Australian Government
Department of Health
Therapeutic Goods Administration

Notice of final decision to amend (or not amend) the current Poisons Standard - cannabidiol

15 December 2020

TGA Health Safety Regulation

Contents

1 Notice of final decision to amend (or not amend) the current Poisons Standard

This web publication constitutes a notice in relation to two proposed amendments for the entry to cannabidiol for the purposes of regulation 42ZCZS and 42ZCZX of the *Therapeutic Goods Regulations 1990* (the **Regulations**). In accordance with regulations 42ZCZS and 42ZCZX, this notice publishes:

- the decision made by a delegate of the Secretary pursuant to regulation 42ZCZR;
- the reasons for the final decision; and
- the date of effect of the decision.

2 Final decision on proposed amendments to the current Poisons Standard under regulation 42ZCZR

2.1 Final decision on proposed amendments referred to the Advisory Committee on Medicines and Chemicals Scheduling in joint session (Joint ACMS-ACCS #25 and #26)

Final decision in relation to cannabidiol (private application and delegate initiated)

Final Decision

Pursuant to regulation 42ZCZR of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendments to cannabidiol made the following final decision:

- in relation to the proposed amendment in the private scheduling application, made a final decision to confirm the interim decision not to amend the current Poisons Standard to exclude cannabidiol from scheduling and allow its general sale.
- in relation to the proposed delegate-initiated amendment, made a final decision to vary the interim decision and amend the current Poisons Standard in relation to cannabidiol, cannabis and tetrahydrocannabinol as follows:

  Schedule 8 – Amend Entry

  # CANNABIS (including seeds, extracts, resins and the plant, and any part of the plant) when prepared or packed for human therapeutic use, when:

  a) cultivated or produced, or in products manufactured[1], in accordance with the *Narcotic Drugs Act 1967*; and/or

  b) for use in products manufactured in accordance with the *Narcotic Drugs Act 1967*; and/or

  c) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the *Therapeutic Goods Act 1989*; and/or

  d) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*,

  except when:

  i) it is in a product to which item 4, 8, 10, 11 or 12 of Schedule 5A to the *Therapeutic Goods Regulations 1990* applies; or

  ii) separately specified in the NABIXIMOLS entry in this Schedule; or

  iii) captured by the CANNABIDIOL entry in Schedule 4 or Schedule 3.

[1] "Cultivation", "production" and "manufacture" have the same meaning as in the *Narcotic Drugs Act 1967*

Schedule 8 – Amend Entry

TETRAHYDROCANNABINOLS when extracted from cannabis for human therapeutic use, when:

e) included in products manufactured in accordance with the *Narcotic Drugs Act 1967*; and/or

f) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the *Therapeutic Goods Act 1989*; and/or

g) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*,

except when:

i) it is in a product to which item 4, 8, 10, 11 or 12 of Schedule 5A to the Therapeutic Goods Regulations 1990 applies; or

ii) separately specified in the NABIXIMOLS entry in this Schedule; or

iii) captured by the CANNABIDIOL entry in Schedule 4 or Schedule 3.

Schedule 4 – Amend Entry

CANNABIDIOL in preparations for therapeutic use or analytical and scientific research where:

a) cannabidiol comprises 98 per cent or more of the total cannabinoid content of the preparation; and

b) any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and comprise 2 per cent or less of the total cannabinoid content of the preparation;

except when included in Schedule 3.

Schedule 3 – New Entry

CANNABIDIOL in oral, oromucosal and sublingual preparations included in the Australian Register of Therapeutic Goods (ARTG) when:

a) the cannabidiol is either plant derived, or when synthetic, only contains the (-)-CBD enantiomer; and

b) the cannabidiol comprises 98 per cent or more of the total cannabinoid content of the preparation; and

c) any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and comprise 2 per cent or less of the total cannabinoid content of the preparation and of which tetrahydrocannabinol (THC) can only comprise 1 per cent of the total cannabinoid content; and

d) the maximum recommended daily dose is 150 mg or less of cannabidiol; and

e) packed in blister or strip packaging or in a container fitted with a child-resistant closure; and

f) in packs containing not more than 30 days' supply; and

g) for adults aged 18 years and over.

Appendix F, Part 3 – New entry

POISONS (other than agricultural and veterinary chemicals) TO BE LABELLED WITH WARNING STATEMENTS OR SAFETY DIRECTIONS

POISON	WARNING STATEMENTS	SAFETY DIRECTION
CANNABIDIOL when included in Schedule 3.	67, 111	
67: Do not use if pregnant or likely to become pregnant. 111: Do not use if breastfeeding or planning to breastfeed		

Appendix K – Amend Entry

CANNABIS **except** cannabidiol when included in Schedule 4 or Schedule 3

TETRAHYDROCANNABINOLS **except** cannabidiol when included in Schedule 4 or Schedule 3

Index

CANNABIDIOL
cross reference: NABIXIMOLS, CANNABIS, TETRAHYDROCANNABINOLS

Schedule 4
Schedule 3
Appendix F, Part 3

Materials considered

In making this final decision, the Delegate considered the following material:

- the private scheduling application and delegate-initiated amendment to amend the current Poisons Standard with respect to cannabidiol;
- the 5409 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations;
- the advice received from the Joint meeting of the Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS#25);
- the advice received from the Joint meeting of the Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS#26);
- the 36 public submissions received in response to the interim decision consultation under regulation 42ZCZP of the Regulations;
- subsection 52E(1) of the *Therapeutic Goods Act 1989*, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health;
- the Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018);

- the Scheduling handbook: Guidance for amending the Poisons Standard;
- a review by McGregor *et al*., Access to cannabinol without a prescription: A cross-country comparison and analysis (2020);
- a review by Chesney *et al*., Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials (2020);
- a review by Larsen and Shahinas, Dosage, Efficacy and Safety of Cannabidiol Administration in Adults: A Systematic Review of Human Trials (2020); and
- a review by Dos Santos *et al*., Serious adverse effects of cannabidiol (CBD): a review of randomized controlled trials (2020).

Summary of Joint ACMS-ACCS #26 to the Delegate

At the November 2020 meeting, the Delegate sought further advice from the Joint ACMS-ACCS, on the following specific criteria that had been incorporated into the interim decision to down-schedule low dose CBD:

- an Appendix M entry to limit supply to medicines included in the Australian Register of Therapeutic Goods (ARTG);
- dose restrictions;
- age restrictions; and
- advertising restrictions.

In addition to the above criteria, the Delegate sought feedback on including a reference to synthetic (-)-CBD in the Schedule 3 entry, as well as a reference to analytical use of CBD in the Schedule 4 entry.

The Committee restated its previous advice on the down scheduling of CBD that it is premature to down schedule CBD before a suitable preparation is included in the Australian Register of Therapeutic Goods, consistent with the terms of the proposed new entry.

Notwithstanding the Committee's previous advice, the Committee recommended amendments to the proposed new Schedule 3 entry for CBD in the current Poisons Standard and recommended that the Delegate reassess the dose cut-off, on the basis of the available safety data.

The Committees recommendations were:

- The requirement for inclusion in the Australian Register of Therapeutic Goods (ARTG) should be specified in the Schedule 3 entry rather than Appendix M.
- The Committee recommended that the delegate review the maximum daily dose cut-off, to assess whether there was evidence to support adjusting it.
- The Schedule 3 entry should specify the (-)-CBD enantiomer.
- Over the counter availability of CBD should be limited to adults [over the age of 18].
- Advertising was not appropriate at this time.
- Topical preparations were not appropriate to be included in the Schedule 3 entry at this time.
- The Schedule 4 entry should be amended to include reference to analytical use of CBD.
- Pregnancy and breastfeeding warning statements should be included.

Members agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of the substance; (b) the purpose for which the substance is to be used and the extent of use; (c) the toxicity of the substance; (d) the dosage, formulation, labelling, packaging and presentation of the substance; (e) the potential for abuse of the substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

a) the risks and benefits of the use of a substance

The Committee identified the following benefits:

- The TGA Safety Review identified low dose CBD (up to 60mg/day) as having an acceptable safety and tolerability profile.

The Committee identified the following risks:

- CBD, being an inhibitor of CYP3A4, CYP2D6, CYP2C19, CYP2C9 and P-glycoprotein, is likely to have interactions with the majority of pharmaceuticals available for human use. Pharmacodynamic interactions with drugs that cause CNS depression (opioids, benzodiazepines, antipsychotics, gabapentinoids, sedating antihistamines), are likely.

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

- The Committee considered that restriction of the Schedule 3 entry to preparations included in the ARTG would ensure that such products had a defined indication appropriate for supply as a Pharmacist Only Medicine.

c) th*e toxicity of a substance*

- The Committee agreed that the toxicity is reduced at low doses.
- The Committee identified that there is potential to increase risk of toxicity from other drugs through inhibition of their metabolism or efflux.

d) the dosage, formulation, labelling, packaging and presentation of a substance

- The Committee noted concerns from stakeholders that the proposed 60 mg per day dose may be too low to be efficacious. The Committee recommended that the Delegate reassess the dose cut-off, on the basis of the available safety data. In particular, to assess whether the 60 mg/kg dose should be adjusted based on 1 mg/kg/day and the average weight in the Australian context.

e) the potential for abuse of a substance

- The Committee acknowledged that CBD has low abuse potential at low doses.
- There is a possible risk of overuse or misuse of low dose CBD for inappropriate indications.

f) any other matters that the Secretary considers necessary to protect public health

- The Committee noted that the current proposal may not change consumer access to low dose CBD if sponsors cannot provide the evidence of efficacy required to register a preparation on the ARTG.
- The Committee agreed that the inclusion of the ARTG restriction for CBD in Schedule 3 can be viewed as consistent with the purposes for which Appendix M was created. However, there was concern raised by state and territory members with regard to

adoption of Appendix M in respective medicines and poisons legislation. The Committee agreed the best option for incorporating the requirement for preparations to be included in the ARTG, was to add it to the S3 entry, rather than Appendix M.

Reasons for the final decision (including findings on material questions of fact)

I have made a final decision, to **confirm** my interim decision, in the following manner:

- not to exempt CBD from inclusion in the current Poisons Standard;
- to facilitate greater access to cannabidiol (CBD) by down-scheduling the substance from Schedule 4 to Schedule 3 of the current Poisons Standard, subject to a number of criteria being satisfied.

I have made a final decision, to **vary** my interim decision, in the following manner:

- to specify the requirement for inclusion in the Australian Register of Therapeutic Goods (ARTG) in the Schedule 3 entry rather than Appendix M;
- to modify the dose specified in the Schedule 3 entry from 60 mg/day to 150 mg/day;
- to include a limit on tetrahydrocannabinol (THC) in the Schedule 3 entry, which will only comprise 1 per cent of the total cannabinoid content of the preparation;
- to amend the Schedule 4 entry to include reference to analytical and scientific use of CBD; and
- to exempt CBD when in Schedule 3, from the Schedule 8 and Appendix K entries for cannabis and THC.

In making my final decision, I have taken into account the material detailed in the interim decision, the additional advice received from the Joint meeting of the Advisory Committees on Medicines and Chemicals Scheduling (Joint ACMS-ACCS#26) and the 36 public submissions received before the second closing date in response to the call for further submissions published on 9 September 2020 under regulation 42ZCZP of the Regulations.

The detailed reasons for my decision are outlined in the interim decision with the following qualifications and additional observations.

I have considered the concerns raised by the Joint ACMS-ACCS #26 regarding the Appendix M entry to limit supply of Schedule 3 CBD medicines included in the ARTG. I understand, that Appendix M is not currently adopted by all states and territories and that this would require new regulations to incorporate the requirements of Appendix M or adopt Appendix M by reference. To ensure consistency across Australia, I have made the decision to incorporate the requirement for preparations to be included in the ARTG into the S3 entry, rather than Appendix M.

I have considered the concerns raised in the public submissions and the recommendation from the Joint ACMS-ACCS #26, to review the dose of 60 mg/day, specified in the Schedule 3 entry. I find that the main argument made in the public submissions, was that the proposed dose is potentially sub-therapeutic and may present a barrier for sponsors to register a Schedule 3 preparation on the ARTG. Furthermore, I accept the Committee's concern regarding the CBD dosage calculation, which was based on the body mass of a 60 kg person, given the average body mass for Australian women is 72 kg and men is 87 kg. Many of the submissions provided references supporting a higher dose, while still maintaining a safety profile that aligns with a Schedule 3 medicine. Accordingly, I have considered these submissions alongside a number of reviews detailed below and I have resolved that a maximum daily dose of 150 mg is consistent with the expected safety profile of a Schedule 3 medicine.

In forming this view, I considered the findings of a recent systematic review of clinical trials, which concluded that CBD is well tolerated across a wide range of dosages. I note that CBD is rarely associated with severe adverse events, and that non-serious adverse events appear significantly lessened at lower dosages. The study demonstrates that, outside of the treatment of epilepsy, diarrhoea is the only adverse event that is more prominent than placebo. I note that similar margins of safety were reported in two separate systematic reviews and meta-analyses published in 2020 (Larsen and Shahinas *et al*., 2020 and Dos Santos *et al*., 2020).

I have considered the evidence presented in a submission, which outlined the findings of a confidential report on efficacy and safety of oral CBD. I find the evidence presented in this report to be credible and relevant and I have attached weight to this report on the basis that this is a current and comprehensive scientific review of the literature.

I have also considered the findings of a recent review, which found that all countries studied, except Australia and New Zealand, have CBD products available without a prescription in varying forms and strengths. I note that the recommended daily doses provided by non-prescription products were, with one exception, below 150 mg. The study notes "that high quality scientific studies around the potential benefits of low CBD doses are yet to be conducted and so efficacy at these doses remains to be demonstrated." In any event, the inclusion of a substance in a Schedule does not indicate that the substance is available; nor that is has been approved or is efficacious for any use that may be specified in a Schedule; nor does it negate any obligation for registration of a preparation containing that substance.

I have decided to ensure the THC content of the Schedule 3 cannabidiol preparation, is kept well below intoxicating levels, by limiting it to 1% of total cannabinoids. In making this decision, I note that applications to register a Schedule 3 low dose CBD preparation on the ARTG would involve assessment of safety and efficacy data to support the proposed dose and indication.

I have considered a submission to amend the Schedule 4 CBD entry to include reference to 'analytical use'. I agree with the Committees' advice to broaden this reference to 'analytical and scientific research'. I am of the view that this clarification will prevent bench top research and laboratory analysis from being inadvertently captured in Schedule 9, as well as reducing regulatory burden for researchers.

I note, in 2018 a decision was made to exempt CBD when in Schedule 4, from the Schedule 8 and Appendix K entries for cannabis and THC. For consistency, I have made a decision to specifically exclude CBD when in Schedule 3, from these entries.

I have decided to confirm my interim decision to limit synthetic CBD in the Schedule 3 entry to the (-)-CBD enantiomer. The evidence supporting the scheduling of CBD pertains to cannabis based products containing (-)-CBD and there is limited evidence related to (+)-CBD contained in synthetically derived products.

I confirm the reasons set out in my interim decision regarding advertising restrictions and age restrictions on Schedule 3 CBD medicines. I note that there was agreement, among the Joint ACMS-ACCS #26 members, in their advice on this matter, that CBD should not be listed in Appendix H and that OTC availability of CBD should be limited to the treatment of adults.

I have reconsidered the implementation date and consider that an implementation date of 1 February 2021 is appropriate, as there is no need to delay until 1 June 2021 as proposed in my interim decision.

Date of effect of the decision

1 February 2021.