MCC 70th Meeting, Medsafe Regulatory Advice – CDB March 2023 for MCC 70th Meeting

Low dose cannabidiol (CBD) was presented as agenda item 8.2.1a of the 69th Medicines Classification Committee (MCC) meeting. This was for consideration for harmonisation with Australia, following a decision made by the Secretary to the Department of Health and Aged Care in Australia. There are no approved low-dose CBD products in Australia and no applications in progress. The following information was provided to the MCC for their review at the 69th meeting:

- the publicly available information published by the Therapeutic Goods Administration (TGA)
- regulatory advice for commenters on the agenda item published by Medsafe https://www.medsafe.govt.nz/profs/class/Agendas/Agen69/CBDHarmonisationRegulatoryGuidance.pdf
- comments from public consultation.

The MCC made a recommendation that the classification of low dose CBD remain unchanged in New Zealand. The Minister's delegate has requested that the MCC be provided with additional contextual information for further review, consideration, and a recommendation.

Data requirements for a New Medicine Application submission

Data requirements are outlined in Medsafe Guidelines. Consistent with other medicine regulators, Medsafe takes a risk-based approach to evaluation of medicine applications. Data requirements are generally greater for medicines in high and intermediate risk categories (which include most prescription medicines), compared to those in lower risk categories (which include most over the counter medicines, including pharmacist only medicines). An over-the-counter medicine is a medicine that can be purchased without a prescription.

Quality and manufacturing data required to support active ingredient manufacture is much lighter for lower risk medicines, due to their lower risk. For example, active ingredients for lower risk medicines usually contain active ingredients that are listed in a pharmacopoeia, and exposure to over-the-counter medicines is lower as they are typically taken for shorter durations.

Non-clinical (pharmacologic, pharmacokinetic, toxicological) data is not required for an over-the-counter medicine application.

The extent of Clinical data required to support an indication for a lower risk medicine application for CBD, would need to be justified by the applicant. In the first instance, safety and efficacy data is typically generated from randomised, placebo controlled clinical trials conducted in accordance with ICH Guidelines. However lower risk medicines usually claim indications for which there is sufficient supportive published literature, as in most cases the medicine has a history of being marketed as a prescription medicine.

Medsafe accepts new medicine applications based on literature reviews. Naturally the data provided must provide appropriate and sufficient evidence for the indication being sought. Medsafe applies the Australian guideline for these types of applications. The Indications being sought would be a key determinant as to whether a literature-based submission would be appropriate, with minor and self-limiting conditions (e.g., *helps manage short term pain*) being more likely appropriate compared to serious conditions (e.g., *treatment of epilepsy*).

https://www.tga.gov.au/resources/resource/guidance/pre-submission-guidance-literature-based-submissions-lbs

Safety information

Published data regarding known and suspected drug interactions for CBD is sparce as there are currently no approved products in New Zealand and very few products with marketing authorisations globally. However, there is evidence for some drug interactions with CBD.

The Medsafe Pharmacovigilance Team has recently published a report detailing CBD potential drug interactions with systemic mTOR and calcineurin inhibitors. This report highlights studies which have demonstrated increased drug levels of mTOR or calcineurin inhibitors following use of cannabis products. The mechanism by which CBD contributes to drug-drug interactions is via enzymes and transporters involved in drug metabolism, notably CYP450 enzymes and P-glycoprotein.

There is also evidence that concomitant use of sodium valproate and cannabidiol at doses 10 to 25 mg/kg may increase the incidence of transaminase enzyme elevations.

https://www.medsafe.govt.nz/profs/datasheet/e/Epilimtabsyrliqiv.pdf

There are currently no approved low dose CBD products and therefore there is currently no New Zealand data sheet available for any low dose CBD products. Pharmacist-only medicines require a datasheet, which must be supported by relevant data. This would provide pharmacists with dosing and safety information, including information on potential drug interactions for approved CBD products.

Potential impacts of a restricted (pharmacist only) classification for low dose CBD

There are lower data requirements for over-the-counter medicines compared to prescription medicines, and corresponding lower application fees. It's possible for CBD products, this could reduce the cost barrier to development of new products and incentivise product development and subsequent New Medicine Applications. It should be noted, however, that data required to support an approved medicine, even an over-the-counter product, remains far greater than that required to demonstrate a product meets the minimum quality standard under New Zealand's Medicinal Cannabis Scheme. A large factor of cost for medicine applications is manufacturing to the standard required and running clinical trials.

The evidence to support low dose CBD efficacy for any indication is limited as few studies have directly assessed its effects in isolation. It is likely that current evidence is insufficient to support a successful medicines application. There are numerous cases in the literature where low dose CBD has been placed in a Randomised Control Trial but in combination with THC, making conclusions about its effects alone immeasurable. For this reason, the literature to support any efficacy of low dose CBD alone is even more scarce.

This provides an excellent opportunity for new clinical research to be undertaken with low dose CBD products that addresses the question of efficacy in a range of indications including in secondary symptom control. This is beneficial to the knowledge base as it will stimulate greater research interest and further our understanding of CBD and its utility as a medicine more broadly.