Scheduling Evaluation Report

BRIEF DESCRIPTION OF SCHEDULING PROPOSAL

This report responds to a submission to amend the Schedule 4 listing of Cannabidiol in preparations for therapeutic use to

(a) remove from Schedule 4 Cannabidiol preparations comprised of 98% or more Cannabidiol with < 0.2%Tetrahydrocannibinol and
(b) to include in Schedule 4 products where synthetic or semi-synthetic Cannabidiol comprises a minimum of 98%, and other cannabinoids of 2% or less may be synthetic or semi-synthetic cannabinoids

[Applicant]

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1. EXECUTIVE SUMMARY

Cannabidiol products for therapeutic use with greater than 98% cannabidiol and less than 2% tetrahydrocannabinol are currently regulated in Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

There is enthusiasm from consumers for greater availability of products containing Cannabidiol.

Cannabidiol has low toxicity. Adverse events are common and include drowsiness, fatigue, diarrhoea and vomiting. Drug interactions are possible.

There is a paucity of evidence for many of the indications for Cannabidiol for which there is public demand, particularly in pain, anxiety and sleep. These conditions have effective non-pharmacological and pharmacological treatments.

Amending of the Schedule for Cannabidiol products for therapeutic use with greater than 98% cannabidiol and less than 0.2% delta-9-tetrahydrocannabinol could be considered, with inclusion of these products in Schedule 3.

2. PURPOSE OF APPLICATION

Regulatory background issues

Currently in Australia, cannabis related products for therapeutic use are regulated under Schedule 8 or Schedule 4 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).(1) A cannabis related medicine is listed in Schedule 8 except when it contains 98% or more of Cannabidiol, and 2% or less of naturally occurring cannabinoids, when it is listed in Schedule 4.

In 2018, the World Health Organisation Expert Committee on Drug Dependence recommended that products consisting of pure Cannabidiol should not be scheduled under the 1961 or 1971 Conventions.(2)

Globally, there is increasing easy availability of a number of Cannabidiol containing products from a variety of outlets.

In Australia there is public pressure for increased access to Cannabidiol.

Current entries in SUSMP

The current entry for CANNABIDIOL in Schedule 4 is:

CANNABIDIOL in preparations for therapeutic use 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.

The current entry for CANNABIS in schedule 8 is:

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.

Proposed changes

CANNABIDIOL in preparations for therapeutic use where:

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

b) cannabidiol is a synthetic or semi-synthetic copy of the molecule and comprises 98 per cent or more of the total cannabinoid content of the preparation; and any other synthetic or semi-synthetic cannabinoids, other than cannabidiol, must comprise 2 per cent or less of the total cannabinoid content of the preparation;

except when cannabidiol comprises 98 per cent or more of the total cannabinoid content and the tetrahydrocannabinol (THC) content is less than or equal to 0.2 per cent of the total cannabinoid content of the preparation.

Proposed new wording of Schedule 8 entry in relation to cannabis:

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

iv) it is a whole plant cannabis product or distillate or isolate which contains at least 98 per cent cannabidiol and less than or equal to 0.2 per cent tetrahydrocannabinol (THC)

3. SUBSTANCE

Pharmacology

CANNABIDIOL

Cannabidiol is one of the major naturally occurring cannabinoids found in the cannabis plant.

CAS Registry number: 13956-29-1

IUPAC Name: 2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol

It has a molecular weight 314.5 g/mol, and chemical formula of $C_{21}H_{30}O_2$.(3)

Cannabidiol is lipid soluble and is often delivered with lipid vehicle when administered orally. When taken orally, it has poor bioavailability of around 6%, with a time to maximum concentration up to 4 hours. When inhaled, bioavailability increases to 31% and the time to maximum concentration is 5-10 minutes. The volume of distribution is large at 32 l/kg, and there is probable redistribution to fat. Cannabidiol is metabolised by enzymes of the CYP450 family. A wide range of elimination half-lives (1-32 hours) are reported which may reflect redistribution. (4, 5)

The pharmacodynamic actions of cannabidiol are complex, and it acts at multiple receptor subtypes. Unlike delta-9-Tetrahydrocannibol (9THC), it does not activate the CB1 or CB2 receptor, and is not psychoactive. (6, 7) Cannabidiol blocks adenosine re-uptake, is an agonist at 5HT1A and TRPV1 receptors, an antagonist at the orphan GPR55, and may be a negative allosteric modulator at the CB1 receptor.(7) As an allosteric modulator, action at any one time may be dependent of the state of activation of the biological system.

The naturally occurring stereoisomer is (-)Cannabidiol.(8) Cannabidiol is typically understood to, and in this document will unless explicitly stated, describe the properties of the naturally occurring (-) stereoisomer. There are some differences in pharmacology between naturally occurring (-)Cannabidiol and synthetic (+)Cannabidiol. Of particular relevance to this application is that (+)cannabidiol has much higher affinity for both the CB1 and CB2 receptor than (-)Cannabidiol.(9)

SYNTHETIC CANNABINOIDS

The term synthetic cannabinoids encompasses a wide array of substances, including nabilone, dronabinol, and many other substances such as AB-CHMINACA, MDMB-FUBINACA, JWH-398 and CP 47,497. Many of the synthetic cannabinoids have high affinity for the CB1 receptor with prolonged half-lives. By December 2016, 169 synthetic cannabinoids had been notified to the European Monitoring Centre for Drugs and Drug

Addiction.(10) Given the multitude of substances that are classified as synthetic cannabinoids, a comprehensive summary of their pharmacology will not be provided.

4. EVALUATION

Substance characteristics in relation to the Scheduling Factors[1]

Cannabidiol

Cannabidiol has for the most part limited toxicity. While it is pro-apoptotic (promotes programmed cell death) in cancer cell lines, this is not seen in non-transformed cells. It has no effect on embryonic development. High concentrations of CBD may alter sex hormone synthesis in rats. In healthy humans, small studies suggest changes in cortisol response to stress, but no effect on Growth Hormone or Prolactin. Cannabidiol has no effect on blood pressure or heart rate in animal and human studies. It may stimulate the immune system at low dose but be immune-suppressive at higher dose. Psychological and psychomotor performance is not affected in humans by Cannabidiol.(6, 11)

In clinical studies, Cannabidiol has been trialled in doses up to 1500mg. Adverse events have been most systematically studied in trials in epilepsy and are common. The majority of adverse events in these trials were not mild. Adverse events experienced include diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting. (12-14). Significant elevations in liver transaminases were seen, predominantly in participants taking valproate.(12, 13)

A number of drug-drug interactions with the anti-epileptic drugs topiramate, rufinamide, clobazam, zonisamide and eslicarbazepine have been identified as a result of CYP 450 inhibition.(15)

There is a reasonable body of data supporting Cannabidiol in seizures in Dravets and Lennox-Gastaut Syndromes with a reduction in seizures.(12, 14) One small trial in Parkinson's Disease showed improved Quality of Life with 300mg Cannabidiol, but no improvement in motor function and no neuroprotective effect.(16) In a small cohort study of 6 patients with Parkinson's Disease treated with Cannabidiol in doses ranging from 150mg to 600mg, there was some improvement in psychotic symptoms.(17) A recent meta-analysis identified minimal benefit of Cannabidiol in schizophrenia.(18) Doses trialled ranged from 600mg to 1000mg.(19) A phase 2 trial of 300mg of Cannabidiol daily for 37 days showed some benefit in reducing Graft Versus Host Disease (GVHD) after bone marrow transplant.(20)

Other emerging areas of potential therapeutic benefit include anxiety, depression, Post Traumatic Stress Disorder (PTSD) and pain. However, the recent meta-analysis in mental

[1]Scheduling Policy Framework https://www.tga.gov.au/publication/scheduling-handbook-guidance-amending-poisons-standard

health problems identified a lack of evidence in anxiety, depression or PTSD.(18) The evidence for efficacy of Cannabidiol as a sole agent in pain is similarly lacking.(21) Many studies are confounded by the use of products containing high ratios of 9THC to Cannabidiol.

Animal models show that Cannabidiol has low abuse liability. Human data has not thus far identified significant abuse potential or misuse. There are no published reports of Cannabidiol abuse or dependence.(2)

There is no requirement for specialist training or personal protective equipment to handle cannabidiol.

Preclinical data identify potential for Cannabidiol to have therapeutic efficacy in multiple different disease states including epilepsy, Parkinson's Disease, cancer, neurodegenerative disorders, psychosis, immunomodulation, nausea and vomiting, anxiety, depression, pain, sleep and glaucoma.(6, 7) With the exception of some seizure disorders, therapeutic benefit of cannabidiol has not been substantively demonstrated in clinical trials. Nonetheless, there is much interest from the general public in having cannabidiol products available.

SUBSTANCE CHARACTERISTICS IN RELATION TO THE SCHEDULING FACTORS FOR SCHEDULE 2, 3 AND 4

SCHEDULE 4 FACTORS

1. **The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention[1].**
   Diagnosis, management or monitoring of the medical condition is such that it requires medical, veterinary or dental intervention before the substance is used.

   Chronic pain and anxiety are generally thought to result from neuroplasticity and disruption of cell signalling, and not inflammation as suggested in the applicant's submission.(22, 23) The first important step in diagnosis in pain includes exclusion of sinister pathology such as cancer or spinal cord compression.(24) Optimal management of chronic pain is through active self-management strategies using exercise and psychological techniques. Judicious use of medicines to facilitate this require medical oversight and co-ordination.(25) Optimal management of chronic insomnia is similarly focussed on non-pharmacological strategies.(26) Assessment of anxiety includes exclusion of underlying physical health disorders such as hyperthyroidism, exclusion of mood disorders and diagnosis of the anxiety disorder.(27) These disorders are not managed optimally by use of over the counter medication, and require medical assessment for management.

2. **The use of the substance requires adjunctive therapy or evaluation or specialised handling for administration.**

Adjunctive therapy could include other medicines, non-pharmacological measures, or specialised medicine delivery devices. Evaluation could include laboratory tests or additional clinical assessments.
For human medicines, a requirement for administration by injection will usually mean medical or dental supervision is required because of the additional risks and complexity of this route of administration.

Optimal therapies of pain, anxiety and insomnia are the adjunctive treatments of psychology for all conditions and exercise for sleep and pain.(25-27) Antidepressants and anti-epileptic drugs may be considered in anxiety(27) and pain.(28)

3. **The use of the substance at established therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use. Control of access and duration of therapy by a medical, veterinary or dental practitioner is required.**

   There is minimal potential for misuse and dependence.

4. **The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical, veterinary or dental practitioner is required to minimise the risk of using the substance.**

   Most of the systematic study of adverse events related to cannabidiol has been undertaken in trials for epilepsy. In one RCT, 93% in the cannabidiol group experienced adverse events of which 75% were deemed to be related to CBD. The placebo group experienced much lower rates of adverse events (75%) of which only 36% were related to the trial intervention.(13) In the extension study of this trial, adverse events occurred in 93.2% of participants of which only 36.7% were mild and 39% moderate. Adverse events experienced were diarrhea (34.5%), pyrexia (27.3%), decreased appetite (25.4%), and somnolence (24.6%). 17.2% (all taking valproate) had significant liver transaminase elevations.(14)

5. **The margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical, veterinary or dental intervention to minimise the risk of using the substance.**

   Cannabidiol has a wide therapeutic index.

6. **The seriousness or severity and frequency of the interactions of the substance (medicine-medicine, medicine-food, or medicine-disease) are such that monitoring or intervention is required by a medical, veterinary or dental practitioner.**

Cannabidiol is a potent inhibitor of multiple CYP isozymes including CYP3A4 and CYP 2D6. (11, 29, 30) Antidepressants commonly used in anxiety and pain can alter CYP 450 activity.(31) Many of these medicines are also metabolised by CYP 450 isozymes.(32) There has been no formal assessment of drug interactions in people using these very commonly prescribed medications and Cannabidiol. Thus far, drug interactions have only been systematically studied in people using anti-epileptic drugs. Oversight from a pharmacist or medical practitioner is required to assess for drug interactions.

7. **The use of the substance has contributed to, or is likely to contribute to, communal harm.**
   For example, the development of resistant strains of microorganisms. Appropriate use, and/or the decision to continue treatment, requires evaluation by a medical, veterinary or dental practitioner.

   This is not an issue for Cannabidiol.

8. **The experience of the use of the substance under normal clinical conditions is limited.**
   Unexpected effects of the substance may only become evident after widespread use. Close monitoring of the patient is required by a medical, veterinary or dental practitioner to monitor for unanticipated effects.

   The experience of the use of the substance although widespread has for the most part not had clinical oversight. This is made more complex as multiple products, modes of delivery and products with varying amounts of 9THC are used.

SCHEDULE 3 FACTORS

1. **The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine. There may be potential for harm if used inappropriately.**

   The consumer can identify the ailments or symptoms that may be treated by the medicine but counselling and verification by a pharmacist is required before use. Consumer consultation with a pharmacist is necessary to reinforce and/or expand on aspects of the safe use of the medicine.

   Chronic pain and anxiety are complex problems, often with complex medication regimens. Critical aspects of management are ensuring an adequate diagnostic workup to exclude sinister pathology.(24, 27)

   There is a potential for complex drug interaction and side effects (see above). (14, 29, 30) There is limited data on long term use.

2. **The use of the medicine is not expected to produce dependency at either the established therapeutic dose or at supratherapeutic doses. Where risk of misuse,**

abuse or illicit use is identified, the risk can be minimised through pharmacist-consumer consultation.

The use of the medicine is not expected to produce dependency or misuse.

3. **The risk profile of the medicine is well defined and the risk factors for adverse effects, interactions and contraindications are known, identifiable and manageable by a pharmacist.**

   Side effects of Cannabidiol have been well described in patients with epilepsy.(12-14) The risk factors for drug interactions (drugs metabolised by or affecting CYP 450 function) are known, identifiable and manageable by a pharmacist. (11, 29, 30)

4. **Where the medicine is intended for recurrent or subsequent treatment of a chronic condition, pharmacist intervention is required to monitor safe use of the medicine following recommendation by a medical practitioner or other authorised prescriber. The consumer may not be able to self-monitor the safe ongoing use of the medicine. The condition does not require medical diagnosis or only requires initial medical diagnosis, and the consumer does not require close medical management.**

   Given the limited long-term safety data, and potential for drug interactions, ongoing pharmacist intervention is required to ensure safe use of the medicine.

5. **The use of the medicine at established therapeutic dosage levels may mask the symptoms or delay diagnosis of a serious condition.**
   Pharmacist-consumer consultation is required to detect the risk of masking a serious disease or compromising medical management of a disease, and to deal with it appropriately.

   With both chronic pain and anxiety, pharmacist intervention is required to detect the risk of masking a serious disease and to detect drug interactions which could compromise medical management of a disease. There are no robust data around established therapeutic dosing in pain, anxiety and insomnia.

SCHEDULE 2 FACTORS

1. **The quality use of the medicine can be achieved by labelling, packaging, and/or provision of other information; however, access to advice from a pharmacist should be available to maximise the safe use of the medicine.**
   The medicine is for minor ailments or symptoms that can easily be recognised and are unlikely to be confused by the consumer with other more serious diseases or conditions. Treatment can be managed by the consumer without the need for medical intervention. However, the availability of a pharmacist at the point of sale supports the consumer in selecting and using the appropriate medicine.

Anxiety and chronic pain are not minor ailments and are associated with significant morbidity and mortality. Red flags in pain must be excluded.(24) Other physical or psychiatric diagnoses must be excluded in anxiety.(27) They require medical intervention for assessment and optimising management.

2. **The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low.**
   Suitable for diagnosis and treatment by the consumer in the management of minor ailments
   In general, chronic pain and anxiety are not minor, short term illnesses. They are complex multifactorial, long term problems. It is likely that Cannabidiol use in these conditions would not be short term.

3. **The use of the medicine is very unlikely to produce dependency (at either the established therapeutic dose or supratherapeutic doses) and the medicine is very unlikely to be misused, abused or illicitly used.**
   Medicines which do not meet this factor are not suitable to be classified as Schedule 2 Pharmacy Medicines, irrespective of any other applicable factors.

   The use of the medicine is not expected to produce dependency or misuse.

4. **The risk profile of the medicine is well defined, and the risks can be identified and managed by a consumer through appropriate packaging and labelling, including consultation with a health professional if directed by labelling.**
   There is a low and well-characterised incidence of adverse effects; interactions with commonly used substances or food and contra-indications.

   Adverse events in epilepsy trials are frequent, but in other conditions are poorly characterised. (12-14). There is a risk for significant drug interactions with antidepressants that has not been well characterised. (11, 29, 30) These risks are best addressed with pharmacist review.

5. **The use of the medicine at established therapeutic dosage levels is not likely to mask the symptoms or delay diagnosis of a serious condition.**

   There are no established therapeutic doses for the likely most common indications of pain anxiety and insomnia. Is important in both pain and anxiety to ensure adequate assessment for other significant pathologies or disease states.

Synthetic cannabinoids

The term synthetic cannabinoids covers a wide array of substances, including nabilone, dronabinol, and many other substances such as AB-CHMINACA, MDMB-FUBINACA, JWH-398 and CP 47,497. Many of the synthetic cannabinoids have high affinity for the

CB1 receptor with prolonged half-lives.(10) A number of these moieties are highly toxic (33, 34) and a number are regulated as poisons or drugs of dependence.(35, 36) Dronabinol and nabilone are listed in Schedule 8 of the SUSMP.(1)

Considerations under section 52E of the Therapeutics Goods Act 1989

CANNABIDIOL

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

Risks

The risks associated with Cannabidiol use include side effects of diarrhea, somnolence, pyrexia, vomiting and fatigue. Abnormal liver function tests, particularly when using valproate can occur.(12, 14) Drug interactions as a result of CYP 450 inhibition may also be seen.(15)

The most common reasons for use of Cannabidiol include anxiety, pain depression and sleep. There is a need for exclusion of significant and/or sinister pathologies in these conditions.

Benefits

Despite extensive pre-clinical data, the clinical data supporting the use of cannabidiol in conditions other than epilepsy is very limited. Trials have small numbers, short follow up, and are often retrospective or cross sectional case series.(37, 38) They can be confounded by the co-administration of 9-THC with Cannabidiol and the use of Cannabidiol as smoked herbal cannabis. For example, in autism, two studies identify benefit of Cannabidiol, but in both studies substantial amounts of THC were co-administered with cannabidiol (1:20 ratio of THC to Cannabidiol).(39, 40) In the Australian regulatory framework, this product with 4.7% 9-THC would list in Schedule 8.

Fitzcharles identifies cautious hope for Cannabidiol in pain but identifies the data as currently insufficient.(21) Despite promising experimental data(41), Black et al identify insufficient evidence to guide treatment of mental disorders, including depression and anxiety.(18)

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

Surveys of Cannabidiol users indicate that the most common reasons for use are pain, anxiety, depression and sleep.(38, 42) It is likely that similar patterns of use would be seen if there was increased access to Cannabidiol in Australia.

Figure 4 of the applicants submission indicates the most frequent reasons for which prescriptions of Cannabidiol are sought in Australia in descending order are chronic pain (56%), anxiety (22%), epilepsy (4%), neuropathic pain (3%), autism spectrum disorder (4%), and cancer pain and symptom management (2%).

It is likely that if Cannabidiol were more freely available in Australia, there would be quite widespread use.

(c) the toxicity and safety of a substance

Cannabidiol has, for the most part, limited toxicity. While it is pro-apoptotic in cancer cell lines, this is not seen in non-transformed cells. It has no effect on embryonic development. High concentrations of CBD may alter sex hormone synthesis in rats. In healthy humans, small studies suggest changes in cortisol response to stress, but no effect on Growth Hormone or Prolactin. Cannabidiol has no effect on blood pressure or heart rate in animal and human studies. It may stimulate the immune system at low dose but be immune-suppressive at higher dose. Psychological and psychomotor performance is not affected in humans by Cannabidiol.(6, 11) Safety in pregnancy or breastfeeding is not established.

In clinical studies, Cannabidiol is frequently associated with adverse events including diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting. Abnormal liver function tests may occur particularly when co-administered with valproate.(12, 14)

A number of drug-drug interactions with the anti-epileptic drugs topiramate, rufinamide, clobazam, zonisamide and eslicarbazepine have been identified as a result of CYP 450 inhibition.(15)

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

In the majority of reviewed studies, Cannabidiol is taken orally as an oral liquid or capsule.(19) A wide range of Cannabidiol doses have been investigated in humans, with daily doses ranging from 10mg to 1500mg.(19, 41)

There is a reasonable body of data for efficacy of Cannabidiol in epilepsy in doses ranging up to 50mg/kg.(19) Single doses of 15mg-600mg have been used safely in experimental models of anxiety.(41, 43) A retrospective case series investigated doses ranging from 25-75mg daily for up to 12 weeks in sleep and anxiety with some benefit. (37) CBD at doses up to 22.5mg was tolerated in a study in mixed pain.(44) Gulbransen et al. describe improvements in pain, anxiety, mood and sleep from prescribed Cannabidiol in doses ranging from 40-300mg daily. There was no dose response, and the medication was well tolerated in the prescribed doses, although 5% of patients reported drowsiness and 5% reported vivid dreams. The methodology of this audit is unclear.(38)

As there is some evidence of benefit in anxiety in repeat dosing of 25-75mg daily, a maximum daily dose of 75mg Cannabidiol could be considered for a Schedule amendment.

Interactions due to CPY 450 enzyme inhibition are recognised. Important potential interactions with other drugs metabolised by CYP 450 can be identified and managed by a pharmacist. This can be re-inforced with Consumer Medicines Information (CMI) included in the packaging.

Epilepsy, GVHD Parkinsons and psychosis are complex diseases with complex management. Care for these conditions, including consideration of Cannabidiol, should be provided with medical oversight. In other conditions where cannabidiol benefit is less evident, such as anxiety, depression and chronic pain, other effective therapies (both pharmacological and non-pharmacological) are available. Pharmacological management of these conditions is often with sedating medications. Pharmacy oversight is warranted to ensure adequacy of assessment of the condition and management with other treatment modalities.

Labelling should identify drowsiness as a potential problem with appropriate advice on not driving if affected and potential interactions with other drugs or alcohol.

(e) the potential for abuse of a substance

There is currently no evidence in animal or human studies that Cannabidiol has abuse potential, and no published reports in humans of misuse or dependence.(2)

(f) any other matters considered necessary to protect public health

The efficacy and safety data of Cannabidiol described above relates to the (-)isomer, Synthetic Cannabidiol may contain the + stereoisomer. (+)CBD has a different pharmacological profile to (-)CBD.(7)

SYNTHETIC CANNABINOIDS

Synthetic cannabinoids are a diverse range of substances, with diverse and serious harms. (10, 33, 34) and a number are regulated as poisons or drugs of dependence.(35, 36)

Any application to include synthetic cannabinoids in Schedule 4 should specify the cannabinoid, and an assessment of the specific cannabinoid should be undertaken.

5. CONCLUSIONS

There is significant consumer demand for Cannabidiol containing products. In the US, UK and Europe, there is increasing availability of Cannabidiol products from a variety of commercial outlets. The most common reasons cited for use of these products are chronic pain, sleep, depression and anxiety. While animal and preclinical data suggest benefit in these conditions, Cannabidiol has not been rigorously trialled for these conditions. One retrospective study has indicated benefit of Cannabidiol in doses between 25mg and 75mg daily in anxiety and sleep. Safety data indicate that Cannabidiol is generally safe, but side effects are common. There is a potential for drug interactions due to CYP 450 inhibition.

In interrogating the scheduling factors with cannabidiol, the Schedule could be amended to allow low doses of 98% Cannabidiol with less than 0.2% THC to be exempted from Schedule 4 and to be regulated through Schedule 3. The risks of cannabidiol do not conform to the requirements for Schedule 2 listing. These risks include adverse events and complex drug interactions. The largely speculative nature of much of the data on Cannabidiol efficacy in the conditions for which it is most used (chronic pain, sleep anxiety and depression) also argue against listing in Schedule 2.

As some benefit in anxiety has been demonstrated with Cannabidiol doses between 25mg and 75mg, daily doses in a Schedule 3 product should not exceed 75mg. This should be for use in adults who are not pregnant or breastfeeding. Labelling should identify the risk of drowsiness and give direction on driving or operating machinery if affected. CMI should be included to re-inforce the pharmacist discussion about drug interactions.

The need for pharmacist oversight, labelling and CMI to ensure safe and appropriate use precludes Cannabidiol preparations being made available on a schedule less restrictive than Schedule 3.

Synthetic cannabinoids generically should not be included in Schedule 4 of the SUSMP. Any proposed change in schedule for use of synthetic cannabinoids should include a clear and specific definition of the cannabinoid, and in the case of Cannabidiol, the stereo-isomer should be identified.

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