



Medicinal cannabinoids: current regulations for prescribing

Recent amendments have been made to regulations concerning the prescription of some medicinal cannabis products. For primary care, these changes will have minimal impact as there is presently only one approved product available for prescription for use in some patients with multiple sclerosis, and no products that are subsidised. This is, however, an emerging area of interest and new products are being developed internationally. Primary care health professionals may find it useful to be aware of the requirements around prescribing medicinal cannabinoids and to review the evidence of effectiveness of these products.

People have been using cannabis for recreational or medical purposes for centuries. Over the last few decades there has been increasing scientific interest in identifying the active ingredients in cannabis and their pharmacological effects, and developing these into medicines. Public interest in the medical use of products derived from cannabis has recently heightened in New Zealand after a number of highly publicised cases of people applying for access to cannabis products for treating conditions such as severe epilepsy, multiple sclerosis and chronic pain. Furthermore, in September, 2017 new amendments came into effect which exempted cannabidiol, a non-psychoactive component of cannabis, from the requirements of the Misuse of Drugs Regulations.¹ This was followed by the introduction of a bill to Parliament in December, 2017, proposing a statutory defence for the use and possession of cannabis by terminally ill people and removal of cannabidiol from the Misuse of Drugs Act.

As a result of this increased attention, clinicians in primary care in New Zealand are likely to field questions from patients about the use of cannabis products* for medical purposes.

* This article discusses the prescription of cannabinoid-based products, and not cannabis itself (i.e. unprocessed or partially processed plant material). For further information, see: "Botanical cannabis for medical use"

Categories of medicinal cannabinoid products and prescribing regulations

The Ministry of Health defines four categories of cannabinoid products:

1. Cannabidiol (CBD) products –

- Cannabinoid content comprises \geq 98% CBD (a non-psychoactive component of cannabis – see terminology), and contains no other controlled drug or psychoactive substance
- No products currently approved by Medsafe in New Zealand
- There is one unapproved product currently available in New Zealand in two strengths
- CBD products can be prescribed in the same way as other unapproved prescription medicines, for a three-month period
- No additional Ministry of Health approval is required

The following classifications refer to products that do not meet the requirements of a CBD product

2. Pharmaceutical grade cannabinoid products that are approved in New Zealand –

- Medsafe has assessed the product and determined that it meets acceptable safety and efficacy requirements
- Sativex, approved for the treatment of multiple sclerosis symptoms, is the only product that currently meets these requirements in New Zealand

- Sativex can be prescribed for patients with multiple sclerosis who meet certain criteria (see below), for a one-month period; no additional approval is required
- Sativex may be prescribed for other patients as an unapproved use, upon application to the Ministry of Health (see below)


- If other cannabis products become approved in New Zealand, prescribing requirements are likely to be determined on a case-by-case basis

3. Pharmaceutical grade cannabinoid products that are not approved in New Zealand –

- Such as a product manufactured by a pharmaceutical company overseas
- The manufacturer has not applied for approval in New Zealand (or application is pending)
- An application must be made to the Ministry of Health for approval to prescribe

4. Non-pharmaceutical grade cannabinoid products –

- Not manufactured to internationally recognised pharmaceutical standards
- Such as a product manufactured by a company outside of the pharmaceutical industry
- An application must be made to the Ministry of Health for approval to prescribe

 A flowchart to assist prescribers is available from: www.health.govt.nz/system/files/documents/pages/summary-of-approvals-required-to-prescribe-cannabis-based-products.pdf

Terminology of cannabis

The plant *Cannabis sativa* contains approximately 100 chemical compounds, known as cannabinoids.² **Tetrahydrocannabinol (THC)** and **cannabidiol (CBD)** are the most recognised and studied of these. **THC** is the key psychoactive ingredient responsible for the “high” associated with use of cannabis.² **CBD** does not produce a high; it is thought to block the effects of THC and may suppress pain and nausea.³ Cannabis also contains other components, such as volatile terpenes, but there is little evidence regarding what effects these, or the remaining cannabinoids, have in the body.

The term “**medicinal cannabis**” refers to all forms of cannabis used to treat a medical condition or symptoms.

This includes unprocessed, or partially processed, plant material and products derived from natural or synthetic components of cannabis (usually cannabinoids).

For the purposes of this article, products manufactured from components of cannabis will be referred to as “**cannabinoid products**” and the cannabis plant itself as “**botanical cannabis**”.

Marijuana is an alternative name for cannabis when it is used as a psychoactive substance; it usually refers to the dried, crushed flowers and leaves.² Other colloquial names include: pot, dope and weed. **Hashish**, or hash, usually refers to the resin derived from the cannabis plant.

CBD products: no approval required to prescribe


Regulations introduced on 7 September, 2017 exempted CBD products from previous restrictions under the Misuse of Drugs Regulations.¹ This means that clinicians can now prescribe cannabinoid products in which the cannabinoid content comprises $\geq 98\%$ CBD, in the same way they prescribe other medicines, for up to three months supply. A controlled drug form (triplicate form) is no longer required for prescription and CBD products do not have to be included in controlled drug records.⁴


There are currently no CBD products approved for use in New Zealand, but there is one unapproved product available (unsubsidised) – it is an oral liquid in an oil base, available in two strengths. If a practitioner wishes to prescribe an unapproved medicine, they should consider the evidence and clinical experience of use and weigh up the risks and benefits, as well as gain informed consent from the patient. Pharmacies that are requested to dispense a prescription for a CBD product that is available in New Zealand can order it from the wholesaler. Medical practitioners and pharmacies may also import CBD products from other countries, without an import licence.⁴


CBD products are an emerging area

To meet the definition, a CBD product must have a cannabinoid content of at least 98% CBD. The remaining cannabinoid content (up to 2%) may include THC, but no non-cannabinoid psychoactive substances or controlled drugs can be contained in the medicine. There are currently few CBD products in development internationally that meet these standards. Products are still being assessed in clinical trials to evaluate their potential for the treatment of a variety of conditions, including anxiety, schizophrenia and refractory forms of epilepsy.^{2,5,6}

There are numerous CBD-type products manufactured to less stringent standards. Analyses of these products have found that their composition varies widely and the concentration of CBD and THC reported on labelling is often not accurate.^{7,8}

 For further information about prescribing CBD products, see: www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/cbd-products

 For further information on importing medicines, see: www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/bringing-medicines-new-zealand


 For further information on prescribing unapproved medicines, see: www.bpac.org.nz/bpj/2013/march/unapproved-medicines.aspx

Prescribing approved cannabinoid products: Sativex is currently the only option

Sativex is the only cannabinoid product approved by Medsafe in New Zealand. It has an approved indication as an add-on treatment for improving symptoms in patients with moderate to severe spasticity associated with multiple sclerosis; other uses are not approved. Sativex is available on prescription, unsubsidised, as an oral spray. It contains both THC and CBD.⁹

Sativex can be prescribed for its approved indication without an application to the Ministry of Health.^[9] Prescriptions must state the condition being treated (multiple sclerosis) and be endorsed by a neurologist.

An application can be made to the Ministry of Health to prescribe Sativex for an unapproved use for patients with other medical conditions.⁹ Patients need to have first trialled, or have contraindications to, approved medicines typically used for the treatment of their condition. The application needs to be endorsed by a relevant specialist to the condition being treated.

 An application form for unapproved use of Sativex is available from: www.medsafe.govt.nz/profs/riss/SativexForm2.doc

Prescribing unapproved cannabinoid products: apply to the Ministry of Health

Clinicians can apply to the Ministry of Health for approval to prescribe unapproved cannabinoid products which do not meet the definition of CBD products. There are separate application forms and criteria for prescribing pharmaceutical grade and non-pharmaceutical grade products.

To prescribe an unapproved cannabinoid product, the patient must have had an adequate trial of all available conventional treatments for their condition, at appropriate doses and duration, and these treatments have not provided benefit, are not tolerated or are contraindicated. The nature of an unapproved product, including a reasonable estimate of its benefits and risks, must be explained to the patient, and informed consent gained.

Applications must be endorsed by a relevant specialist, e.g. a neurologist for the treatment of a patient with epilepsy. Applications require supporting information, including evidence regarding the potential beneficial effects of the product for the treatment of the condition in question and known adverse effects, and a plan for how the treatment will be administered and withdrawn if the patient experiences adverse effects or does not sufficiently benefit from the product. Once an application has been approved, information will be provided on how to obtain the product. Applications for products that are not available in New Zealand or cannot be imported legally will not be approved.

Summary of prescribing categories for cannabinoid products:

Category of product	Availability in New Zealand (as of February, 2018)*	How to prescribe
CBD ≥ 98%	No approved products One unapproved product	On standard prescription form
Pharmaceutical grade product approved for use in New Zealand	One approved product for multiple sclerosis: Sativex oral spray	On approved controlled drug prescription form if criteria are met – need to state condition being treated (i.e. multiple sclerosis) and must be endorsed by a neurologist, for further information, see: gazette.govt.nz/notice/id/2016-go6803 For unapproved use, apply to Ministry of Health – www.medsafe.govt.nz/profs/riss/Sativexform2.doc
Pharmaceutical grade product not approved for use in New Zealand	No products available [†]	Apply to Ministry of Health; must be endorsed by relevant specialist, have already trialled conventional medicines, and include a treatment protocol.
Non-pharmaceutical grade product not approved for use in New Zealand	One unapproved product [†]	Once approval has been granted, prescribe on an approved controlled drug prescription form. Pharmaceutical-grade product application form: www.health.govt.nz/system/files/documents/pages/cannabis-based-product-application-form-pharm-grade-19-05-2016.doc Non-pharmaceutical-grade product application form: www.health.govt.nz/system/files/documents/pages/cannabis-based-product-application-non-pharm-grade-19-05-2016.doc

* New products may become available after the publication of this article. Unapproved products cannot be referred to by brand name in this article as their availability cannot be legally advertised.


† It is anticipated that the non-pharmaceutical grade product currently available in New Zealand will be reclassified as a pharmaceutical grade product upon the arrival of new stock

Travelling with cannabis

The Misuse of Drugs Act 1975 regulations allow people arriving in New Zealand to bring up to one month's supply of a controlled drug, as long as they have been lawfully supplied in the country of origin for the purpose of treating their medical condition. Cannabis-based products supplied in the United States are not considered lawfully supplied under federal legislation and cannot be carried into New Zealand.¹⁰ Some other countries also have limitations in place restricting people from leaving the country with cannabis-based products.

For further information on bringing medicines into New Zealand, see: www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/bringing-medicines-new-zealand



 Application forms for prescribing unapproved cannabis-products are available from: www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/prescribing-cannabis-based-products

Cannabinoid products have limited evidence of effectiveness for treating medical symptoms

There is a lack of quality evidence available to conclusively assess both the benefits and harms of the use of cannabinoid products for treating medical symptoms.¹¹ A major contributor to this is that there are limited pharmaceutical grade products available for quality clinical trials and observational studies.

The best available evidence suggests that cannabinoid products may provide some improvement in symptoms for patients with:^{11–16}

- Spasticity associated with multiple sclerosis
- Seizures associated with refractory epilepsy, such as patients with Dravet syndrome or Lennox-Gastaut syndrome
- Chronic pain; specifically neuropathic pain, with some preliminary evidence for fibromyalgia and rheumatoid arthritis
- Chemotherapy-induced nausea and vomiting (moderate to low quality evidence)
- Weight gain in HIV infection (low quality evidence)
- Tourette syndrome (low quality evidence)

Cannabinoid products have been used for a wide variety of other medical conditions for which there is insufficient evidence of effectiveness, including depressive disorders, post-traumatic stress disorder, Parkinson's disease, Alzheimer's disease, glaucoma and Crohn's disease.¹⁵

There is less clinical experience of use of cannabinoids in children and adolescents, but a recent systematic review concluded that the evidence of benefit was strongest for use in chemotherapy-induced nausea and vomiting, with some evidence of benefit in epilepsy. The limited studies which are available lack long-term follow up, so the adverse effects associated with the use of cannabinoids in children are unknown.¹⁷

Potential adverse effects of cannabinoid products

Limited evidence suggests that use of a cannabinoid product may result in dizziness, dry mouth, nausea, vomiting, diarrhoea, fatigue, somnolence, euphoria, disorientation, drowsiness, confusion, loss of balance and hallucinations.[12] No studies have evaluated long-term adverse effects. It is not known if the adverse effects associated with botanical cannabis, such as an increased risk of psychosis, also apply to cannabinoid products;


this is likely to be dependent on the particular cannabinoids and other constituents in the product being used.

Potential for interactions between cannabinoid products and conventional medicines

Interactions between cannabis-based products and conventional medicines are possible. Pharmacokinetic studies have shown that CBD is a potent inhibitor of CYP2C, CYP2D6 and CYP3A enzymes.² A recent literature review concluded that THC and CBD are inhibitors of CYP450 enzymes involved in the metabolism of numerous psychotropic medicines.¹⁸ Many other medicines are metabolised through CYP pathways, e.g. anti-epileptic medicines, therefore it is important to monitor for adverse drug interactions and be aware that cannabinoid products may alter the effects of any concurrent medicines.

Cannabinoid products should be considered a “last resort”

Discussing use of a cannabinoid product with a patient is more likely to be focused on the potential risks rather than being able to provide clinical certainty of benefits. Risks include adverse effects of treatment, interactions with conventional medical treatments, risks of using an unapproved and/or non-pharmaceutical grade product and adverse financial consequences of funding the treatment. Trialling a cannabinoid product is only an appropriate course of action for a patient who has ongoing symptoms despite optimal use of all available conventional treatments, or if the patient has contraindications to using those treatments. A plan should be in place for assessing the magnitude of improvement in symptoms from baseline, and monitoring for the development of any adverse effects. The decision to continue treatment should be regularly re-assessed.

 **Patient information** on the use of cannabis-based products is available from: www.healthnavigator.org.nz/medicines/c/cannabis-based-products/

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Botanical cannabis for medical use

Current policy in New Zealand is that applications to prescribe cannabis itself, i.e. as unprocessed or partially processed plant material, will not be approved because the cannabinoid content of unprocessed or partially processed plant material is unknown, as is the levels of potential contaminants such as pesticides and heavy metals. However, smoking cannabis is widely associated with claims of benefit in alleviating symptoms, such as pain, and some countries lawfully allow this use, e.g. the United States and Canada. Primary care clinicians may therefore be asked by patients on their opinion on using botanical cannabis for medicinal purposes.

While bpac^{nz}, or the medical profession in general, does not advocate the use of cannabis, the following points may be helpful in guiding discussion:

- There is no conclusive evidence that smoking cannabis has significant clinical benefits for any medical condition
- Levels of THC and other pharmacologically active components in cannabis vary between strains, meaning that it is difficult to assess the efficacy of cannabis for medical purposes, and it is not possible to standardise a daily dose^{8,19}
- There is reasonable strength evidence that the long-term use of cannabis is associated with an

increased risk of motor vehicle accidents, cannabis hyperemesis syndrome (severe cyclical vomiting) and psychosis, including hallucinations, delusions and cognitive impairment.^{16,20,21} There is also emerging evidence that the use of cannabis is associated with an increased risk of cardiovascular events.²²

- As cannabis is an illegal drug, use is likely to result in adverse social, financial and legal consequences
- Cannabis is not subject to any evaluation or regulation therefore its safety or usefulness as a medical treatment cannot be guaranteed
- Procuring cannabis illegally means that its composition is uncontrolled and different batches may contain varying levels of THC, as well as containing other harmful and/or psychoactive substances
- There are many conventional medicine options, with evidence of efficacy and safety, as well as non-pharmacological treatments, that can be discussed and trialled before resorting to the use of cannabis
- If cannabis is being considered, a pharmaceutical-grade cannabinoid product is preferable as this has a known composition and can be delivered in a standardised dose

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