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Safety of low dose cannabidiol

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- The review found that cannabidiol presents a good safety and tolerability profile at the low dose range of under 60mg/day.
- The review identified that there were potential conditions for low dose cannabidiol that would not require oversight by a medical practitioner.
- Low dose cannabidiol for plant derived CBD or synthetic CBD which only contains the (-) CBD enantiomer would be suitable for consideration for down scheduling, potentially to Schedule 3, given that the conditions for which it is proposed for use require oversight by a healthcare professional and there remains the potential for drug-drug interactions.

Safety of low dose cannabidiol

Introduction

Cannabidiol (CBD), a cannabinoid derived from the Cannabis plant, is being supplied as a medicine in Australia, but often as a component of oils and extracts of cannabis. A purified product has recently been approved for treatment of certain paediatric epilepsies in the US and is under regulatory evaluation in Australia as a registered medicine. There is increasing use, patient demand and health care practitioner interest in its use in clinical practice, as well as widespread use in over the counter medicines, complementary medicines and cosmetics in some countries.

In Australia CBD is currently a schedule 4 substance and therefore only available with a prescription. This access is seen by many as too restrictive noting it is available as an over the counter product (if provided without medicinal claims) in some jurisdictions such as the UK and some US states; and is widely available in some countries in other non-prescription products. However, currently there are no CBD medicines registered on the Australian Register of Therapeutic Goods (ARTG). Access is only available through the Special Access Scheme (SAS) or Authorised Prescriber (AP) scheme upon application by a clinician.

On 14 November 2019, the Senate referred an inquiry into *the current barriers to patient access to medicinal cannabis in Australia* to the Senate Community Affairs References Committee for inquiry and report by 26 March 2020.

The Department of Health made a submission to this Inquiry in January 2020 and in this submission included that the TGA was currently undertaking a safety review of CBD at lower doses, noting that there were only limited published studies. In the submission, the Department also noted that depending on the outcome of the review, that the scheduling status of low dose CBD products would be considered.

The Senate Inquiry recommended 'as soon as practicable after a safety review and public consultation process is completed, the Department of Health make any appropriate application to the Advisory Committee on Medicines Scheduling in relation to the down-scheduling or de-scheduling of cannabidiol and other non-psychoactive cannabinoids.' (Recommendation 13). The Senate Inquiry also noted that, due to the differences in regulatory control internationally and the current restrictions regarding access to an S4 medicine, there was a desire to assess whether it could be more accessible to the Australian public, especially at low doses.

If deemed appropriate for increased public access, the regulatory options available and their relative characteristics must be considered. These are outlined in Table 1 below.

Table 1 – Regulatory options available for increased access to CBD

Level of regulation	Regulatory pathway and the relevant characteristics
Scheduled Schedule 3 includes medicines such as orlistat, chloramphenicol eye drops and pseudoephedrine and levonorgestrol (morning after pill)	**Schedule 3-Pharmacist Only Medicine** • Available at pharmacies only and **kept behind the counter**. Requires professional advice from pharmacist to **assess appropriate use**. • Regulatory pre-approval is required prior to supply of medicines containing the S3 substance. • Efficacy, safety and quality is pre-assessed. • Any changes to the medicine that affects the quality and/or safety and/or efficacy of the medicine are either preapproved or notified to the regulator. • Product Information and Consumer Medicine Information documents are required.
Scheduled Schedule 2 includes medicines such as paracetamol and ibuprofen in greater than pack sizes of 24, diclofenac 12.5mg or less in a pack size of 20 or less, corticosteroid nasal sprays	**Schedule 2-Pharmacy Medicine** • Available at pharmacies only. Typically available on **accessible** pharmacy **shelves**. Purchase does not require advice from a pharmacist. • Regulatory pre-approval is required prior to supply of the medicine containing the S2 substance. • Efficacy, safety and quality is pre-assessed. • Any changes to the medicine that affects the quality and/or safety and/or efficacy of the medicine are either preapproved or notified to the regulator.
Scheduled Schedule 3 complementary medicines include One-A-Week colecalciferol 7000IU (175mcg).	**Schedule 3 Registered complementary medicines** • The active ingredient must be an eligible complementary medicine ingredient, as defined in schedule 14 of the regulations, each having a clearly established identity and a traditional use. CBD being a plant or herbal material is an eligible ingredient. • Available at pharmacies only and **kept behind the counter**. **Requires** professional advice from pharmacist to **assess appropriate use**. • Pre-approval is required prior to supply of the medicine. • Efficacy, safety and quality is pre-assessed. • Any changes to the medicine that affects the quality and/or safety and/or efficacy of the medicine are either preapproved or notified to the regulator.

Level of regulation	Regulatory pathway and the relevant characteristics
Scheduled Schedule 2 complementary medicines include iron products that contain > 24mg/ daily dose and folic acid products that contain >500mcg/ daily dose.	**Schedule 2 Registered complementary medicines** • The active ingredient must be an eligible complementary medicine ingredient, as defined in schedule 14 of the regulations, each having a clearly established identity and a traditional use. • Available at pharmacies only. Typically available on **accessible** pharmacy **shelves** and does not require advice from a pharmacist. • Pre-approval is required prior to supply of the medicine. • Efficacy, safety and quality is pre-assessed. • Any changes to the medicine that affects the quality and/or safety and/or efficacy of the medicine are either preapproved or notified to the regulator.
Unscheduled Includes small pack sizes of paracetamol (pack size of 20 or less) and ibuprofen (pack size 25 or less); complementary medicines such as vitamins and minerals	**Assessed listed medicines** • Ingredient must be unscheduled (not included in the Poisons Standard in the intended form and quantity). • Ingredient (CBD) must be assessed by TGA and if deemed suitable must be included in the 26 BB Permissible ingredient list. Currently CBD is not included as a permissible ingredient. • The evidence for efficacy of the indications are pre-assessed prior to marketing approval. • Quality and safety are not pre assessed. • The medicine is readily available in retail outlets without access to advice from a health professional. • Lower regulatory oversight over changes to manufacture.
	Listed medicines • Ingredient must be unscheduled (not included in the Poisons Standard in the intended form and quantity). • Ingredient (CBD) must be assessed by TGA and if deemed suitable must be included in the 26 BB Permissible ingredient list. Currently CBD is not included as a permissible ingredient. • Self-listing and self-certifying pathway with pre-set IT rules. • **Quality, safety, and efficacy are not pre assessed.** • Lower regulatory oversight over changes to the medicine manufacture. • The medicine is readily available in retail outlets without access to advice from a health professional.
	Registered OTC medicines • Available for general sale e.g. from supermarkets. • Pre-approval is required prior to supply of the medicine. • Efficacy, safety and quality is pre-assessed. • Any changes to the medicine that affects the quality and/or safety and/or efficacy of the medicine are either preapproved or notified to the regulator. • The medicine is readily available in retail outlets without access to advice from a health professional.

Level of regulation	Regulatory pathway and the relevant characteristics
	Registered complementary medicines • The active ingredient must be an eligible complementary medicine ingredient, as defined in schedule 14 of the regulations, each having a clearly established identity and a traditional use. • Available for general sale e.g. from supermarkets • Pre-approval is required prior to supply of the medicine. • Efficacy, safety and quality is pre-assessed. • Any changes to the medicine that affects the quality and/or safety and/or efficacy of the medicine are either preapproved or notified to the regulator.

Background

Cannabidiol (CBD) and tetrahydrocannabinol (THC) are the major cannabinoids present in Cannabis, from the glandular trichomes that occur most abundantly on the floral calyxes and bracts of female plants.

Unlike THC, CBD is does not cause psychomotor or cognitive impairment or strong psychoactive effects as it has relatively weak affinity for CB1 receptors primarily located in the central nervous system (the major mediator in THC for these effects) and CB2 receptors found in the periphery on cells with immune function and in the gastrointestinal tract. In preclinical studies, CBD has been found to demonstrate both a favourable safety profile and a wide range of pharmacological activity with potential therapeutic use[2].

Recently Epidiolex, which contains purified CBD (≥ 99% CBD) as the only active ingredient, has been approved as a prescription medicine for use in certain paediatric epilepsies in the United States. The prescribing information (PI) for Epidiolex provides that treatment is initiated at 2.5 mg/kg and escalated to efficacy. Epidiolex was designated an orphan drug in Australia on 22 November 2019.

Given that CBD has not been widely used in clinical practice and the evidence for which conditions it is effective has not been thoroughly characterised, it remains important that whether or not a safe limit can be identified, that the appropriate regulatory controls are maintained to ensure both safety and quality of products containing CBD. Any re-consideration of the current regulatory status of CBD, must ensure that a medicine supplied under lower medical oversight is not used to substitute medicines in conditions where medical supervision is required. For example, in the treatment of epilepsy or schizophrenia where medical supervision is required and known drug-drug interactions and pharmacodynamics interactions could lead to patient harm.

A reconsideration of the current scheduling status of CBD necessitates a consideration of a possible dose cut off, particularly taking into account potential for drug-drug interactions as well as the safety of CBD itself.

Aims

The aim of this review is to assess the current clinical literature to investigate if there is a low dose for cannabidiol with potential therapeutic effect and if so, what that low dose would be. It also sought to determine if the safety profile and characteristics of the low dose CBD lends itself to consideration for down scheduling.

The review focused on safety and therefore did not look at the efficacy of low dose CBD in the management of specific conditions. The review also does not make specific recommendations about possible indications for low dose products.

Methods

Search strategy

The objective was to identify a broad base of clinical and chemistry literature, which could answer the following questions:

- What dose range of cannabidiol is currently being used in clinical practice?
- Is there a low dose? What is the low dose?
- What is the overall clinical safety profile of low dose cannabidiol?

The following literature search in relation to cannabidiol was undertaken:

- Literature published in the last five years
- Synthetic pathways: extractions and chemical synthesis including a recent review of all the current methods available and chemical characterisation with impurity profile and related substances
- Clinical trials of cannabidiol at any dose and for any indication
- Dose ranging studies
- Reported adverse events, investigation of adverse events, case reports

The search strategy is outlined in **Appendix A**. The search was conducted on 18 December 2019.

Results

The literature analysed consisted of a mix of meta-analyses, randomised controlled trials (RCTs), clinical investigations, explorative studies, case series and patent applications. This literature was utilised for dose analysis.

Pharmacokinetics of cannabidiol

CBD can be delivered via different routes including orally, via inhalation, vaporisation and topically.

Oral delivery has been assessed in humans and absorption can be erratic resulting in a variable pharmacokinetic profile. Bioavailability is estimated to average 6% due to significant first-pass effect metabolism and is rapidly distributed into tissues, due to its high lipophilicity is preferentially absorbed in adipose tissue[18].

CBD has been shown to interact with other drugs and this is further discussed in the safety and adverse section of this report.

Dose range for therapeutic use

It has been reported that similarly to cannabinoids, CBD produces a biphasic response with variable and even opposing effects at different doses of CBD[1]. High doses of CBD have been observed to increase sleep duration whilst low doses (15 mg) appear to have alerting properties[2]. The Israeli clinical guide for medical grade cannabis[3] also notes this biphasic response and provides that in the immune system potentially high doses may correlate with an inhibitory effect whilst low doses may result in the stimulation of immune system processes.

Some studies have claimed that cannabidiol may possess a U-shaped effect, such that very low or very high doses are more effective than medium doses[1]. We set out to determine if a low dose can be determined from the literature search results.

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.

The summarised clinical literature was reviewed to determine broad dose ranges currently utilised. The dose ranges were stratified and classified as high to low and their use for each dose range tier determined. The clinical studies reviewed were conducted in various locations and the average BMI and weight of subjects varied according to location. As dose is closely related to weight, to make the data from clinical trials more widely interpretable and applicable, dose is often reported in mg/kg/day. Where the dose in the literature is reported as mg/day it was converted to mg/kg/day using the global average body mass of 62 kg[4] (adult), the same conversion method is used to convert back to mg/day (where required) from mg/kg/day. Thus, a dose of 1mg/kg/day is equivalent to 62 mg/day and 50 mg/kg/day is equivalent to 3100 mg/day.

The results of the dose stratification are provided below.

High dose range (10 to ~up to 50 mg/kg/day)

Cannabidiol is being investigated in a wide range of clinical conditions. Treatment of refractory epilepsy is the most studied condition with dosages of 10 mg/kg/day to 20 mg/kg/day being successfully utilised predominantly in children and young adults, with the occasional use of a very high dose of 50 mg/kg day[5]. Studies in schizophrenia, bipolar disorder, Huntington's disease at what would be considered a high dose also have mixed results in terms of efficacy outcomes[20,21,22].

Medium dose range (1 to ~10 mg/kg/day)

Studies pertaining to the management of symptoms associated with Parkinson's disease consist of both controlled trials and case studies in dose ranges of 1.25 to 7 mg/kg/day[22]. A dose of 5 mg/kg/day has been used in graft-vs-host disease and cannabis dependence[5].

Low dose range (Less than or equal to 1 mg/kg/day)

1 mg/kg/day or less has been used in anxiety and insomnia secondary to post traumatic stress disorder (25 to 40 mg/day) in a child of 10 years of age[6] and in adults[7] (mainly 25 mg/day, some 50 and 75 mg/day). CBD in doses of 1 mg/kg/day or less has also been utilised both locally and systemically in chronic pain of different aetiologies. In chronic refractory pain or defects of neurological function[8] (22.5 mg/day, 0.4 mg/kg/day) and pain related to systemic sclerosis skin ulcers[9] (10 mg orally (Systemic), 2 mg locally, 0.2 mg/kg/day).

Low dose cannabidiol (10mg per day) was safe but not effective in the treatment of Crohn's Disease in a randomised controlled trial[1].

Cannabidiol thus has been proposed to have a wide dose range for possible therapeutic use from less than 1 to 50 mg/kg/day[5]. In the literature, cannabidiol in the range of 150 to 600 mg/day (~2.5 to 10 mg/kg/day (adult)) has been classified as 'high dose'[10,2] with a dose of 15 mg/day (~0.2mg/kg/day) being classified as low dose[2].

Recommended low dose range – up to 60mg/day based on a dose of 1 mg/kg/day

From the above analysis, a dose of less than or equal to **1 mg/kg/day** (≤62 mg/day (adult) or ~60 mg) is determined to be low dose. To be suitable for down scheduling to a non-prescription schedule (schedule 3 or schedule 2), low dose CBD should have minimal crossover with conditions which require medical supervision (S4). CBD should have an accepted safety profile for an over the counter medicine, including minimal drug-drug interactions and to treat conditions that are considered to be suitable for a pharmacist to manage.

As noted above, a dose range of 150 mg to 600 mg (or above 2 mg/kg/day) is classified in the clinical literature as high dose and is typically used in conditions such as epilepsy that require medical supervision. Cannabidiol in less than or equal to 1 mg/kg/day (up to ~60 mg/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 recommended daily dose is based on weight and therefore is limited to evidence about the safety profile for low dose CBD in in essentially an adult population (that is people of at least 60kg).

There is limited evidence about the use of low dose CBD (single case study) in children and therefore evidence for and knowledge of the safety of CBD in children is extremely limited. Consideration should be given to whether when considering down scheduling that low dose CBD, i.e. 60mg/day should be limited to management of conditions in adults (i.e. those over 18 years of age).

Safety and adverse events

The most commonly reported side effects associated with the use of CBD were tiredness, diarrhoea, changes in appetite /weight, transaminase elevations, sedation, sleep disturbances, infection and anaemia. Additionally, catalepsy was not found to be induced and physiological parameters such as heart rate, blood pressure and body temperature were not altered, and psychological and psychomotor functions not adversely affected[11,12,13].

Bergamaschi et al has reported that adverse events typically displayed a general dose-response relationship[14]. However, whilst several meta-analyses on the safety and adverse effects of clinical use of cannabidiol exist[14]; they largely cover the higher dose ranges of 2 mg/kg/day and above. 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). Hence, relevant large case series and small-scale case studies along with phase I clinical data in healthy volunteers was assessed to ascertain the safety profile of the lower dose range.

Dose related transaminase elevation and hepatic injury was reported for 10 and 20 mg/kg/day (620 to 1240 mg (adult)) dose of cannabidiol[14]. Hepatic injury or abnormal liver function tests were not observed at the lower dose range of 60 mg/daily (i.e. 1mg/kg/day) and below[1,6,7,8,9].

A single dose pharmacokinetic study of oral cannabidiol **10 mg**, **100 mg** and a combination of 10.8 mg THC with 10 mg CBD in healthy volunteers reported that overall, all formulations were considered safe and tolerable. No adverse events were considered serious, and none resulted in withdrawal of a subject from the trial. Headache was the most frequently reported adverse event

(14%– 21%). All adverse events resolved spontaneously without sequel. No clinically significant abnormalities in vital signs, ECG recordings, physical findings or safety laboratory tests were noted[15].

In a case study utilising approximately **40 mg** of cannabidiol per day over 5 months in the treatment of paediatric anxiety and insomnia in a single patient, no side effects were observed from taking the CBD oil. The investigators routinely monitored for headache, fatigue, and change in appetite or agitation in addition to conducting a routine psychiatric evaluation and no adverse effects were reported[6].

A case series of 72 adults on the use of low dose CBD to manage anxiety and sleep, which utilised mainly **25 mg**/day of cannabidiol (maximum duration 3 months, with a handful of patients receiving 50 mg/day or 75 mg/day); CBD was reported to be well tolerated with few patients reporting side effects[7]. Two patients discontinued treatment due to fatigue, three reported sedation (which abated in the first few weeks) and one patient with a developmental disorder (aged 21 years) was taken off the CBD regimen because of increased sexually inappropriate behaviour. However, dose relation was difficult to ascertain, as the authors did not report the specific doses for these subjects.

A study which looked at placebo, THC:CBD and CBD spray in the treatment of chronic pain in 34 patients (12 weeks duration) found that while CBD alone was not as effective as THC:CBD in managing pain this difference was not marked. In the study, a dose of **22.5 mg** of CBD was used. Reported adverse events were mild drowsiness and mouth dryness. Rates of daily occurrence of dysphoria/euphoria and drowsiness were lower in users of CBD alone[8].

In a study of Crohns disease utilising **20 mg**/daily of cannabidiol (20 subjects, 8 weeks duration) the Haemoglobin, albumin, kidney, and liver function tests remained unchanged. No side effects were observed. Patients did not report withdrawal symptoms on treatment cessation and the authors reported the tolerability and safety profile to be excellent[1].

A dose of approximately **12.5 mg** of cannabidiol daily was used to treat the pain of systemic sclerosis skin ulcers (10 mg systemically and an additional 2 mg applied locally during debridement of the ulcer). The safety of CBD was evaluated by examining the patient's records for evidence of side effects. Vital signs and laboratory parameter variations were monitored at each weekly medication. No reported significant side effects were reported with CBD oil[9].

The review by Brown and Winterstein found that CBD and its primary active metabolite 7-hydroxyCBD had similar reported effects on a number of CYP450 enzymes[15]. The range of potential medicines that could be affected was wide ranging including immunosuppressants, antidepressants, opioids, statins, fungal treatments, antiepileptics, cimetidine and sartans. The review also found that risks of adverse events occurring depended on exposure and that while inhibitory actions or drug transport and pharmacodynamics interactions would be immediate in most cases, inductive effects require prolonged exposure (such as greater than 21 days). Therefore, some adverse effects such as somnolence, insomnia and sleep disturbances are likely to occur with sporadic and acute exposure, other effects such as liver function test abnormalities and weight loss would require prolonged exposure. They also observed that adverse effects appeared to be dose dependent but not necessarily proportional to dose.

Iffland and Grotenhermen[12] undertook an update to the review performed by Bergamaschi et al in 2011 on CBD safety and side effects. They describe that in general the previously described favourable safety profile of CBD use in humans was confirmed and that CBD did not lead to serious adverse effects. The main use of CBD was in the treatment of epilepsy and psychotic disorders. The most commonly reported side effects were tiredness, diarrhoea and changes of appetite/weight. They noted that further study was needed on the action of CBD on hepatic enzymes, drug transporters and interactions with other drugs.

Drug interactions

CBD has been reported to show potent inhibitory activity against drug metabolising enzymes CYP2C, CYP2D6 and CYP3A[16] and has also been reported to affect drug excretion through the drug transporter p-glycoprotein. Thus, the potential for drug-drug interactions with other commonly used medications is high[14,23,24].

A study looking at the interaction between CBD and clonazepam, a CYP2C19 substrate in 25 children with refractory epilepsy found that when administered together it resulted in a greater a 60 to 500% increase in mean plasma levels of clonazepam and its metabolite after 4 weeks. Therefore, it is expected that other drugs metabolised through the CYP pathways may interact with CBD[18].

This CYP mediated drug-drug interaction has been observed at clinically relevant doses in an open label safety study[17] investigating interactions of CBD with commonly used antiepileptic drugs. Where administration of CBD was initiated at 5 mg/kg/day and increased at 5 mg/kg/day every two weeks to a maximum of 50 mg/kg/day and co-administered with common anti-epileptic drugs, increases in topiramate, rufinamide, and N-desmethylclobazam and decreases in clobazam serum levels were seen with increasing CBD dose. While abnormal liver function (AST/ALT levels significantly higher) were noted in participants taking concomitant valproate, the same effect was not found with the concomitant use of other epileptics[19]. In four of the 14 children in the study taking concomitant valproate treatment, both CBD and valproate was discontinued due to liver function tests increasing to greater than three times the upper level of normal. Treatment with valproate only was discontinued in one of 8 adults where their liver function increased to two times the upper level of normal.

In animal studies (rats and mice) the inhibitory effect of CBD on drug metabolising enzymes have been observed for both chronic low dose and high dose[15], presenting similar potential for drug-drug interaction at low doses as well. As there is little published data in relation to the investigation of drug-drug interaction at the lower CBD dose range of 60 mg/day or below, the observation in rats and mice remains unconfirmed and uncertain in humans.

Therefore, whilst CBD has been reported to be well tolerated with minimal adverse effects at the low dose range of 60 mg daily and below, the potential for drug-drug interactions should be a consideration for the scheduling of the substance for therapeutic use and the designation of the required level of medical supervision.

Other matters for consideration

Optical Isomers (Enantiomers)

Cannabidiol is a chiral compound. Only the (-) CBD enantiomer is present in the Cannabis plants. Consequently, plant derived cannabidiol is present only as (-) CBD and has low affinity for the CB1 and CB2 receptors, and thus is not psychoactive. Synthetic cannabidiol has the potential to be a racemic mixture, the non-psychoactive (-) CBD or the alternative (+) CBD enantiomer. (+) CBD and its derivatives have been reported to bind to both CB1 and CB2 receptors, displaying selectivity towards CB1[18,24] and is therefore likely to be psychoactive and present different pharmacological activity. Therefore, the use of synthetic CBD may have psychoactive potential that would not be found in plant-derived cannabidiol. This should be considered in any decision to down-schedule CBD.

Entourage effect

Some researchers have claimed that the endocannabinoid system demonstrates an ‘entourage effect’, whereby ‘inactive’ metabolites and closely related molecules increased the activity of the

endogenous cannabinoids, however the existence of an entourage effect remains disputed[19]. Some studies have also suggested that the presence of THC and other cannabinoids in varying ratios, affects the efficacy in different clinical settings.

Formulation

Most of the clinical literature reviewed was in relation to oral route of administration and solution dosage form (oral solution). Noting that aerosolised CBD has been reported to yield rapid peak plasma concentrations in 5-10 minutes and ~31% bioavailability, bioavailability from oral delivery was estimated to be 6% due to significant first-pass metabolism.

Bioavailability from oral mucosal and sublingual routes are considered similar to oral delivery, as they are both subject to the first pass effect and hepatic metabolism. There is potential for further enhancement of absorption and plasma concentrations from oral delivery through optimisation of drug formulation[8].

There is scope for further clinical investigation of CBD administration via the other routes of administration and dosage forms in addition to optimised oral delivery. Vast differences in bioavailability based on dosage forms and route of administration is feasible.

Conclusion

Doses in the range of 1 mg/kg/day (**up to ~60 mg/day**) and less may have possible clinical utility when used via the oral route in the management of some conditions that do not require medical practitioner oversight and thus could be considered for down scheduling.

Given that the safety profile is based on cannabidiol having low affinity for the CB1 and CB2 receptors, and thus is not exhibiting psychoactive effects, down scheduling should be limited to plant derived CBD as it is present only as (-) CBD or synthetic cannabidiol only containing the (-) CBD enantiomer.

At low doses, CBD appears to have an acceptable safety and tolerability profile, although it was evident that there is a high potential for drug-drug interactions when used concomitantly with many other commonly prescribed drugs that are metabolised via CYP pathways. Currently there is insufficient evidence as to whether these would not occur with the use of low dose CBD.

Whilst there are some minor signals of adverse effects such as mild drowsiness and fatigue, this could be managed as for similar S3 medicines, such as requiring a label that indicates should not use if driving or operating machinery as for other medicines that can cause potential drowsiness. Schedule 3 requires that both Product Information and Consumer Medicine Information is available. These documents could include information about drug-drug interactions. In addition, a S3 medicine requires interaction with a pharmacist that would further reduce any unintended drug-drug interactions.

The consideration of down scheduling of low dose CBD should only apply to adults (people over 18 years of age), as low dose is defined as 60mg/day based on a dose of 1mg/kg/day. At this stage there is little evidence of use in children and therefore of its safety profile in this group. Therefore, down scheduling should also consider the person's age and therefore S3 provides the best mechanism to ensure appropriate and safe use. A dose of 60mg/day would not be suitable in children, as a child of 20 kg given a 60mg dose per day would be receiving 3mg/kg per day.

The recommended low dose range for consideration of down scheduling to Schedule 3 is up to a **maximum of 60 mg/day** and use in adults over the age of 18 years for plant derived CBD or synthetic CBD, which only contains the (-), CBD enantiomer**.**

Appendix A

Search strategy

The objective was to identify a broad base of clinical and chemistry literature, which could answer the following questions:

- What dose range of cannabidiol is currently being used in clinical practice?
- Is there a low dose? What is the low dose?
- What are the differences between the herbal extract and synthetic cannabidiol?
- What is the overall clinical safety profile of low dose cannabidiol?

Assistance was sought from the TGA library. The following literature search in relation to cannabidiol was requested:

- Last five years
- Synthetic pathways: extractions and chemical synthesis and chemical characterisation with impurity profile and related substances.
- Clinical trials of cannabidiol (all clinical use)
- Dose ranging studies
- Reported adverse events, investigation of adverse events, case reports

The following search terms were used to search the OVID database:

1. exp cannabidiol derivative/ or exp cannabidiol/ (4325)
2. cannabidiol.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (4924)
3. 1 or 2 (4924)
4. exp drug therapy/ (2694500)
5. exp drug dose/ (640306)
6. 4 or 5 (2734399)
7. exp adverse drug reaction/ (514633)
8. exp adverse drug reaction/co, dt, si [Complication, Drug Therapy, Side Effect] (222685)
9. major clinical study/ or exp drug contraindication/ or drug safety/ (3905058)
10. exp drug toxicity/si [Side Effect] (2562)
11. 7 or 8 or 9 or 10 (4247370)
12. exp drug contamination/an [Drug Analysis] (22)
13. exp drug analysis/ (388126)
14. exp drug comparison/ (128930)
15. exp drug concentration/ (290941)

16. exp drug development/ (93022)
17. exp drug administration/ (1184001)
18. drug absorption/ (81563)
19. 12 or 13 or 14 or 15 or 16 or 17 or 18 (1851501)
20. exp drug bioavailability/ (63800)
21. exp drug metabolism/ (180654)
22. drug delivery system/ or exp drug structure/ (352666)
23. exp drug synthesis/ or drug delivery system/ (373855)
24. synthetic pathways.mp. (1069)
25. chemical synthesis.mp. or exp synthesis/ (610346)
26. physical chemistry/ or controlled study/ or chemical composition/ (7188130)
27. 20 or 21 or 22 or 23 or 24 or 25 or 26 (7951305)
28. 3 and 6 and 11 and 19 and 27 (62)
29. from 28 keep 1-62 (62)

The search was restricted to the last five years and conducted on 18 December 2019. A total of 150 citations were obtained (Embase and Medline). The titles and abstracts were reviewed to determine relevancy. Articles were excluded from further review based on the following characteristics: literature on cannabis alone, cannabidiol of purity less than 95%, mix of cannabinoids (such as THC and CBD) without the purified cannabidiol as a comparator and non-clinical (animal or molecular) studies. The remaining articles were reviewed in full and those found to be relevant to the enquiry included.

The following data was extracted from the included articles and analysed: The study type and design, population, the dose, form and characterisation of the CBD investigated, the duration, adverse events and efficacy.

Once broad dose ranges were determined, the primary search results were supplemented with additional (secondary) searches for low dose cannabidiol of 25 mg daily or less (Library) and in google scholar for: ‘cannabidiol phase I in healthy volunteers’.

Appendix B

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