

Security classification: In-Confidence

File number: PP05-08-0
Action required by: Routine

External Consultation on Guidelines to Assess Applications for Ministerial Approval to Prescribe Cannabis-based Products

To: Hon Peter Dunne, Associate Minister of Health

Copy to: Hon Dr Jonathan Coleman, Minister of Health

1. Purpose

As requested by you the Ministry of Health has consulted with external stakeholders on the guidelines used to support decisions on applications for Ministerial approval to import, prescribe and administer cannabis-based products. This paper outlines the key themes from the consultation and seeks your agreement to amend the guidelines.

2. Key points

Prescribers with experience in applying for approval to prescribe cannabis-based products consider the process sound and do not find the guidelines or the application process a barrier.

The recommended amendments to the guidelines are the previously proposed removal of the guidance that a patient is hospitalised when treatment with a non-pharmaceutical grade cannabis product is initiated and the word *all* from the guideline that reasonably applicable treatments have been trialled.

The requirement in the guidelines for specialist input and peer review was seen by some stakeholders as a useful mechanism. It is particularly helpful when prescribers are faced with a patient/family who consider that they have a right to access cannabis-based products before the full range of conventional, evidence-based medications are trialled.

The primary barriers to prescribing of cannabis-based products are the lack of efficacy data to support their clinical use, the cost of pharmaceutical grade products and the lack of products available.

Even where early efficacy data for cannabis-based medicine is positive, its use is not creating widespread excitement amongst specialists. This is because for many patients the level of improvement from a cannabis-based product is similar to that achieved via other newer pharmaceutical treatments.

Prescribers believe that if cannabis is being used as a medicine the same criteria should be used in determining whether to prescribe as is used as for any other medicine. Clinicians want to know what the active ingredients are, what form and dosage is most effective, its interaction with other medicines and, most importantly, that there is some evidence of efficacy for its use in a particular patient.

Persons who self-administer cannabis based on their own knowledge or beliefs are not using cannabis within a medical framework and are outside the legal framework for controlled drugs and prescription medicines.

Social and media reports on cannabis and cannabis-based medicines tends to be misleading and can be highly emotive, but these reports are sometimes given greater credence by patients and their carers than a prescriber's clinical qualifications and experience.

Prescribers were concerned that social and media reporting encouraged the incorrect belief that cannabis, in particular cannabidiol (CBD), is natural and therefore safe (i.e. has no side effects or interactions with other medicines).

The availability of information and professional development for prescribers on cannabis-based products tends to correlate with the level of prescribing by the different specialities.

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Recommendations

The Ministry recommends that you:

- a) **Agree** to the proposed amended guidelines to assess applications to prescribe non-pharmaceutical grade controlled drugs regulated by Regulation 22 of the Misuse of Drugs Regulations 1977 (Appendix 1). Yes No
- b) **Agree** the guidelines to assess applications for Ministerial approval to prescribe pharmaceutical grade controlled drugs with or without consent for distribution in New Zealand are not amended at this time, except for formatting changes and additional guidance to aid readability of the guidelines (Appendix 2). Yes No

[Signature removed]

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**Acting Director
Protection, Regulation and Assurance**

**Minister's signature:
Date:**

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External Consultation on Guidelines

1. In March 2016 the Ministry completed an internal review of the guidelines used to support decisions on applications for Ministerial approval to import, prescribe and administer cannabis-based products under Regulation 22 of the Misuse of Drugs Regulations 1977. As a result of the review the Ministry recommended removing the guidance that a patient is hospitalised when treatment with a non-pharmaceutical grade cannabis-based product is initiated.
2. You then requested that the Ministry undertake external consultation with clinicians who have experience with prescribing these products and with the New Zealand Medical Association (NZMA) to gain wider input on how the guidelines are working in practice. The Ministry was also asked to obtain information on the level of prescriber education and professional awareness of cannabis-based products.

Consultation process

3. Prescribers and organisations who have either prescribed cannabis-based products or represent services where use of cannabis-based products is, or has potential to be beneficial, were contacted. The initial list of stakeholders was provided by your office. With your office's agreement this list was supplemented by the Ministry and referrals from stakeholders identified. A total of ten persons (listed in Appendix 3) provided input. The stakeholders covered a range of specialties including, neurology (paediatric and adult), palliative care (paediatric and adult) and pain medicine.
4. The consultations were undertaken by teleconference or by face to face meetings with Ministry staff from the Medicines Control and Policy teams. Some prescribers did not take part in a meeting but provided information verbally or by email and this is also incorporated into the report.
5. Five prescribers consulted had made at least one application to prescribe Sativex in New Zealand and two of the prescribers were also involved in the successful applications for non-pharmaceutical grade cannabis-based products.

Application process and the guidelines used to assess applications

6. Feedback was unanimous that the current guidelines and process are sound. The guidelines were considered to balance patient autonomy with physician professionalism while protecting the vulnerable.
7. The three categories of products within the guidelines are retained:
 - i. Pharmaceutical grade products with consent for distribution in New Zealand.
 - ii. Pharmaceutical grade products without consent for distribution in New Zealand.
 - iii. Non-pharmaceutical grade products.
8. No amendments are recommended to the guidelines to assess applications for Ministerial approval (currently delegated to the Ministry of Health) to prescribe pharmaceutical grade controlled drug products with or without consent for distribution in New Zealand. Formatting changes and additional guidance have been applied to aid readability of the guidelines (Appendix 2).
9. Removal of the guideline requiring the patient to be hospitalised when treatment is initiated with a non-pharmaceutical grade cannabis-based product was suggested. This was a recommendation of the internal review of the guidelines provided to you on 4 April 2016.
10. Other changes suggested are the removal of the word "all" from guideline b) which currently requires "all reasonably applicable treatments to have been trialled". If interpreted literally this could be overly onerous for the prescriber and the patient. The guidelines are also re-ordered to make the flow more logical and modifications made to the examples of what would constitute adequate peer review to allow for non-hospitalised patients. The proposed revised guidelines for non-pharmaceutical grade products requiring Ministerial approval are provided as Appendix 1.

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11. It was stated that a robust application process requiring peer review provides support for prescribers from over-zealous patients or care-givers. Some patients or care givers consider that they have a right to trial cannabis-based products. Instead of following conventional, evidence-based medicines they request a trial of cannabis-based products after, at times, as few as two conventional medicines have failed to fully control the condition.
12. Starship paediatric neurologists would like the specialist endorsement requirement for Sativex to remain (most paediatric neurology applications are associated with Starship). Several prescribers noted that the type of patients being treated with cannabis-based products, predominantly patients with neurological syndromes or undergoing palliative care, are on multiple medications and very susceptible to drug interactions and adverse effects. It was commented that most GPs struggle with the management of patients with complex medication regimens (i.e., more than three medications), particularly those on multiple anti-convulsants.
13. Those with experience in making applications were satisfied with the time taken to process applications. They did not find the application process onerous and it was commented that they were used to filling in forms. It was noted that, except in the rare circumstances, such as status epilepticus or terminal cancer, cannabis is not an emergency medicine. The current average turnaround for applications to prescribe cannabis-based products is 13 working days; conditions requiring more rapid responses are prioritised.

Use of cannabis-based products in clinical practice in New Zealand

14. Consistent feedback was that cannabis-based products should be treated in the same way as other medicines, in particular, evidenced based principles should be followed. The principles of good quality medicines and prescribing should not be undermined by one product or group of products. The preferred pathway is the use of pharmaceutical grade products. Products without consent for distribution in New Zealand should be treated consistently with other unapproved medicines and other controlled drugs.
15. A prescriber needs to be clear about:
 - (i) the purpose for using the product
 - (ii) what the product is – what it contains, at what strength and the quality of the manufacture
 - (iii) the dose and frequency of dose
 - (iv) how the constituents work and the interactions with other medicines
 - (v) the monitoring process that is in place.
16. A paediatric neurologist has only one of her four Sativex patients continuing on the medicine principally because it has not been found to be effective. She considers that this may be because the dose of cannabidiol (CBD) is not able to be titrated up sufficiently high due to the adverse effects that start to be experienced due to the THC component. Data suggests that CBD alone may be moderately effective in childhood epilepsy but this is not creating that much excitement as the level of improvement in seizures found (30-40%) was similar to that found from some of the other newer anti-convulsants. There is no evidence to suggest that CBD will become a first line treatment for seizures and no one has become seizure free on cannabis-based products.
17. An adult neurologist stated that cannabis-based products are rarely prescribed in adult epilepsy.
18. A paediatric palliative care specialist stated that from a purely clinical perspective, he had not had to consider using a cannabis-based product for symptom control in a child with either a cancer or non-cancer condition. The major reason for this is that there are pharmaceutical and non-medicinal treatment options available that have provided satisfactory control.
19. In adult palliative care cannabis-based products may be useful in some cases to stimulate appetite, reduce nausea and reduce anxiety. The usefulness for cancer pain is more for its “dissociative” effects rather than as an analgesic, that is, it makes the pain matter less. The use of substances for their dissociative or euphoric effects is a subject of medical debate but is not new. Morphine, when

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prescribed above its analgesic dose, has this effect; benzodiazepines can be used for a similar purpose. There is no evidence of efficacy in chronic non-malignant pain.

20. The use of cannabis by people with terminal illnesses is widespread however it is a misconception to describe this as a medicinal use. It is not being prescribed by a medical practitioner following the normal guidelines for prescribing and following an evidence-based approach. A prescriber would not prescribe opium resin instead of morphine; similarly they will not prescribe raw or partially processed cannabis bud and leaf. As one prescriber stated, the cannabis conversation with his patients is currently one-way; the patient telling the doctor what they are taking.
21. No one consulted was strongly opposed to the use of cannabis-based products. All considered that it may have some clinical benefits, but for most prescribers cannabis-based products were stated to be a fourth or fifth line treatment at best and, as there are virtually no products currently available, it is not an area of significant interest.

Funding and access barriers to use of cannabis-based products

22. Cost is the primary barrier to treatment with cannabis-based products once it has been determined that a trial is appropriate for a particular patient. Prescribers reported that PHARMAC has declined all applications for funding even for patients where Sativex has clearly provided significant clinical benefit.
23. Availability of pharmaceutical grade products, particularly CBD only products for childhood epilepsy, is a further barrier and it was suggested that any new pharmaceutical grade products, such as Epidiolex, were also likely to be expensive.
24. The lack of products and the cost of the only pharmaceutical grade product available in New Zealand results in cannabis-based products not having a high priority for prescribers even in branches of medicine where there is some evidence that they may have therapeutic benefit. This can mean that their knowledge base is not high because there is little need to know. There are conventional, more affordable products available that have established efficacy.
25. The NZMA stated that many prescribers are quite nervous and cautious about cannabis and question what is allowed under the law. Prescribers need to be comfortable with their prescribing decisions and they are wary of activists encouraging patients to lobby them.

End of life access schemes

26. Any proposed scheme to allow patients at the end of their life to self-administer non-pharmaceutical grade cannabis products, prior to the availability of pharmaceutical grade products with demonstrated evidence of efficacy, sits outside the health legislative framework. This is because the products would not be prescribed by a clinician, there is no efficacy basis for their use and variable information on the quality and active components of products.
27. It is noted that the New South Wales Government (NSW) terminal access scheme is administered by the NSW Department of Justice. It is a scheme that allows the NSW police to use their discretion not to charge adults with terminal illnesses who use cannabis to alleviate their symptoms.
28. A terminal access scheme is not recommended by the Ministry due to the lack of a legal mechanism to obtain the product. The palliative care prescribers consulted advise that the Government should wait for properly conducted clinical trials to produce results and follow the evidence.

Public perception of cannabis/Media reporting/Social media

29. One prescriber considered that the standard of media and social reporting is a public health issue. She considered that people in the community are genuinely interested, but the reporting in the press is biased and highly emotive. This creates an element of conflict and a difficult dynamic in the patient-prescriber relationship.
30. The medical profession had anticipated pressure to prescribe resulting from social media hype. This is coming to fruition with cannabis. For some patients the views expressed in social media are considered to be of more value than prescriber's clinical qualifications and experience.

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31. Common misconceptions that should be de-bunked are:

(i) Cannabis is natural thus it is safe.

- Cannabis is biologically active and works at the level of receptors in the body and like any substance that may produce beneficial effects, it also has adverse effects.
- Up to 70% of paediatric neurology patients, experience adverse effects. These effects include nausea, diarrhoea and stomach cramps. The potential for mental health issues and psychosis in children and adolescents also needs to be considered if cannabis is to be used long term.
- Raw cannabis is such a mixture of substances that adverse effects cannot be accurately anticipated or dismissed. One in 10 adults become addicted to cannabis and there is an increased risk of motor vehicle accidents, particularly if taken in combination with alcohol or other drugs.

(ii) CBD can just be dropped in and out of a patient's medication profile.

- CBD inhibits the metabolism of some other drugs. It is often being advocated for complex patients on a number of other medications. CBD's impact on other medications needs to be recognised and managed.

(iii) Cannabis is a wonder drug.

- Most of the medicinal efficacy promoted for cannabis by non-scientific internet sites and social media is not backed by scientific research. Even those conditions for which there is some evidence of efficacy, cannabinoids may not be any better than standard therapies.

Doctor education/guidelines

32. The availability and interest in professional development and guidelines relating to cannabis varied depending on the area of medicine in which the respondents practised. It was stated that you could not go to an epilepsy seminar without some discussion of cannabis-based products. It was considered that the New Zealand knowledge base was very much in keeping with international research. However the use of cannabis-based products in the palliative care field is not an area of high interest and is not on the agenda for an upcoming palliative care conference.
33. Starship has further formalised their peer review process of applications to prescribe cannabis-based products by establishing a panel in which two to three peers assess an application before it is submitted for approval.
34. Many organisations have produced guidelines on the use of cannabis-based products. Those noted are listed in Appendix 4.

END.

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Appendix 1

Proposed amended guidelines to assess applications for Ministerial approval to prescribe non-pharmaceutical grade controlled drug products

Ministerial approval to prescribe a controlled drug product covered by Regulation 22 of the Misuse of Drugs Regulations 1977 has not been delegated to Ministry of Health officials.

The following matters are taken into account when assessing applications for Ministerial approval to prescribe non-pharmaceutical grade controlled drug products regulated by Regulation 22 of the Misuse of Drugs Regulations 1977:

- a) severe or life-threatening condition
- b) evidence that reasonably applicable conventional treatments have been trialled and the symptoms are still poorly controlled
- c) evidence that the risk/ benefit of the product has been adequately considered by qualified clinical specialists – that is, the risk of treatment with an unproven product is less than the risk of non-treatment and account has been taken of any evidence of potential benefit and weighed against known adverse effects
- d) application from a specialist appropriate to the medical condition being treated or the Chief Medical Officer of a District Health Board
- e) applicant or specialist prescriber has sought adequate peer review e.g., Hospital Ethics Committee approval, Drug or Therapeutics Committee review, review by other specialists in the condition being treated and/or specialist colleagues involved in the treatment of the patient
- f) provision of a Certificate of Analysis, preferably from an accredited laboratory, so that the concentration of the active ingredient(s) is known
- g) patient or guardian has provided informed consent.

Products that are not pharmaceutical grade or not pharmaceutically prepared will not be approved for use in clinical trials.

The guidelines to assess applications to prescribe a non-pharmaceutical grade cannabis-based product are more rigorous than the guidelines to prescribe pharmaceutical grade products with or without consent for distribution in New Zealand. This reflects the lack of authoritative quality and safety data and the lack of robust efficacy data for these products.

The use of a non-pharmaceutical grade product will not contribute meaningful data to the pool of scientific research on the safety and efficacy of cannabis-based products in the condition being treated. This is due to the inability to replicate the results (due to variation in the strength and composition of the product) and the inability to generalise results from a single patient to a broad patient group.

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Appendix 2

Guidelines to assess applications for Ministerial approval to prescribe pharmaceutical grade controlled drug products with consent for distribution in New Zealand

The following matters are taken into account when assessing applications for Ministerial approval to prescribe pharmaceutical grade controlled drug products with consent for distribution in New Zealand (for both approved and unapproved conditions), regulated by Regulation 22 of the Misuse of Drugs Regulations 1977:

- a) Application from an appropriate specialist, usually in conjunction with a general practitioner
- b) Evidence that there will be close follow up of patient by a prescriber
- c) Evidence that a wide range of conventional treatments have been trialled and symptoms are still poorly controlled
- d) Condition is an approved condition for use (for Sativex[®] this is multiple sclerosis), *or*
- e) Condition is one for which there is some evidence of efficacy, preferably in clinical trials, for example for Sativex[®]:
 - i. chronic pain
 - ii. neuropathic pain
 - iii. cancer pain
- f) Ministry clinicians assess application is appropriate if for other non-approved use, for example the use of Sativex[®] for intractable childhood epilepsy
- g) No history of abuse or diversion of controlled drugs
- h) The patient has no known contraindication to the use of the product
- i) Initial approvals usually for six months
- j) Baseline clinical indicators generally required and evidence of improvement before a new approval is given.

Guidelines to assess applications for Ministerial approval to prescribe pharmaceutical grade controlled drug products without consent for distribution in New Zealand

The following matters are taken into account when assessing applications for Ministerial approval to prescribe pharmaceutical grade controlled drug products without consent for distribution in New Zealand, regulated by Regulation 22 of the Misuse of Drugs Regulations 1977:

- a) Application from an appropriate specialist
- b) A manufacturer has demonstrated a commitment to the development of the product as a pharmaceutical *or*
- c) The product has been prepared pharmaceutically and the characteristics and formulation are clearly described and defined
- d) The product has completed animal studies demonstrating proof of concept and potential clinical benefit
- e) The product is undergoing an appropriately designed Phase II clinical study *or*
- f) The product has completed clinical trials and is marketed overseas but is not approved for distribution in New Zealand
- g) The product is available for use

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h) The following are met where relevant:

- i. Evidence that there will be close follow up of patient by a prescriber
- ii. Evidence that a wide range of conventional treatments have been trialled and symptoms are still poorly controlled
- iii. Condition is an approved condition for use, *or*
- iv. Condition is one for which there is some evidence of efficacy, preferably in clinical trials
- v. Ministry clinicians assess application is appropriate if for non-approved use
- vi. No history of abuse or diversion of controlled drugs
- vii. The patient has no known contraindication to the use of the product
- viii. Initial approvals usually for six months
- ix. Baseline clinical indicators generally required and evidence of improvement before a new approval is given.

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Appendix 3

Persons consulted

Russell Wills, Children's Commissioner.

Professor Edward (Ted) Shipton, Dean and Fellow of the Australian and New Zealand Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists, Medical Director of pain specialists at Burwood Hospital.

Lesley Clarke, CE New Zealand Medical Association (NZMA) and **Dr Stephen (Steve) Child**, Chair of NZMA and a respiratory specialist with an interest in education and training.

Dr Rupert Bird, Psychiatrist, Bay of Plenty DHB.

Dr Claire Spooner, Paediatric Neurologist, Starship Children's Health.

Dr Ian Rosemergy, Adult Neurologist at Capital & Coast DHB.

Dr Ross Drake, paediatric palliative care physician at Starship..

Professor Rod McLeod, senior staff specialist palliative care, HammondCare, Sydney and conjoint Professor in Palliative Care at the University of Sydney. Professor McLeod was nominated by Hospice NZ and works in Sydney and New Zealand.

Dr Brian Ensor, Director Palliative Care, Mary Potter Hospice & Clinical Advisor, Hospice NZ.

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Appendix 4

Guidelines provided by the specialists and organisations consulted

- Australia and New Zealand College of Anaesthetists, Faculty of Pain Management Statement on Medicinal Cannabis with particular reference to its use in the management of patients with chronic non-cancer pain, version April 2015.
- Royal Australian College of Surgeons Position Paper on the Use of Cannabis for Medicinal Purposes, issue date June 2013.
- American Academy of Neurology, Position Statement: Use of Medical Marijuana for Neurological Disorders (undated).
- Epilepsy Society of Australia, Marijuana and its derivatives in the treatment of epilepsy (undated).
- NZMA Position Statement on Cannabis Use, revised July 2012.