Cannabis for Medicinal Purposes

An Overview for Healthcare Professionals

SpectrumTherapeutics™

A CANOPY GROWTH COMPANY

This guide provides background information for healthcare professionals (HCPs) who are interested in prescribing medicinal cannabis products. This guide covers the science of cannabinoids and the endocannabinoid system, dosage forms, methods of administration, general prescribing guidance, and safety information about medicinal cannabis. For further information about medicinal cannabis and access in Australia, please visit the Therapeutics Goods Administration (TGA) website on https://www.tga.gov.au or contact medical information on medinfo.au@canopygrowth.com. Spectrum Therapeutics medicinal cannabis products are not included on the Australian Register of Therapeutic Goods (ARTG).

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Spectrum Therapeutics™

Understanding medicinal cannabis has never been simpler

Spectrum Therapeutics, the medical division of Canopy Growth, operates at the forefront of a rapidly evolving medicinal cannabis industry.

With established medicinal cannabis operations around the globe, we maintain the highest standards of production and drive forward research and real world evidence data collection to support understanding and innovation in the field of cannabinoid-based medicine.

Spectrum Therapeutics offer industry-leading accredited education, resources, and support for healthcare professionals.

In Australia, Spectrum Therapeutics is committed to ensuring patients have access to affordable medicinal cannabis in a range of formats to suit their needs. Spectrum Therapeutics is also the Australian distributor for the STORZ & BICKEL Medic range, giving patients access to the only ARTG-included medical vaporisers for use with inhaled medicinal cannabis (ARTG listing: 319028).

Your guide to The Spectrum Framework

The Spectrum Framework is a colour-coding system designed to assist healthcare professionals with medicinal cannabis product selection.

Each colour represents a category of products according to their ratio of Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Depending on the patient's needs, you might recommend a product containing THC, CBD, or a mixture of both.

Red represents products that are THC-dominant with little CBD.

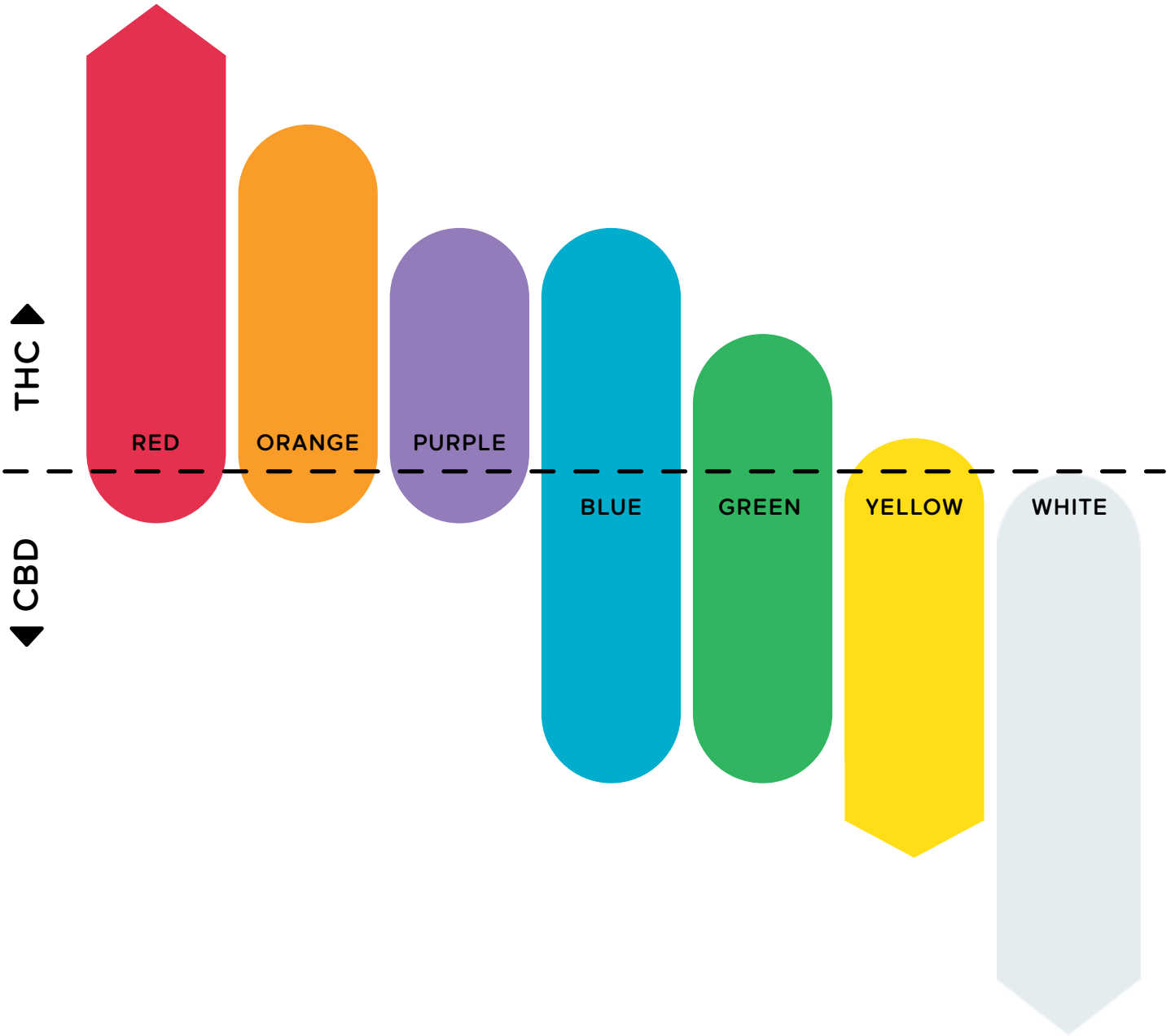
Blue represents products that have a more balanced ratio of THC and CBD.

Yellow represents products that are CBD-dominant with little THC.

White represents products that are high in CBD.

If you would like further information about the Spectrum Therapeutics medicinal cannabis range, please contact Medical Information on medinfo.au@canopygrowth.com or your local Medical Science Liaison.

The Spectrum Framework



Red, Blue, Yellow, and White are the only Spectrum product colours available in Australia.

Cannabis, Cannabinoids, and the Endocannabinoid System

The use of medicinal preparations of cannabis can be traced back over five thousand years, making it one of the oldest medicinal plants.[1]

Cannabis

Cannabis sativa L. contains more than 500 chemical compounds. Bioactive compounds are produced in high concentration in the glandular trichomes, which are hair-like, resin-secreting glands found on the surface of female cannabis flowers.

Cannabinoids

Cannabinoids are bioactive compounds that interact with the body's endogenous cannabinoid system. Based on their origins, cannabinoids can be classified into three groups:

- **Endocannabinoids**, which are naturally produced in the body.
- **Phytocannabinoids,** which are found in many plants, but in highest concentrations in cannabis. There are more than 100 phytocannabinoids found in the cannabis plant.
- **Synthetic cannabinoids,** which include synthetically-produced pharmaceuticals that have the same chemical structure (e.g., dronabinol), or are analogues (e.g., nabilone) of cannabinoids.

Terpenes and flavonoids

Terpenes and flavonoids are natural compounds that are present in many different types of plants, including cannabis. Terpenes are aromatic compounds that give cannabis cultivars their characteristic scents and flavours. Flavonoids are made up of groups of polyphenolic compounds that act as secondary metabolites to a myriad of plants. Flavonoids provide plants with pigmentation and colour and assist terpenes in producing their distinct odour and scents. Terpenes and flavonoids may be present in whole plant extract medicinal cannabis products.

A word about varieties – Indica vs. Sativa

The terms 'indica' and 'sativa' are used in plant taxonomy as subspecies names and refer to the phenotype of the *Cannabis sativa L.* plant. These names are also commonly used by medicinal cannabis patients, though there is disagreement about the validity of these distinctions.

Recent analyses of cannabis varieties have found that, although the genetic makeup of varieties referred to as indica or sativa was moderately correlated to their reported ancestry, the names can be misleading. Even though *C. indica* and *C. sativa* are two distinct species, it would be rare to find a pure indica or sativa variety due to centuries of cross-breeding. Instead, most cannabis varieties today are hybrids, created by crossbreeding two varieties, that may be indica or sativa dominant.

Some individuals believe that sativa varieties tend to be energising and indica more sedating. When a patient asks if a variety is sativa or indica, they may want to know if the product will make them feel energised, and therefore good for daytime use, or sleepy, and therefore more suited to evening use.

Activation of phytocannabinoids

The two major cannabinoids, Δ^9- tetrahydrocannabinol (THC) and cannabidiol (CBD) naturally exist in their acid forms, tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA), in the cannabis plant.

Decarboxylation is a process that removes the carboxyl group of the acidic compounds THCA and CBDA, converting them to their neutral forms, THC and CBD, that interact with endocannabinoid system.[2]

Decarboxylation occurs when dried cannabis flowers are heated, for example, by vaporisation. Most medicinal cannabis ingestible products, such as oils and capsules, already contain heat-activated cannabinoids that provide standardised concentrations and consistent dosing.

Δ^9-Tetrahydrocannabinol (THC)

THC interacts with cannabinoid receptors and may have the following effects[3-5]:

- ❑ analgesic
- ❑ antispasmodic
- ❑ reduces chemotherapy-induced nausea and vomiting
- ❑ stimulates appetite
- ❑ decreases intestinal motility

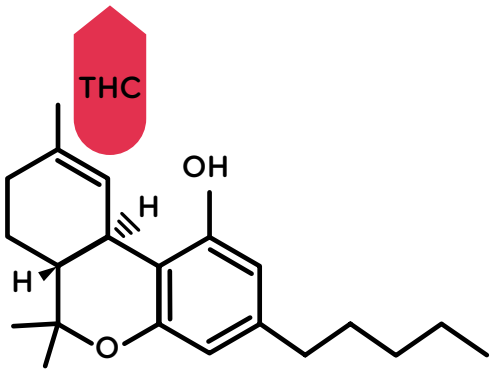
THC also has psychotropic effects, and high concentrations of THC can cause anxiety, disorientation, and intoxication in some patients.

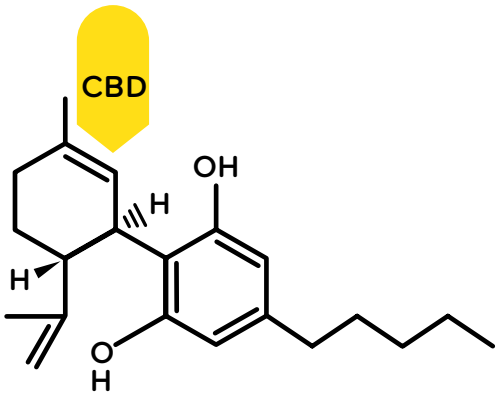
Cannabidiol (CBD)

CBD may have the following effects[5-7]:

- ❑ anti-inflammatory
- ❑ analgesic
- ❑ antiemetic
- ❑ antipsychotic
- ❑ anxiolytic
- ❑ antiseizure

CBD lacks the intoxicating, euphoric effects of THC, although it has potential benefit as a treatment for anxiety disorders.[8]

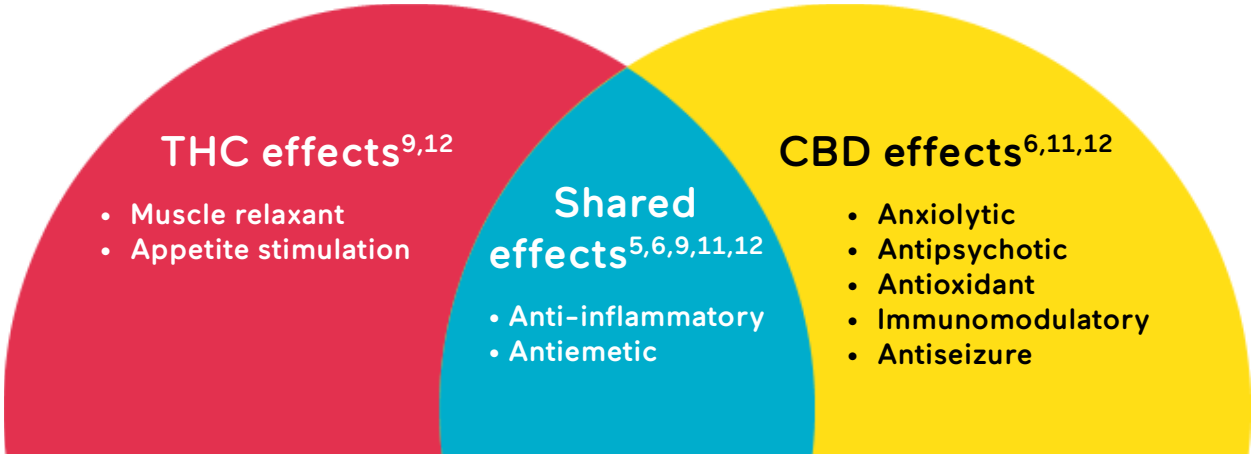




THC and CBD synergy

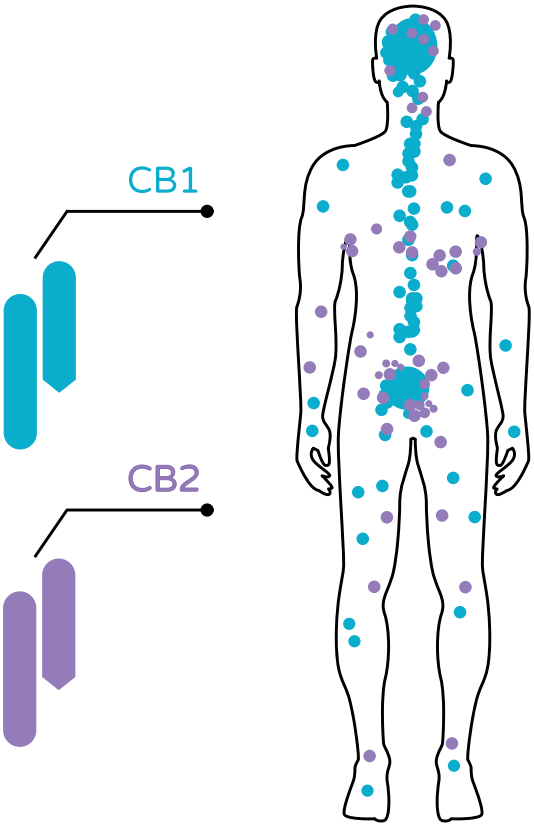
When used in combination, THC and CBD may increase clinical efficacy while reducing unwanted side effects. More specifically, the mechanism of action of these major cannabinoids includes:

- THC is a partial agonist of CB1 and CB2 receptors.[5,9,10]
- CBD has low affinity for CB1 and CB2 receptors and affects the activity of other enzymes and receptors.[5,9,11]
- CBD moderates THC-related effects by modulating the metabolism of THC (inhibits the conversion of THC to the more psychoactive 11-hydroxy-THC.[11,12]



The Endocannabinoid System

The Endocannabinoid System (ECS) is a ubiquitous lipid signaling system present in all vertebrates and plays an important role in the regulation of homeostasis throughout the human body. It has been implicated in a broad range of physiological and pathophysiological processes, including neural development, immune function, inflammation, appetite, metabolism and energy homeostasis, cardiovascular function, digestion, bone development and bone density, synaptic plasticity and learning, pain, reproduction, psychiatric disease, psychomotor behaviour, memory, wake/sleep cycles, and the regulation of stress and emotional state.[5]
The ECS consists of endogenous receptors, ligands, and metabolic enzymes.



Cannabinoid receptors are located on cell surfaces throughout the body

Receptors

The cannabinoid receptors are G-protein coupled receptors (GPCR) named cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2). CB1 receptors are the most abundant GPCRs in the central nervous system (CNS) and are found in highest concentration in the CNS, peripheral nervous system and the gastrointestinal system. CB2 receptors are found primarily in the immune system, including the tonsils, spleen, lymph nodes, and circulating lymphocytes and neutrophils.[5,13]

Endocannabinoid Ligands

Two endogenous agonists (ligands) to cannabinoid receptors (i.e., endocannabinoids) have been identified: anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Anandamide is derived from the Sanskrit term 'ananda', which means bliss. AEA can reproduce the typical effects of THC, such as euphoria. In addition, endocannabinoid synthesising (*N*-acyl-phosphatidylethanolamine-specific phospholipase D and diacylglycerol lipase) and degrading enzymes (fatty acid amide hydrolase and monoacylglycerol lipase) are responsible for the regulation of endocannabinoid levels and thus, activation of the receptors.[5,13]

Receptor activation

Cannabinoid receptor activation initiates a signaling cascade with differing results depending on the type and location of the receptors. In the CNS, endocannabinoids are produced on demand in the post-synaptic terminal in response to cellular, tissue, and organ demands. Cannabinoids (both endogenous and exogenous) can work on many pathways and in a variety of mechanisms. One way is by binding to CB1 receptors located on the presynaptic terminal with the overall effect of suppressing neurotransmitter release (e.g., glutamate, GABA, dopamine, and cholecystokinin). This retrograde signaling mechanism allows for the regulation of neurotransmission in a precise spatio-temporal manner.[1] Phytocannabinoids provide benefits via complex interactions with other receptors and ion channels in addition to CB1 and CB2 activation. For example, CBD is an agonist of serotonin (5-HT1A) receptors[14] and vanilloid (TRPV1) receptors.[15]

Methods of Administration

There are important differences between inhaled and ingested methods of medicinal cannabis administration. Some patients may require the use of more than one type of product to address their therapeutic needs.

Inhalation

Vaporising is a way to inhale the bioactive components of medicinal cannabis without burning the plant material. Cannabis is heated to a temperature that vaporises without combusting, the cannabinoids and other plant constituents, substantially reducing toxic by-products. In addition to reducing harm associated with smoking, vaporising is a more efficient way of extracting the chemically active constituents from cannabis. It also reduces the loss of cannabinoids in sidestream smoke, which occurs in smoking.[16-20]

Dried flower

Whole flowers from female cannabis plants are harvested, the leaves are trimmed, and the flowers are dried to a specific moisture content. As the flower is usually supplied in whole bud form, it needs to be milled or ground before being placed in the vaporiser.

Considerations:

- Onset time is seconds to minutes and duration of effect is up to 6 hours or longer[21,22]
- Full spectrum, whole plant products with a broad spectrum of cannabinoids and terpenes, not typically present in more refined dosage forms
- May be suitable for patients who are unable to swallow or have allergies to the ingredients in oil or softgel preparations
- Requires dexterity to administer via a medical vaporiser.

Vaporisation

Typically, a small amount of milled cannabis flower is placed into the chamber of a medical vaporiser. The cannabis is progressively heated to vaporise the bioactive components, but not high enough to cause combustion or burning. The primary bioactive components in cannabis will vaporise around the following temperatures:[23]

- THC: 157°C (315°F)
- CBD: 160–180°C (320–356°F)
- CBN: 185°C (365°F)

Vaporisers require sufficient time to heat up to properly vaporise the bioactive components of the cannabis plant. The vapours are then collected in a secondary chamber or directly inhaled, resulting in little product loss to the environment when compared with smoking. The set temperature of some vaporisers can be changed, which can impact the amount of bioactive cannabinoids that are present in the vapour. Patients should read and follow the instructions that come with the vaporiser they purchase.

Medical vaporisers

A variety of vaporising technologies are on the market. If vaporised medicinal cannabis is to be used, it is recommended that devices that have been studied in a research setting and found to be safe and effective are chosen for use.[25,26] The Vapormed Medic devices manufactured by STORZ & BICKEL are included on the ARTG (ARTG listing: 319028). The inclusion on the ARTG covers the MIGHTY MEDIC, MIGHTY+ MEDIC, and VOLCANO MEDIC 2 devices. The STORZ & BICKEL device technology has been studied in research settings (both independent and commissioned).
The studies can be accessed at:
www.vapormed.com.au/pages/science.

The TGA authorises dried flower for inhalation via vaporisation only, not smoking

Ingestion

Ingesting medicinal cannabis oil from an oral dosing syringe or in softgels ensures accurate dosing. It is not recommended to add oil to baked goods or other food (e.g., yoghurt) as dosing precision is lost. Medicinal cannabis products consumed as oils or liquid capsules are more slowly absorbed. It can take 30 minutes to 1.5 hours, or longer, after consumption to feel the effects. It is important to allow at least 3 hours between administration of single oral doses to avoid possible overconsumption. Effects can last for 12 hours and up to 24 hours.[5,20] Oils and softgels are intended for oral consumption and are not designed to be vaporised, combusted, or administered sublingually.

Oil

Concentrated resin, containing cannabinoids and other potentially bioactive compounds, is extracted from cannabis flowers that have undergone thermal decarboxylation. The resin is diluted with a pharmaceutical-grade medium-chain triglyceride (MCT) oil to make a finished product that has defined cannabinoid concentrations to facilitate oral administration.

- **Cannabis oil:** extract from the cannabis plant that contains major and minor cannabinoids, and other plant compounds. Terpenes and minor cannabinoids may vary from batch to batch.
- **CBD isolate oil:** extract from the cannabis plant that has been highly purified to isolate CBD. It will contain minimal amounts of terpenes, flavonoids and other cannabinoids.

Considerations:

- Controlled dosing and small dosing increments
- Requires dexterity to draw up syringe to administer dose.

Softgels

Softgels consist of 2 hermetically sealed halves filled with cannabis oil to form a single capsule. Softgels may provide patients with a convenient and discreet option for their medication while avoiding the taste of the cannabis oil.

Considerations:

- Dosage uniformity
- Discreet administration
- Avoid the taste of the cannabis oil
- Smaller load of MCT oil (0.15 mL per capsule)
- Administration may be easier for patients with limited dexterity or low vision who have trouble using the syringe mechanism with oil products.

Inhalation

Ingestion

STARTING DOSE

1 inhalation

2.5 mg of THC and equal amount CBD

ONSET

seconds to minutes

30 minutes to 1.5 hours, or longer

DURATION

up to 6 hours, or longer

up to 12 hours, or longer

HOW IT'S ABSORBED

through the lungs directly into the bloodstream

from the GI tract and metabolised in the liver before entering the bloodstream

	Inhalation	Ingestion
Pros	• Rapid action • Advantageous for acute or episodic symptoms e.g., nausea or pain	• Long-acting effects • Allows titration with controlled doses • Advantageous for chronic disease and symptoms
Cons	• Dexterity required to grind flower and use medical vaporiser • Requires additional equipment to be purchased - Medical vaporisers and milling devices	• Dexterity required for oils and syringe administration • Slow absorption • Longer onset time • Lower bioavailability compared to vaporisation

General Dosing Guidance and Monitoring

Dosing Guidance

Medicinal cannabis dosing is individualised and relies on gradual titration. It is important to take a "start low, go slow" approach to medicinal cannabis dosing.

If this is your patient's first-time using Spectrum Therapeutics oil or softgels, you could use the starting dose suggested in our Spectrum Product Explainer. The patient should wait at least a day before dosing again. If the starting dose is ineffective, have them consume the titration dose and wait at least a day to assess the effects before consuming more. Continue in this manner until the patient reaches a dose that provides optimal benefit with minimal side effects.

Once-daily dosing is recommended during the dose escalation phase for oil and softgels. Once the patient has identified their optimal dose, they can adjust dose frequency based on the severity of symptoms throughout the day (e.g., take a morning and an evening dose). Though most people will find their ideal dose in the first few days, it may take longer for others.[20]

Taking Spectrum Therapeutics oil or softgels with a fatty meal may increase the effects that your patient experiences. Patients should consume their medicinal cannabis consistently with or without food to minimise dosing variability. Spectrum Therapeutics oils or softgels should be used regularly at the same time each day.

Vaporising

The following is one method commonly used by physicians and patients to determine the therapeutic dose:

- Start with 1 inhalation and wait 15 minutes before consuming more
- Increase by 1 inhalation every 15 to 30 minutes until the optimal dose (i.e., number of inhalations) is achieved
- If unwanted side effects occur, then the patient may try a lower dose or a product with a different CBD to THC ratio
- Once the optimal dose has been determined, including the duration of effect, it can then be dosed regularly or as needed.[20]

Start Low, Go Slow

Oral administration

Follow the 3 steps below to help find the right dose for oils and softgels.

1 STARTING

Select product format

Start with once-daily dosing at the lowest dose

In treatment-naïve patients, start with higher CBD concentration products

Wait at least 1 day to assess effectiveness

2 INCREASING

If necessary, increase starting dose

Maintain the same frequency of once-daily dosing

Most patients find their ideal dose within a few days

3 ADJUSTING

For persistent symptoms, consider switching to a higher THC product

For breakthrough symptoms, consider more frequent dosing, as needed

Some patients may benefit from a combination of products and/or formats

Once the optimal dose is identified, patients can adjust their dosing frequency based on the severity of symptoms throughout the day

Slower titration and care should be taken with the elderly and those with complex health conditions

Monitoring

It is recommended to monitor patients for clinical response to medicinal cannabis, in addition to monitoring for response to other pharmaceutical agents that could interact with medicinal cannabis.

Patients should use a diary to help keep track of their dosing and symptoms. Spectrum Therapeutics has a Patient Dosing Diary available for patients who have been prescribed Spectrum Therapeutics products.

While initiating and titrating medicinal cannabis, it is not recommended to change other medications. Once the optimal dose of medicinal cannabis is found, the use of other medication can be changed. Patients who are taking any other medications that could have a potential drug-drug interaction, should be monitored closely and consideration to start at a lower dose should be made.

For more information, please refer to the TGA's *Guidance for Access to Medicinal Cannabis in Australia: Overview.*[25]

Please report any adverse events or drug interactions directly to the TGA or contact Medical Information on medinfo.au@canopygrowth.com.

Patient counselling

1. It can take 30 minutes to 2 hours or longer to feel the effects of oil or softgels.
2. The effects of ingestible products can last up to 12 hours or longer. Patients should allow enough time for the effects to pass to understand how they are affected.
3. These products should not be consumed by women who are pregnant or breastfeeding.
4. Always store medicinal cannabis products in their original packaging and keep out of reach of children and pets.
5. It is not recommended to add oil to baked goods or other food (e.g., yoghurt) as dosing precision is lost.
6. Avoid consuming alcohol in combination with cannabis in any form.
7. Fatty meals may increase the effect that your patient experiences.
8. Do not drive or operate heavy machinery while using a THC-containing product.
9. Talk your patient through the Consumer Medicine Information leaflet provided.

If you need more assistance, please contact Medical Information (medinfo.au@canopygrowth.com) or your local Medical Science Liaison. Please note that Spectrum Therapeutics cannot provide treatment advice for individual patients.

Prescribing Considerations

Prescribing considerations

Medicinal cannabis is not considered a first-line therapy for any condition and is generally used as an add-on to the patient's current treatment regime. You might consider prescribing medicinal cannabis when:

- ❑ Patient has trialled therapies evaluated by the TGA and included on the ARTG that have failed to manage symptoms or disease
- ❑ Patient has a contraindication or experiences unacceptable side effects to therapies evaluated by the TGA and included on the ARTG
- ❑ A significant number of case reports with good preclinical evidence of likelihood of efficacy are available to support its use
- ❑ The patient's medical condition and history, prescribed medications, ability to manage side effects, and tolerability have been evaluated.[25]

Commencing treatment[25]

Before treating a patient with medicinal cannabis, you should:

- ❑ Complete a comprehensive clinical assessment and screen for risk factors
- ❑ Create a treatment and monitoring plan
- ❑ Discuss the inability to drive and/or operate heavy machinery
- ❑ Have your patient sign a written informed consent form
- ❑ Obtain the relevant TGA and state approvals prior to prescribing.

Contraindications and precautions[5,20,25]

Medicinal cannabis, particularly THC-containing products, are not appropriate for:

- ❑ Patients who have known sensitivities to cannabis, THC, CBD, any other cannabinoid (including pharmaceutical products e.g., Nabiximols), or products used in manufacture
- ❑ Patients who have a previous psychotic disorder, or concurrent active mood or anxiety disorder
- ❑ Patients who are pregnant, planning on becoming pregnant, or breastfeeding
- ❑ Patients who have severe and unstable cardio-pulmonary disease or risk factors for cardiovascular disease.

Care should be taken in prescribing medicinal cannabis to:

- ❑ Patients who are under 25 years of age due to the potential adverse effects of THC on the developing brain
- ❑ Patients who have severe liver or renal disease
- ❑ Patients who are drug dependent or have substance use disorder, particularly heavy alcohol use
- ❑ Paediatric or elderly patients as these age groups are likely to be more sensitive to the pharmacological effects.

Psychiatric disorders

For those with a family history of schizophrenia or bipolar disorder, using cannabis at a younger age is associated with increased risk and worse outcomes for these illnesses.[26,27] This information is derived from recreational cannabis use and there is insufficient data to discuss the effects of low-dose THC or CBD on those at risk of schizophrenia or bipolar disorder. CBD, when used as an adjunctive therapy, may have beneficial effects for patients diagnosed with schizophrenia.[28]

Young people

The use of cannabis among young people is of significant concern as this population is at higher risk. Youth who use cannabis for recreational purposes, typically when under 15 years of age, are at significantly higher risk of developing Cannabis Use Disorder (CUD) and social dysfunction.[29] Population-based studies that looked at youth who began cannabis use at a young age suggest they are at increased risk of impaired cognitive function as an adult.[30]

Tolerance

Tolerance to cannabis can develop, which may reduce the therapeutic effects and/or adverse events that a patient experiences. For medicinal cannabis patients, a slow upward dose titration promotes tolerance to the psychoactive sequelae of THC, which is especially important for naïve users. Tolerance to most of the effects of medicinal cannabis can develop after a few doses, and often disappears rapidly following cessation of use.[5] Some patients may not experience concomitant tolerance to the benefits, and therefore, can maintain the same daily dose of medicinal cannabis.[20]

Dependence

Clinicians are often concerned that patients who use medicinal cannabis will become addicted. There are no studies that look at the rate of addiction in patients who are prescribed medicinal cannabis as compared to those using it recreationally. Therefore, information about rates of dependency and addiction are only based on recreational users.

In a cannabis context, addiction has been replaced by CUD in the Diagnostic and Statistical Manual V (DSM-V). CUD is a problematic pattern of cannabis use that leads to clinically significant impairment or distress. This includes certain clinical features such as tolerance and dependency.[5]

Simply having tolerance and dependency is insufficient to be diagnosed with CUD if the individual does not exhibit clinically significant impairment or distress. While cannabis used for medicinal purposes may lead to tolerance and dependency, rarely do patients develop CUD that leads to clinically significant impairment or distress requiring treatment.

Withdrawal

Both physical and psychological dependence on cannabis can develop, particularly with chronic use.[31-33] Withdrawal symptoms related to physical dependence show up within 1 to 2 days when cannabis use is suddenly stopped and wane within 1 to 2 weeks.[5,34] Common symptoms of withdrawal include increased dreaming and other sleep disturbances, irritability, appetite changes, weight loss, headache, anger, and aggression.[33-35] It should be noted that this data is from recreational use and is not controlled for medical users.

Medicinal cannabis and driving

Cannabis can impair a patient's ability to drive and/or operate heavy machinery. Patients treated with medicinal cannabis should not drive or operate machinery. It is important to note that measurable concentrations of THC can be detected in saliva for many hours after administration. In addition, measurable concentrations of THC can be detected in blood or urine many days after the last dose. It may take up to five days for 80 to 90 percent of the dose to be excreted. In Australia, it is an offence to drive with any level of THC in your system. Each state and territory has its own regulatory guidelines for patients who suffer from serious and chronic medical conditions.[24,25]

All medicinal cannabis products will contain some level of THC. Patients should discuss the implications for safe and legal driving with their doctor. For more information or guidance, please contact the NPS Medicines line on 1300 633 424 (1300 MEDICINE).

Pharmacokinetics, Pharmacodynamics, Safety, and Side Effects

Pharmacokinetics and Pharmacodynamics

When cannabis is inhaled, THC and other cannabinoids are rapidly absorbed. Maximum brain concentrations, coinciding with maximum physiological and psychological effects, occur within 15 minutes. These effects plateau for 2 to 4 hours before declining.[21,22] Ingested medicinal cannabis has a longer onset of action (30 minutes to 1.5 hours) and the effects may last up to 12 hours, or longer. It is important to choose the right method of administration, depending on a patient's symptoms and preferences. Some patients will require a combination, e.g., using medicinal cannabis oil to control baseline symptoms and inhaled medicinal cannabis for breakthrough symptoms.[5,20]

Metabolism[5,20]

Cannabis is metabolised via the hepatic cytochrome pathway and excreted via the biliary tract into faeces, along with urinary excretion of acid metabolites.

First phase metabolism:

Cytochrome P450 (CYP450) enzymes are involved in the first phase of metabolism of cannabinoids.

Second phase metabolism:

- ❑ Mainly carried out by transferases
- ❑ Genetic polymorphisms can affect: CYP2C9, CYP2C19 and CYP2D6
- ❑ May significantly alter the speed of metabolism of cannabinoids affecting their levels and duration of effect.

Drug-drug interactions

As the CYP450 enzyme system is implicated in the metabolism of THC and CBD, there are likely to be pharmacokinetic interactions, particularly with drugs that are metabolised by, or either inhibit or induce CYP450 enzymes.

Based on *in vitro* and animal studies with cannabis, THC has the potential to inhibit CYP3A4, CYP2C9, CYP2C19 and CYP2D6, and may induce CYP1A2 (particularly with smoked cannabis). CBD has the potential to inhibit CYP3A4/5, CYP2C19, CYP2D6 and CYP1A2.[5]

CYP inhibitors[5]

Drugs that may increase THC and/or CBD levels include:

- ❑ antiarrhythmics (e.g., amiodarone)
- ❑ antidepressants (e.g., fluoxetine)
- ❑ antimycotics (e.g., itraconazole, posaconazole)
- ❑ calcium antagonists (e.g., diltiazem, verapamil)
- ❑ HIV protease inhibitors (e.g., ritonavir)
- ❑ macrolides (e.g., clarithromycin, erythromycin)
- ❑ proton pump inhibitors (e.g., omeprazole)
- ❑ isoniazid (tuberculostatic agent)
- ❑ grapefruit juice

CYP inducers[5]

Drugs that may decrease the availability of THC and/or CBD include:

- ❑ antibiotics (e.g., rifampicin, rifabutin)
- ❑ antiepileptics (e.g., carbamazepine, phenytoin, phenobarbital, primidone)
- ❑ St. John's wort

There have been few studies conducted to evaluate drug interactions with cannabis. Of those that have been conducted, here are some examples of clinically relevant drug interactions.

CNS depressants

Most drug interactions are associated with the concurrent use of CNS depressants (alcohol, sedative hypnotics) with cannabis. Additive effects may include sedation and cognitive impairment.[20]

Immunotherapy agents

Nivolumab (PD1/PDL1 inhibitor) – possible interaction as demonstrated by decreased Response Rate, without affecting Progression Free Survival or Overall Survival.[36]

Anticoagulants

CBD may interact with CYP2C9 to inhibit metabolism of warfarin, resulting in increased plasma concentrations, INR, and risk of bleeding.[37]

Theophylline

Clearance was reported to be higher in frequent cannabis smokers.[38]

Clobazam

Metabolism is inhibited by CBD (thus increasing clobazam concentrations).[39]

Safety and Side Effects

Most of the known side effects and adverse events associated with medicinal cannabis are extrapolated from studies looking at recreational users. Side effects and adverse events associated with cannabis are varied because cannabis affects the ECS, which plays an important role in many physiological processes.

Acute side effects of cannabis include those mediated by effects on the CNS, such as dizziness, drowsiness, fatigue, impaired motor coordination and motor performance, impaired short-term memory and information processing, altered judgement, and decreased attention.

Other side effects are mediated by the cardiovascular system and include tachycardia, peripheral vasodilation with orthostatic hypotension, and supine hypertension. The gastrointestinal system can be affected by side effects that include nausea, vomiting, appetite and motility changes.

While cannabis has been reported to be beneficial as an anxiolytic, some patients may report increased anxiety. Patients who are susceptible and consume cannabis may experience acute psychotic symptoms.[5,20,40]

For more information about drug interactions or side effects, please refer to the TGA's *Guidance for access to medicinal cannabis in Australia: Overview.*[25]

We take patient safety seriously at Spectrum Therapeutics. Please report any drug interaction or adverse event directly to the TGA or contact our Medical Information team at: medinfo.au@canopygrowth.com.

Side effects of medicinal cannabis

Side Effect	Most common	Common	Rare
Drowsiness/fatigue	✔		
Dizziness	✔		
Dry mouth	✔		
Cough, phlegm, bronchitis (smoking only)	✔		
Anxiety	✔		
Nausea	✔		
Cognitive effects	✔		
Euphoria		✔	
Blurred vision		✔	
Headache		✔	
Orthostatic hypotension			✔
Toxic psychosis/paranoia			✔
Depression			✔
Ataxia/discoordination			✔
Tachycardia (after titration)			✔
Cannabis hyperemesis			✔
Diarrhoea			✔

Adapted from MacCallum and Russo, 2018[20]

Toxicity

Medicinal cannabis products are generally regarded as having low acute toxicity. However, concurrent use of other drugs may mask the effects of cannabis and severe toxicity, including adverse cardiovascular effects and death, may be under-recognised. In mammals, the median lethal dose of THC has been estimated to be >800 mg/kg. CBD appears to have very low toxicity. Doses of 1000 mg/kg CBD are reported to be tolerated safely in humans.[25]

Smoking

Despite smoking being the most common means of consuming recreational or illicit cannabis, this is not a recommended method. Smoking plant substances is associated with serious adverse health effects. Smoking releases toxins and carcinogens, including ammonia, carbon monoxide, tar, and polycyclic aromatic hydrocarbons. Studies looking at the long-term impact of the recreational smoking of cannabis (not vaporising or ingesting) suggest a possible association with worsening of respiratory symptoms and chronic obstructive pulmonary disease episodes. Consuming cannabis during pregnancy, especially if smoked, is associated with a risk of lower birthweight and other perinatal complications.[20]

Long-term safety study

It is critical to obtain data on the long-term effects of cannabis in a medicinal cannabis population. COMPASS (Cannabis for the Management of Pain: Assessment of Safety Study) is a Canadian study published in 2015.[41] This prospective case-control study followed 215 medicinal cannabis patients with chronic pain for one year. Patients had access to cannabis containing 12.5% THC and median use was 2.5 g/day. When compared to controls (chronic pain patients not using cannabis) there was no significant increase in serious adverse events and no difference in cognitive function, lung function, hematology profile, or biochemistry, including liver and renal function. The most common non-serious adverse events were dizziness, nausea, and fatigue. Despite this, patients had a statistically significant improvement in their levels of pain, symptom distress, mood, and quality of life.

Further Resources and Education

Further Resources

What guidance documents are available?

The Australian Government Department of Health, in conjunction with state and territory health departments, has developed a series of clinical guidance documents for prescribers. The guidance documents were endorsed in December 2017 by the Australian Advisory Council for the Medicinal Use of Cannabis. So far, guidance documents have been developed to support prescribers of medicinal cannabis products for treating:

- Nausea and vomiting due to chemotherapy
- Epilepsy in children and young adults
- Chronic non-cancer pain
- MS
- Palliative care

For more information about the conditions where medicinal cannabis may be effective, as well as summaries of evidence for the use of medicinal cannabis, please visit the TGA website: https://www.tga.gov.au/medicinal-cannabis-guidance-documents.

How do I access medicinal cannabis for a patient?

Most medicinal cannabis products in Australia are not included on the ARTG and are only accessible via the SAS, AP pathways or via clinical trials. For further information about accessing unregistered medicinal cannabis products for patients, please visit the TGA website:

https://www.tga.gov.au/medicinal-cannabis-information-health-professionals

What published research is available?

Two major limitations to designing proper clinical studies are regulatory licensing hurdles and the lack of development and supply of a true placebo. Despite these barriers, research efforts have intensified in recent years with a focus on structured randomised controlled trials.

In 2017, the National Academies of Sciences, Engineering, and Medicine conducted a comprehensive systematic review titled "The Health Effects of Cannabis and Cannabinoids—The Current State of Evidence and Recommendations for Research". The expert committee reviewed 10 000 published papers in scientific journals and found that there is:

- Conclusive or substantial evidence that cannabis or cannabinoids are effective (i) for chronic pain in adults; (ii) as antiemetics in the treatment of chemotherapy-induced nausea and vomiting; and (iii) for patient-reported muscle spasticity in MS.
- Moderate evidence that cannabis or cannabinoids are effective for improving outcomes for patients with sleep disturbances associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and MS.
- Limited evidence that cannabis or cannabinoids are effective for improving (i) appetite and decreasing weight loss associated with HIV/AIDS; (ii) clinician-measured MS spasticity symptoms; (iii) symptoms of Tourette syndrome, anxiety and posttraumatic stress disorder (PTSD).[42]

For the most up to date peer-reviewed literature or information on other clinical topics of interest, please contact your local Medical Science Liaison or Medical Information on medinfo.au@canopygrowth.com.

Spectrum Therapeutics support

Spectrum Therapeutics provides a range of accredited and unaccredited education, resources, and support for healthcare professionals.

- Our dedicated Medical Science Liaison team can provide personalised education, support with regulatory access, and evidence-based research
- Webinar recordings from our previous Australian and Canadian medicinal cannabis education series
- Workshops, Masterclasses and Spectrum Academy events
- Case studies with real-life patient stories as a practical learning tool

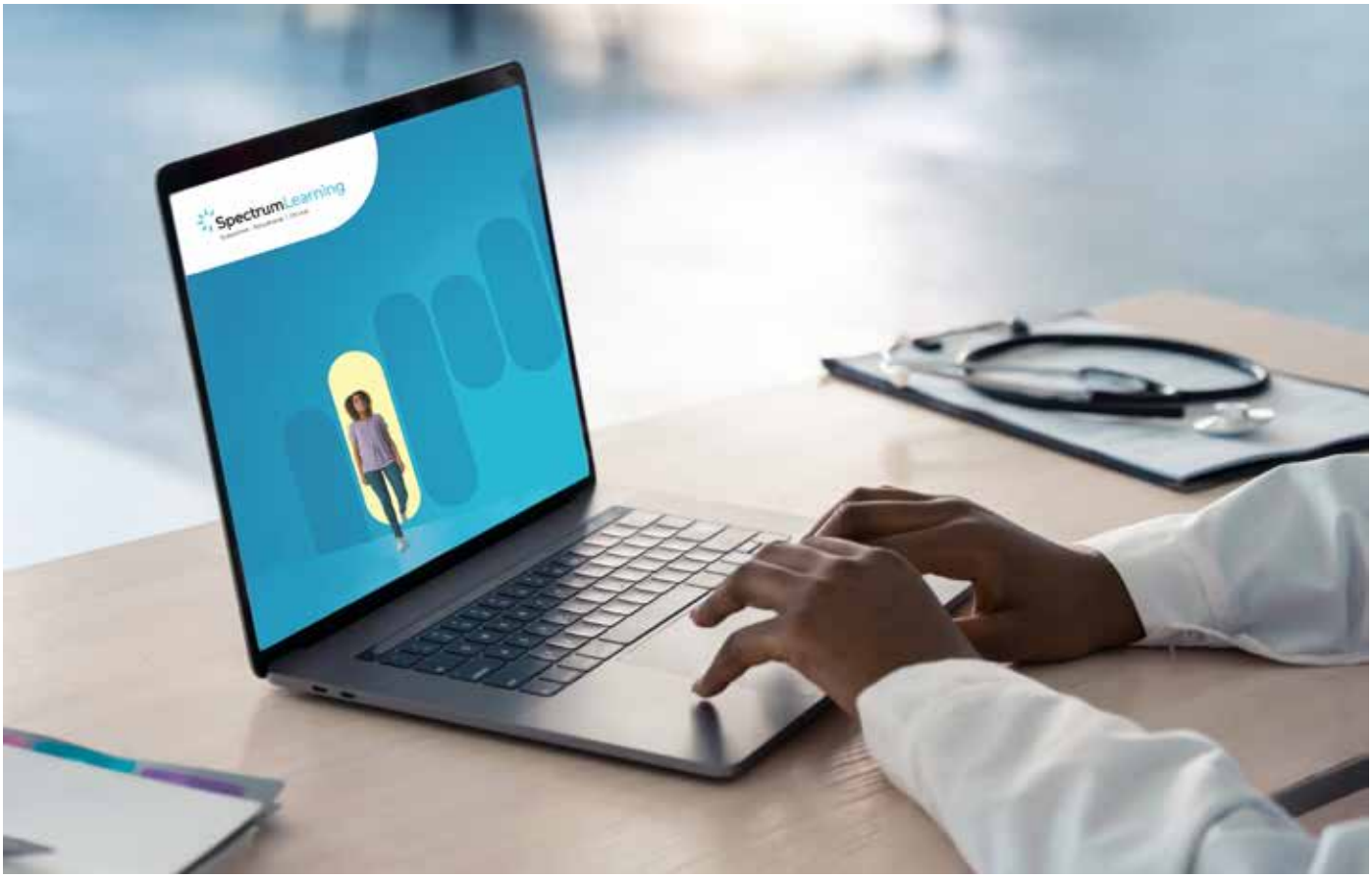
To book an education appointment with our Medical Team or to find out more about upcoming educational events, please visit our Spectrum Therapeutics website:

https://spectrumtherapeutics.au/pages/healthcare-professionals

Two papers on consensus recommendations for the dosing and administration of medicinal cannabis have been published in peer-reviewed journals. These studies were sponsored by Spectrum Therapeutics, but the company had no influence on the study design, data collection, analysis or interpretation, nor the publication process.

- Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process by Bhaskar *et al.* published in the Journal of Cannabis Research (2021).[43]
- Consensus-based recommendations for titrating cannabinoids and tapering opioids for chronic pain control by Sihota *et al.* published in the International Journal of Clinical Practice (2021).[44]

For further information on Spectrum Therapeutics-sponsored research, please contact your local Medical Science Liaison or Medical Information on medinfo.au@canopygrowth.com.



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