results from an ongoing, 28-day evaluation of the same formulation in 23 subjects with moderate to severe facial acne indicated the formulation is safe and well tolerated [10].

Published case reports of the successful use of topical CBD in the treatment of epidermolysis bullosa in three children note that there were no reported adverse effects from the treatment [11].

Although the current body of human safety data for topical CBD is limited, the available data do not raise any safety concerns, and topical CBD appears to be safe and well tolerated.

As already mentioned, the TGA safety review of low dose cannabidiol [4] concluded that oral CBD at a dose of up to 1 mg/kg/day has an acceptable safety and tolerability profile. The potential for drug interactions involving oral CBD was highlighted and subsequently used as the key argument for making CBD a Schedule 3 rather than a Schedule 2 substance in the TGA's current proposal to down-schedule CBD (https://www.tga.gov.au/consultation-invitation/consultation-proposed-amendments-poisons-standard-joint-acmsaccs-meetings-june-2020).

Scheduling of CBD for topical use is not warranted

A potential for drug interactions involving topically administered agents is known to exist when a drug is applied directly to the eye [12, 13]. This is likely due to the eye being a highly vascularised tissue, into which a drug molecule can be readily absorbed and enter the systemic circulation.

However, drug interactions involving drugs applied topically to the skin are not well documented in the literature, suggesting they are rare, and the reduced risk of drug interactions is cited as one of the advantages of administering analgesic drugs topically [14]. Compared with oral administration, topical application to the skin results in low systemic absorption rates, and consequently lower peak plasma levels of the drug molecule [15]. Metabolism may also occur locally, prior to the drug reaching the systemic circulation. Because of these factors, the risk of drug interactions is [redacted]d by the paucity of reported drug interactions involving drugs [redacted]actions arising from the topical use of CBD is very low and certainly less than the risk associated with many unscheduled herbal ingredients, for example St John's Wort (*Hypericum perforatum*) and Licorice (*Glycyrrhiza glabra*). This, combined with CBD's otherwise benign safety profile when used at low doses, in our view justifies the de-scheduling of CBD for topical use.

We have outlined above our view that based on the available evidence, CBD for topical use at low doses would be safe, well tolerated and represent a very low risk of drug interactions. Accordingly, we do not believe the evidence for potential harm warrants the inclusion of low dose CBD for topical use on any Schedule in the Poisons Standard.

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Advantages of removing CBD for topical use from the Poisons Standard

Removing low-dose CBD for topical use from the Poisons Standard would:

- reduce the barriers to patient access to medicinal cannabis in Australia, as per the Terms of Reference of the current Senate Inquiry (https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Medicinalcannabis);
- allow for the potential inclusion of CBD for topical use in the Permissible Ingredients Determination;
- protect the public by making available high quality, TGA-regulated products, which would be far safer than unregulated products of dubious quality bought on the web;
- drive research and innovation in complementary medicines and reinforce Australia's leadership position in this field;
- expand the evidence base for, and scientific knowledge of, CBD; and
- benefit Australian industry.

As noted in the TGA safety review of low dose CBD, there are potential indications for which this ingredient may be suitable, and the knowledge of the therapeutic potential of CBD is expected to expand rapidly in the coming years. A brief outline of the current literature pertaining to topical CBD is provided in Appendix 1.

In conclusion, topical application of CBD may have clinical utility in the management of some conditions that do not require the oversight of a health professional and thus should be considered for use in listed (low-risk) complementary medicines. De-scheduling of CBD for topical use should be limited to low dose, plant derived CBD, which comprises only the (-) CBD enantiomer, which does not exhibit psychoactive effects.

We appreciate the opportunity to respond to the current consultations on CBD and hope the TGA will include in its deliberations the topical use of low dose CBD, which we believe is safe.

Yours sincerely,

[redacted]

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APPENDIX 1

Published studies of topical cannabidiol for therapeutic use

The last few years has seen a spectacular rise in the interest in, and popularity of, various *Cannabis sativa* derived preparations, most notably those featuring the non-psychoactive CBD as the main active ingredient. While most products in the international market are for oral consumption, CBD is also being used as an ingredient in skincare and other topical products.

Topical CBD products are being marketed as having anti-inflammatory, analgesic, hydrating, moisturising and wrinkle-reducing properties and are being promoted for a wide range of complaints and conditions, including skin aging, acne, eczema, psoriasis, pruritis and rosacea [16, 17]. Research has examined the dermatological use of cannabinoids in conditions such as psoriasis, atopic dermatitis, dermatomyositis, wound healing and melanoma [18], and published case studies support the use of topical CBD in the treatment of epidermolysis bullosa [11].

Even though the evidence for topical CBD as a therapeutically active ingredient is currently limited, there is sufficient published information to warrant commercial and research interest, and given the current global interest in cannabinoids generally and CBD in particular, more relevant information will no doubt be published in the near future.

A survey of US dermatology providers found that 94% of respondents supported research into the dermatologic uses of cannabinoids and 86% were willing to prescribe cannabinoids as a topical treatment [18].

Other surveys have shown that a significant proportion of people who use cannabis and CBD for therapeutic purposes do so using topical applications [19, 20].

Human studies, ranging from case studies to RCTs, provide varied levels of support for the topical use of CBD in a range of conditions, including myofascial pain [9], inflammatory skin diseases such as atopic dermatitis and psoriasis [7], epidermolysis bullosa [11, 21], pain in systemic scleroderma [5], and acne [10, 22].

Animal studies using topical CBD as an intervention include models of atopic dermatitis [23], arthritis [24] and multiple sclerosis [25].

A sophisticated study published in a highly-ranked scientific journal has identified CBD as a promising therapeutic agent for the treatment of acne, based on the observed lipostatic, anti-[redacted]ffects [26]. The study was conducted *in vitro* on cultured [redacted]an skin obtained from biopsies. This study found CBD to be a [redacted] wide range of experiments reported in this paper provides extensive insights into the modes of action of CBD. Although not conducted in whole human beings, this high-quality study provides compelling evidence to suggest that CBD could be an effective agent for the treatment of acne.

The transdermal bioavailability of CBD has been demonstrated in an *ex vivo* study using human skin [27] and in the dog [28], mouse [25], rat [24, 29] and guinea pig [29].

The level of current biomedical research into the topical use of CBD clearly demonstrates that this ingredient is active when applied topically to human skin and is under active investigation by the research community in several areas.

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