Clinical Guidance: for the use of medicinal cannabis products in Queensland

March 2017

Queensland Government

Contents

Background

The following document provides interim guidance on the use of medicinal cannabis. As the evidence underpinning the clinical practice for use of medicinal cannabis evolves, it is anticipated, the following guidance will be altered to reflect the evidence. There is further work being undertaken at a national level reviewing the literature to provide national guidance documents in 2017. At that time these guidelines will be replaced by the national document.

Queensland Department of Health (the department) has developed this document in collaboration with the Queensland Medicinal Cannabis Guidance Reference Group considering peer-reviewed literature and international reviews concerning potential therapeutic uses and harmful effects of cannabis and cannabinoids**. It should be noted that medicinal cannabis is not considered a first line therapy for any indication**. Given the public interest, medical practitioners are likely to be asked to prescribe medicinal cannabis, however, as with all therapies medical practitioners must exercise their professional judgement in determining if this is an appropriate treatment for that individual patient. Medicinal cannabis should be considered only where conventional treatments have been tried and proven unsuccessful in managing the patient's symptoms.

The following interim guidance is not meant to be comprehensive and should complement other reliable sources of information. This document, however, may assist practitioners discussing medicinal cannabis use with patients.

This document should not be construed as endorsement from the Queensland Department of Health about the use, in individual patients, of medicinal cannabis products.

Use of medicinal cannabis

Medicinal cannabis products in Queensland include products that are derived from the cannabis plant or synthetic products that act in the same way—and are used for a therapeutic purpose.

Medicinal cannabis products have not undergone the rigorous testing required to ensure safety and efficacy, therefore they are not approved therapeutic goods in Australia.

However, research suggests that there may be some therapeutic benefit from the various cannabinoids contained within the cannabis plant. While research into the use of cannabinoids continues, the Queensland Government has enabled medical practitioners to access medicinal cannabis products for their patients before they have reached the standard required for a pharmaceutical product. This is only permitted if a medical practitioner believes that medicinal cannabis may help relieve a patient's symptoms and/or medical condition.

Medicinal cannabis requires approval from both the State and the Commonwealth's Therapeutic Goods Administration (TGA). TGA approval is required for the supply and

importation of the medicinal cannabis product and is through the TGA Special Access Scheme or Approved Prescriber Scheme, both of which allow access to unapproved therapeutic goods. The TGA cannot guarantee the safety, quality or efficacy of these products because they have not been through the rigorous TGA process required for medicinal registration in Australia.

In addition, State approval is required to prescribe the product(s) to a patient, and, as with any other medication, the decision to prescribe should be made with knowledge of the risks, benefits, potential complications and drug interactions associated with the product. Medical practitioners should ensure they access available literature to determine the efficacy and safety of the product they wish to prescribe, to ensure they are comfortable with prescribing it. In addition, the *Public Health (Medicinal Cannabis) Act 2016*, commencing 1 March 2017, provides protection from civil liability when prescribing medicinal cannabis products provided the medical practitioner has acted in good faith and with due diligence. . This protection may not extend to the TGA approval process.

Queensland Health recommends that medicinal cannabis that contains Tetrahydrocannabinol (THC) is generally not appropriate for patients who:

- have a personal history or strong family history of psychosis or have concurrent active mood or anxiety disorder
- are pregnant, planning in becoming pregnant, or breastfeeding
- have a current or past cannabis use disorder or an active substance use disorder
- have unstable cardiovascular disease.

The use of medicinal cannabis should be restricted to instances when the usual standard of care for the management of a patient's specified clinical condition and/or symptoms has been ineffective or produced intolerable side effects.

It is not anticipated that medicinal cannabis products would be prescribed as first-line therapy at this time.

Types of medicinal cannabis products in Queensland

- Flos/bud—Good Manufacturing Practice (GMP) certified cannabis buds or flower heads of known delta-9-tetrahydrocannabinol (THC)/Cannabidiol (CBD) percentage.
- Oils—varying combinations of THC and CBD.
- Liquid capsules—varying combinations of THC and CBD.
- Oro-mucosal spray—THC and CBD combination.

Methods of administration

- Orally—oral-mucosal spray, sublingual oil or, orally ingested capsules or tablets.
- Vaporisation—using a vaporiser approved by the Therapeutic Goods Administration (TGA) as a medical device or until such a device is approved, devices approved in a similar jurisdiction.
- Trans-dermal application—patches or topical application of gel or cream.

The Volcano Medic and Mighty Medic which are approved medical devices in Canada.

Smoking of medicinal cannabis products will not be approved in Queensland.

Cannabis

Cannabis composition

There are approximately 500 natural components found within the *Cannabis sativa* plant, of which up to 100 have been classified as ‘cannabinoids’; chemicals unique to the plant. The cannabinoids are most abundant in the un-fertilised female flower head and this is the part of the plant utilised in the development of medicinal cannabis products.

The most well-known of the cannabinoids is delta-9-tetrahydrocannobinol (THC). It was isolated in 1964 in Israel. This cannabinoid is responsible for the psychoactive effects of cannabis and is the reason cannabis is used recreationally. However, it appears that THC may also be responsible for some of the medicinal effects of cannabis such as reduction of nausea, vomiting, pain and muscle spasms as well as improvement in sleep and appetite.

A second cannabinoid, cannabidiol (CBD) is also showing promise in the medical field, but has the advantage of not being psychoactive. It appears that CBD may mitigate some of the THC effects and, while research is continuing, there is the possibility that CBD may be useful in the management of seizures, pain, and may have anxiolytic and antipsychotic effects. At this stage, it is not known if THC and CBD act individually or in conjunction with each other.

There are numerous other cannabinoids that may be of interest in the future, including cannabigerol (CBG), tetrahydrocannabivarin (THCV), cannabinol (CBN) and cannabichromene (CBC). Generally, all cannabinoids produced by the plant are in their acid form and in relatively low concentrations.

In addition to the cannabinoids, the cannabis plant also contains more than 400 other components. Of particular interest are the terpenoids or terpenes. These substances give cannabis its flavour and aroma and include terpenes such as myrcene, limonene and linalool.

Unlike the cannabinoids, terpenes are found abundantly in nature and particularly in many foods. Terpenes may also play a part in modulating the effects of THC when taken with cannabinoids, but may also have their own pharmacological effects. Many people who presently use cannabis as a medicine believe that the combined effects of the cannabinoids with the terpenes and the other components of the plant are what is required to achieve the desired ‘medical’ effect—this is commonly referred to as the ’entourage effect’.

The amount of cannabinoids (THC and CBD in particular) in a single cannabis plant varies considerably. Different plants are gown to obtain specific ratio’s of THC to CBD that can then be used to manufacture different strengths of medicinal cannabis products.

Other cannabinoids

There are three groups of cannabinoids:

- Phytocannabinoids—derived from the cannabis plant as described in the cannabis composition section.
- Endocannabinoids—these are natural cannabinoids created by the body and which appear to exert a regulatory function within the body. Anandamide and 2-Arachidonoyl-glycerol (2-AG) are the two most studied endocannabinoids in the human body. They interact with the natural cannabinoid receptors found in the human body—CB1 and CB2.
- Synthetic cannabinoids—these are cannabinoids created in the laboratory. They include some pharmaceuticals such as nabilone (used for the treatment of anorexia and wasting in HIV/AIDS patients) but also other cannabinoids which are used recreationally, which are much more harmful, for example—HU-210 and JWH-018. Synthetic cannabinoids are not only full agonists at both CB1 and CB2 receptors, but they have 50 to 200 times increased affinity for the CB1 receptor compared with naturally occurring cannabinoids.

The endocannabinoid system

The human endocannabinoid system was discovered in the 1990s and it appears to have a regulatory effect on many bodily functions. This cannabinoid signalling system is present in almost every life form, including the most primitive creatures.

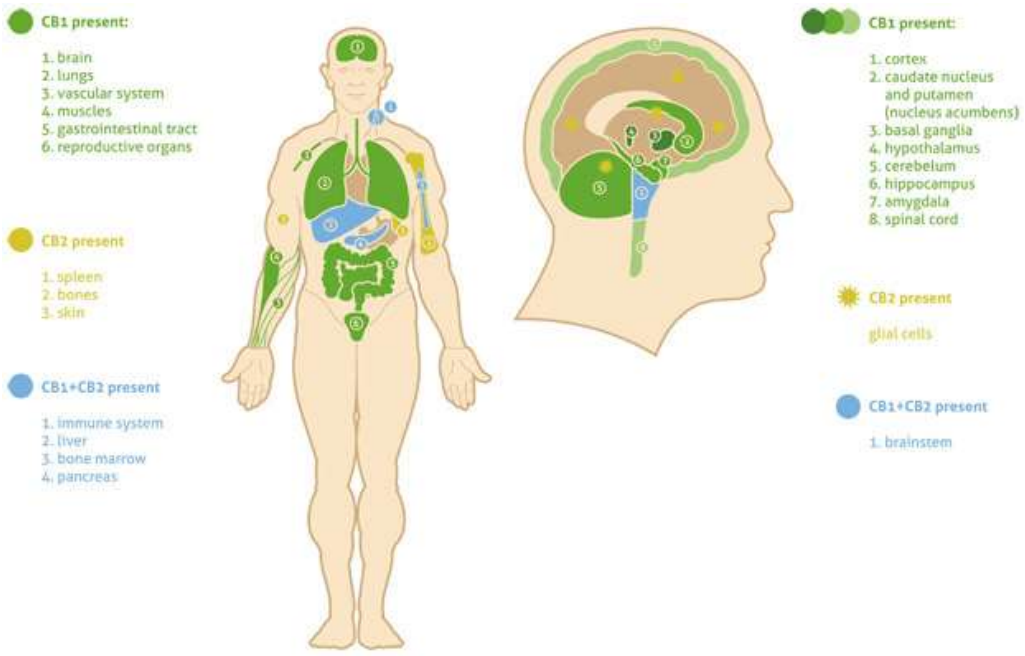
Multiple human and animal studies suggest that endocannabinoids play a key role in memory, mood, brain reward systems, drug addiction, and metabolic processes, such as lipolysis, glucose metabolism and energy balance.

Cannabinoid receptors are found all over the body but appear to be most prevalent in the following areas:

- CB1 receptors—highly concentrated in brain regions related to executive function, memory, cognition, mood, pain perception and movement. They are also found in the heart, intestines and bladder.
- CB2 receptors—found in the spleen, tonsils, thymus gland, bones, skin and the blood (monocytes, macrophages, B-cells and T-cells).

The endocannabinoids that interact with these receptors appear to be involved in the regulation of bodily functions, such as appetite, sleep, pain and inflammation, and may have a protective role in relation to brain function.

Cannabinoids found in the cannabis plant also interact with these receptors, in particular THC producing the euphoric effects most noticeable in recreational users.



Sites of CB1 and CB2 receptors

Pharmacokinetics and pharmacodynamics of cannabinoids

Most data about the pharmacokinetics and pharmacodynamics is related to THC

- Smoking—smoked cannabis results in more rapid onset of action (usually within minutes), higher blood levels of THC and a shorter duration of effect. Peak levels are reached within 30 minutes and the effects may last for two to four hours. Smoking is the most common route of administration for recreational cannabis use but a person's physical response shows considerable individual variability because of the unknown concentration of THC in the products being consumed.

  At least 40 per cent of the THC dose in the cannabis is lost in side stream/combustion when smoked, making it difficult to estimate the amount of THC an individual patient is receiving. For this reason, and due to the well-documented evidence that smoking in general is harmful, smoking of cannabis products will not be approved in Queensland.
- Vaporising—vaporised cannabis results in similar rapid absorption and high blood levels as smoking it. Cannabis is heated at a lower temperature than smoking, producing fewer toxins and no side stream 'smoke', making passive smoking less of a problem. First effects occur within 90 seconds and reach a maximum after 15 to 30 minutes, before wearing off after two to four hours.

  Vaporising heats the cannabis without burning it and releases the cannabinoids and terpenes in the form of a vapour, which is then inhaled. Given the rapid onset of action, vaporising cannabis products is best for symptoms or conditions where rapid relief is required. The amounts of THC and other cannabinoids delivered by the vaporiser are dependent on the temperature, the duration of the vaporisation and the volume of the balloon in the vaporiser.

  No vaporisers are presently registered in Australia as therapeutic goods. The vaporisers shown above are registered as medical devices in Canada and Germany.
- Oral route—medicinal cannabis products consumed in the oral form, such as oils or liquid capsules are more slowly absorbed. They take at least 30 to 90 minutes before any effects are felt. Bioavailability of oral cannabinoids is lower (10 to 20 per cent) because of intestinal and first pass liver metabolism. Peak effects can occur two to four hours after consumption.

  Given the longer time frame for peak effects, it is important to allow at least three hours between administration of single oral doses of to avoid possible overdose. Effects can last for up to eight hours and as long as 24 hours. Given the slower onset and longer duration, it is expected that taking medicinal cannabis products this way would be more useful for medical conditions or symptoms where control over longer periods of time is sought—similar to the use of slow release medications.
- Oro-mucosal sprays—sprays appear to have similar mode of action as oral administration, as it is assumed that some of the product is swallowed. Effects typically start at about 90 minutes after administration and last about the same time as orally administered cannabinoids. Titration of dose may be easier with oro-mucosal spray than with oral formulations.
- Topical—cannabis and THC are hydrophobic and are not absorbed through the skin. CBD and CBN are ten times more permeable than THC and are more likely to be used in topical preparations.

The time of onset and duration of action are unknown. There have been some reports of hypersensitivity reactions, such as a rash and itching, when the skin has come into contact with cannabis.

- Acute toxicity of THC/CBD—though there have been no recorded deaths directly attributable to acute toxicity of cannabis in humans, in animals the median lethal dose (THC) has been estimated to be >800mg /kg. CBD appears to be generally non-toxic. Doses of 500mg CBD appear to have been tolerated safely.
- Metabolism of cannabinoids—most cannabinoid metabolism occurs in the liver and involves the CYP450 pathway. THC accumulates in fatty tissue and is released slowly from this storage site. It is not clear if THC also persists in the brain.
- Excretion—THC and its metabolites are excreted through the faeces and the urine. It may take up to five days for 80 to 90 per cent of the total dose to be excreted; therefore THC is often found in the urine many days after ceasing use.

Commencing treatment with medicinal cannabis

If medical cannabis products are being considered for a patient, it is essential that an accurate and thorough history is taken by the medical practitioner. This should include:

- presenting symptoms—the symptoms for which the medicinal cannabis product is being trialled to alleviate
- medical history—in particular:
  - cardiovascular disease, liver disease and renal disease
  - conventional treatments that have been tried and have failed, as well as the length of time the treatments were trialled and the reasons for ceasing.
- past medical history
- psychological and psychiatric history
  - history of mental illness, particularly schizophrenia.
- risk behaviours associated with drug dependence. While previous cannabis use may not be a contraindication, care should be taken to manage the risk of dependence
  - nicotine dependence (may contribute to patient smoking product)
  - alcohol dependence/abuse
  - previous illicit drug use. (While previous use of illicit cannabis is not necessarily a contra-indication, care should be taken to manage the risk of dependence).
- family health history
  - mental health, particularly a family history of schizophrenia
- social history
  - social support and family support for the use of a medicinal cannabis product
  - child safety considerations
  - employment, especially where it involves driving or operating machinery
  - risk of falls (in older patients)
  - family responsibilities such as caring for young children.
- physical examination
- investigations as needed

- medication review
  - other medications that might interact with medicinal cannabis
  - risk of side effects of medicinal cannabis products.

The initial treatment plan

As stated above, a medical practitioner should complete a comprehensive clinical assessment of the patient that identifies risk factors that will need to be addressed before applying for access to medicinal cannabis. An initial treatment plan should indicate that the medicinal cannabis product will be used as a three-month trial to determine the effectiveness of the medication for the patient's condition/symptoms.

The plan should clearly indicate:

- treatment goals for medical cannabis use—these need to be clearly documented and discussed with the patient, need to be related to the symptoms for which the patient is prescribed the medicinal cannabis and if possible, should be measurable. For example, weight gain in patients with anorexia and, cessation or minimisation of nausea and vomiting.
- if being managed by a general practitioner (GP), patient-specific supportive documentation for use of a particular medicinal cannabis product from a specialist in the field of medicine for which the symptom is being treated (e.g. palliative care) should be documented.
- risk management processes, such as frequency of dispensing. For example, weekly dispensing if there are concerns that a patient may self-escalate their dose.
- monitoring arrangements—weekly/fortnightly/monthly reviews, any blood tests, specialist reviews, other investigations (as needed) for the particular medical condition and/or symptoms being treated.
- an exit strategy for situations where the medication is not helping manage the symptoms or the goals of treatment are not reached.
- that informed consent has been obtained and the patient provided with information about the medicinal cannabis product.
- that the patient has been advised that they are not able to drive while on medicinal cannabis.

The patient should sign and be given a copy of the plan with a copy filed in the patient's medical record.

Contraindications for medicinal cannabis treatment

- History of hypersensitivity to any cannabinoid.
- Severe and unstable cardio-pulmonary disease (angina, peripheral vascular disease, cerebrovascular disease and arrhythmias) or risk factors for cardiovascular disease—THC acts through the CB1 receptors to decrease blood pressure, increase cardiac demand and causes vasodilation. In those who smoke cannabis, there is a four-fold risk of myocardial infarction in the hour following smoking in those patients with unstable ischaemic heart disease.
- Personal or family history of schizophrenia or other psychotic illness.

- Pregnancy/breastfeeding—there are some reports of pre-term labour and low birth weight. Cannabinoids appear in the breast milk.

Relative contraindications

- Care should be taken in prescribing THC containing medicinal cannabis products to patients under 25. Generally THC containing products are not recommended under 25 years
- Severe liver or renal disease
- Drug dependence, including nicotine and heavy users of alcohol
- Other medications especially other sedatives such as opioids and benzodiazepines
- Paediatric and elderly patients—little is known about how these patient groups react to cannabis. As metabolism in the elderly is slower it is likely they will be more sensitive to the pharmacological effects of cannabis. Treatment should therefore be commenced at very low doses and adjusted very slowly.

Therapeutic indications

While there are many anecdotal reports of the therapeutic value of medicinal cannabis, the evidence to support the safety and efficacy of these products is limited. There has been recently strong consumer demand for medicinal cannabis products to be used more widely in the treatment of a number of medical conditions or for patients presenting with poor symptom control.

While animal data shows therapeutic potential and some human research has suggested some therapeutic potential, there is insufficient evidence by contemporary standards, such as randomised controlled trials, for most indications.

A systematic review undertaken by Whiting et. al in 2005 (JAMA June 2015) concluded:

There was moderate quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea, and vomiting due to chemotherapy, weight gain in HIV, sleep disorders and Tourette syndrome. Cannabinoids were also associated with an increased risk of short-term AEs (adverse events).

A more recent review, released in May 2016 by Barnes and Barnes (as requested by the All Party Parliamentary Group for Drug Policy Reform in the United Kingdom) reported the following:

Good evidence for one or more of the cannabis products or 'natural cannabis' in the management of chronic pain, including neuropathic pain; spasticity; nausea and vomiting, particularly in the context of chemotherapy; and in the management of anxiety.

Moderate evidence in; sleep disorders; appetite stimulation in the context of chemotherapy; fibromyalgia; PTSD and for some symptoms of Parkinson's disease.

There was none to limited evidence for other medical conditions and more research was required in conditions such as cancer/tumour control, epilepsy, neurological conditions and mental health illnesses.

Clinical indications for use of medicinal cannabis in Queensland

Queensland Health has provided for three pathways for medical practitioners to prescribe medicinal cannabis products containing THC, CBD or a combination of both.

The a **single-patient prescriber** pathway available for any medical practitioner wishing to apply for a medicinal cannabis approval to treat a medical condition or symptom in an individual patient with medicinal cannabis. Single-patient prescribers will be required to provide evidence as to the safety and efficacy of the product they are requesting for use in that patient. It is anticipated that relevant and up-to-date clinical literature will be included with the application for the treatment of the patient to assist the Expert Advisory Panel in making a recommendation to the Chief Executive.

There is some, albeit limited evidence for use in particular medical conditions/symptoms and Queensland Health has allowed the use of specific medicinal cannabis products in these conditions by patient-class prescribers. Patient-class prescribers are limited to specialists in the relevant area of medicine and will be allowed to treat a group of patients with specific medical conditions/symptoms with specific medical cannabis products if they wish. These specialists will not have to apply for individual patient approvals.

The following medical conditions and/or symptoms will be considered as part of the patient-class prescriber pathway at this time. The medicinal cannabis products mentioned for each group are the products that have been used overseas or are being used in clinical trials here in Australia:

1. Medical condition/symptom: Drug-resistant epilepsy (children)

Children and young adults with severe and drug resistant epilepsy, such as Dravet and Lennox-Gastaut syndromes.

Recommended Product (s) - Medicinal cannabis products containing at least 98 percent CBD (cannabidiol)	
Available Pharmaceutical preparations:	None at present
Clinical Trial products being used at present:	Epidiolex® presently being used in the Compassionate Access trials in New South Wales and Queensland. Epidiolex is 98 per cent CBD in a liquid form.
Evidence of efficacy	
Evidence rating:	• Limited evidence (Barnes & Barnes 2016).

	• No reliable conclusions can be drawn at present regarding the efficacy of cannabinoids as a treatment for epilepsy (Gloss et al, 2014). • Results from Phase 3 Epidiolex trials in the USA are expected to be released early in 2017. Data will also be collected from the compassionate access schemes in New South Wales and Queensland.
Patient-class prescriber:	Paediatric neurologists will be able to treat children with severe and drug resistant epilepsy with these types of products.

2. Medical condition/symptom: Symptom control in palliative care

Loss of appetite associated with weight loss and the management of cachexia (e.g. in AIDS, cancer).

Recommended Product (s) - Medicinal cannabis products containing THC only or combination THC and CBD	
Available Pharmaceutical preparations:	Dronabinol (Marinol). Available overseas
Clinical Trial products being used at present:	Trial product from New South Wales—vaporised Bedrobinol (13.5% THC) 1mg – maximum 18mg THC daily.
Products used in Netherlands for this indication:	• Bedrocan (19% THC:<1% CBD) vaporised • Bedrobinol 12% THC:<1% CBD) vaporised.
Evidence of efficacy	
Evidence rating:	• Low - Whiting et al (2015). • Moderate—Barnes & Barnes (2016). • A multiphase study beginning in New South Wales will focus on quality of life in terminally ill cancer patients. Anticipated that the trial will take 3 years to complete
Patient-class prescriber:	Palliative medicine specialists will be able to use these types of products for patients with loss of appetite and weight loss associated with terminal illness.

3. Medical condition/symptom: Symptoms associated with multiple sclerosis (MS)

Symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.

Recommended Product(s) - Medicinal cannabis products containing 1:1 ratio of THB: CBD	
Available Pharmaceutical preparations:	Nabiximols (Sativex® Oromucosal Spray), 2.7mg (THC) 2.5mg (CBD) in an oro-mucosal spray. Registered in Australia but not available here
Clinical Trial products being used at this time:	None at this time.
Products used in the Netherlands for this indication	• Bediol (6% THC:7.5% CBD) vaporised.
Evidence of efficacy	
Evidence rating:	• Moderate—Whiting et al, 2015. • Good—Barnes & Barnes, 2016. Sativex is approved for use in Australia for patients with spasticity associated with multiple sclerosis, however it has not been marketed in Australia and therefore must be sourced from overseas. This medication is not on the Pharmaceutical Benefits Scheme (PBS).
Patient-class prescriber:	Adult neurologists treating patients with multiple sclerosis.

4. Medical condition/symptom: Chemotherapy-induced nausea and vomiting (adult)

Patients experiencing nausea and vomiting associated with highly emetic chemotherapy for which other medications have not been helpful.

Recommended Product(s) - Medicinal cannabis products that are THC only, or combination THC and CBD	
Available Pharmaceutical preparations:	• Dronabinol—synthetic THC (Marinol®) • Nabilone—synthetic analogue of THC (Cesamet). • Neither product is available in Australia
Clinical Trial products being used at this time:	New South Wales trials are using a 1:1 product (2.5mg THC: 2.5mg CBD) as an oil-filled capsule.
Products used in the Netherlands for this indication	• Bedrocan (19% THC: <1% CBD) vaporised. • Bedrobinol (12% THC: <1% CBD) vaporised.
Evidence of efficacy	
Evidence rating:	• Low—Whiting et al, 2015. • Good—Barnes & Barnes, 2016. • Dronabinol has been suggested (Walsh et al, 2003) as a fourth line therapy for the management of chemotherapy induced nausea and vomiting (adults).
Patient-class prescriber:	Oncologists (or similar specialists prescribing highly emetic chemotherapy) for patients who are experiencing nausea and vomiting not relieved by usual treatments.

Pain management

It is clear from the evidence from USA, Canada and the Netherlands that a large number of patients using medicinal cannabis products do so to manage their chronic pain. While there are some clinical trials to suggest that products high in THC may be useful in managing chronic pain there appears to be a relatively narrow therapeutic window. Because more research needs to be undertaken in this area to determine the types of pain most likely to respond to medicinal cannabis products, pain management has not been included in the patient-class prescriber pathway at this time. Pain specialists or GPs, on the written recommendation of a pain management specialist, may access the single-patient pathway if they believe a trial of medicinal cannabis is warranted for an individual patient. Medical practitioners will be required to provide high-quality and up-to-date evidence of safety and efficacy.

Dosing and administration

There are no precise dosing or established dosing schedules for products such as cannabis flos, vaporised oils, tablets or liquid (oil) capsules taken orally. Dosing is highly individualised and relies on titration of the product, regardless of the cannabinoid content, using the premise **'starting low and going slow'**. Finding the right dose, where therapeutic effect is maximised and adverse effects are minimised, requires patients and doctors to work together to determine the efficacy of the product for that patient and their medical condition.

Doses depend on the type of product used, individual variation, the development of tolerance, interaction with other drugs and previous exposure to cannabis either recreationally of medically. Lower doses are less likely to be associated with adverse effects.

Patients with no prior experience of cannabis who are initiating therapy for the first time are cautioned to begin with a very low dose, such as 1mg daily THC, and to immediately cease the product if they have any side effects. This includes:

- disorientation
- dizziness
- loss of co-ordination
- agitation
- anxiety
- rapid heart rate
- low blood pressure
- hallucinations
- psychosis.

Doses should be increased slowly, preferably weekly, until a satisfactory dose is reached.

When initiating, therapy patients should be advised to have someone with them should they experience any adverse effects. All first doses should be given in the evening to assist with management of side effects.

Doses of THC as low as 2.5–3mg (and even lower), may be associated with a therapeutic benefit and minimal psychoactivity.

Average daily use in the Netherlands is approximately 650–820mg of vaporised cannabis. The THC consumption is then dependent on the strength of the cannabis product being used.

In the absence of studies using orally ingested oils, comparison with pharmaceutical products provides the best estimate of dosing levels. The available evidence for Marinol (oral capsule of synthetic THC dissolved in sesame oil) indicates an average daily dose of 20mg THC per day, with a maximum recommended dose of 40mg THC daily.

Nabilone (Cesamet) indicates a dosing range of 0.2mg–6mg per day.

Preliminary information from recent trials with Epidiolex (orally administered oil containing CBD) suggests a daily dosing range of 5–20mg/kg CBD (dosing in children). There is no known dosing range for adults.

Sativex, an oro-mucosal spray used for the treatment of spasticity associated with multiple sclerosis, recommends commencing treatment with one spray per day (2.7mg THC: 2.5mg CBD) and then titrating to a maximum of 12 sprays per day (maximum 32.4mg THC/30mg CBD daily). Sativex has also been used in a trial of cannabis withdrawal where it produced a short-term significant improvement in withdrawal symptoms when used for the first six days, but no change from placebo in THC use at one month.

Patients should be commenced at the lowest possible dose especially in products containing THC, monitored carefully for adverse effects and increased slowly over days to weeks to determine if the product is effective.

Adverse events

A recent systematic review highlighted that there have been no studies evaluating the long-term adverse events of cannabinoids (Whiting et al, 2015). The research notes that further studies evaluating cannabis were required to improve the evidence of both the effects and the adverse events.

The authors concluded however, that cannabinoids were associated with an increased risk of short-term adverse events ranging from disorientation to psychosis. A summary estimate of adverse events with odds ratio for developing such an event in comparison to placebo or with active comparator was prepared and can be found at Appendix 2.

Any adverse event that requires alteration in the management of the patient, ceasing the medication, should be reported to the Therapeutic Goods Administration (TGA) and Queensland Health—see Appendix 1.

Monitoring of patients

As these products are unapproved medicines, it is important that patients are reviewed regularly to ensure efficacy and to manage any adverse events. While no monitoring regimes are available internationally, it would seem appropriate that using a similar monitoring program to opioids would be clinically useful.

Patients should be reviewed more frequently when commencing on medicinal cannabis products, daily if needed. Once established on a dose, monthly review is recommended.

Queensland medical practitioners prescribing medicinal cannabis will be required to submit a report on a three-monthly basis to the Medicinal Cannabis Unit. This information will be used as a means of collecting information about the use of medicinal cannabis products in Queensland, hopefully informing further research into the area. It is anticipated that this information will be published and provided to medical colleges and networks to inform medical practitioners of the outcomes of medicinal cannabis use in Queensland.

At each review the medical practitioner should ensure the following areas are covered Symptom Control; Adverse events; Aberrant behaviour; Records (SAAR):

- symptom control—is the product improving the patient's symptoms?—For example, are they eating better, experiencing less nausea and vomiting, have improved pain management and spasticity or evidence of less seizures?
- adverse events—are they reporting any side effects? For example, is there any signs of drug-drug interactions that may require adjustment of the product or the other medications?
- aberrant behaviour— are there concerns that the patient may be on-selling their product? For example, are they using more than prescribed at any one time?
- records—it is important to keep adequate records, especially as this is an unapproved medicine.

Transferring to another medicinal cannabis product

If another product is required, the treating medical practitioner should seek additional approval from Queensland Health and the TGA. Approvals will, generally, be issued with a maximum daily dose of one medicinal cannabis product and for 12 months.

Any change in the product will require a new application for approval.

Information for pharmacists and doctors (if supplying)

- Labelling—labels will be prepared in accordance with local regulatory guidelines for Schedule 8 Controlled Drugs and Schedule 4 medicines.
- Storage—medicinal cannabis products must be stored securely, as per the requirements of the Standard for security of medicinal cannabis stock
- All oil based products will require cold-chain management as well as storage requirements for S8 medicines.

  Please contact the Medicinal Cannabis Unit for further information.
- Records—practitioners who obtain and store Schedule 8 controlled drugs must keep a record book. Medicinal cannabis products will need to be recorded ion the Controlled Drugs book. Each different strength of medicinal cannabis will require a separate page.
- Disposal and destruction—any drug that is not dispensed or not used under the terms of the approval must be submitted to Forensic Scientific Services (FSS) for destruction as per the requirements of the destruction of controlled drugs under the Health (Drugs and Poisons) Regulation.

  A completed Destruction of a controlled drug form must accompany all packages for destruction.
- Loss or theft of a controlled drug (Schedule 8) — prescribers and pharmacists are required to report discrepancies, losses or theft of these medicines to the Chief Executive, Department of Health.
- Use the Department of Health notification form to notify the department of discrepancies, lost or stolen scheduled medicines. Email the completed form to MRQ@health.qld.gov.au

Additional Information can be found at:

The following list is not exhaustive but will provide some information that may be useful for health professionals**.**

It is highly recommended that medical practitioners wishing to prescribe medicinal cannabis undertake a search of the literature to establish the safety and efficacy of any products they are requesting to use. This ensures they are able to provide the best possible care for patients when using an unapproved product.

- Access to unapproved therapeutic goods: Therapeutic Goods Administration, Australia

  https://www.tga.gov.au/accessing-unapproved-products

- Cannabis Policy Framework: Centre for Addiction and Mental Health, Canada, October 2014

  https://www.camh.ca/en/hospital/about_camh/influencing_public_policy/documents/camhcannabispolicyframework.pdf

- Cannabinoids for Medical Use: A Systemic Review and Meta-analysis. Whiting et al. JAMA 2015; 313(24)2456-2473

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More information

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Appendices

Appendix 1—Adverse event reporting requirements

Reporter	Reports what?	To whom?	In what format?	In what timeframe?
Treating doctor either in a hospital or in private practice	Any adverse drug	TGA	• TGA Blue Card • Copy of Blue Card information to go to Queensland Health	As promptly as possible, to reach TGA within 15 days
		Sponsor	As required by sponsor	As required by sponsor
		Human Research Ethics Committee (HREC)*	As required by HREC	As required by HREC

* If applicable, according to local rules for use of unapproved products within an institution and/or conditions imposed by HREC on its endorsement of the treating doctor.

http://www.tga.gov.au/sites/default/files/australian-pharmacovigilance-sponsors-00-140604.pdf

Appendix 2—Leading adverse events, including odds ratio (adapted from Whiting et al, 2015)

Adverse event	Odd ratio*
Disorientation	OR 5.41
Dizziness	OR 5.09
Euphoria	OR 4.08
Confusion	OR 4.03
Drowsiness	OR 3.68
Dry mouth	OR 3.50
Somnolence (drowsiness or sleepiness)	OR 2.83
Balance problems	OR 2.62
Hallucination	OR 2.19
Nausea	OR 2.08
Paranoia	OR 2.05
Asthenia	OR 2.03
Fatigue	OR 2.00
Anxiety	OR 1.98
Vomiting	OR 1.67
Diarrhoea	OR 1.65
Depression	OR 1.32
Psychosis	OR 1.09

*The odds ratio is a measure of the increased (or decreased) chance of an event occurring compared to a comparator—in this case usually placebo.

Epidiolex

Indication	Children and young adults with severe and drug resistant epilepsy (e.g. Dravet syndrome, Lennox-Gastaut syndrome)
Product **(THC/CBD combination)**	Epidiolex® www.gwpharm.com/Epidiolex.aspx 100% CBD
Registered product	Epidiolex© is an investigational drug and has not been approved for use by the FDA or any other national regulatory agency.
Adverse events	The most common adverse events (occurring in greater than 10 per cent of Epidiolex-treated patients) were: diarrhoea, somnolence, decreased appetite, pyrexia, and vomiting. Of those patients on Epidiolex who reported an adverse event, 78% reported it to be mild or moderate.
Drug-drug interactions	Both THC and CBD are metabolised via the cytochrome P450 system therefore all other drugs metabolised through this system may be affected by the addition of cannabinoids. Levels of other anti-epileptic medications may increase with the addition of Epidiolex. CBD can induce CYP28 isozymes at very high doses up to 25mg/kg/d (Devinsky et al., 2016) Caution is also advised with utilization of other benzodiazepines, and valproic acid (Russo,E.B, 2016) Few data exist regarding drug interactions with CBD in humans, although there are some theoretical concerns that could have implications for its use in people with epilepsy (Devinsky et al, 2014)
Formulations	Liquid with dropper
Route of administrations	Oral
Dosage	Compassionate access patients were given oral Cannabidiol at 2–5 mg/kg per day, up-titrated until intolerance or to a maximum dose of 25 mg/kg.

Dronabinol—Marinol

Indication(s)	Adults with terminal illness Loss of appetite associated with weight loss in acquired immune deficiency syndrome (AIDS). Management of cachexia (AIDS, Cancer, anorexia nervosa). Chemotherapy-induced nausea and vomiting not responding to standard treatments.
Product **(THC/CBD combination)**	Dronabinol (Marinol®) – Synthetic 100% THC Registered for use in USA and Canada
Action	Onset of action within 30 to 60 minutes Duration of action about four to six hours
Adverse events	Dronabinol may cause side effects including weakness, sudden warm feeling, stomach pain, nausea, vomiting, memory loss, anxiety, confusion, dizziness, unsteady walking, feeling like you are outside of your body, 'high' or elevated mood, hallucinations (seeing things or hearing voices that do not exist), sleepiness, strange or unusual thoughts. Some side effects, such as seizures and fast or pounding heartbeat, can be serious.
Drug-drug interactions	Both THC and CBD are metabolised via the cytochrome P450 system. Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically-significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures Interactions may alter the levels of other drugs. Positive urine drug test for THC.

Precautions	• MARINOL® (Dronabinol) capsules are contraindicated in any patient who has a history of hypersensitivity to any cannabinoid or sesame oil • MARINOL® is not for use in patients younger than 18 years old. • Do not drive or operate heavy machinery • Epilepsy or other seizure disorder • High or low blood pressure • Heart disease; liver or kidney disease • History of alcoholism or drug addiction • Past or present mental illness (depression, schizophrenia, bipolar disorder, psychosis), or • If using other medicines that can affect the central nervous system, such as a tranquilizer, sleep medicine, or anti-psychotic medications. • Older adults may be more sensitive to the effects of this medication • MARINOL® may be habit-forming • Tolerance develops rapidly and is sustained • Do not smoke marijuana while taking MARINOL®, due to possible overdose • Drinking alcohol can increase certain side effects of Dronabinol.
Formulations	Tablets/capsules—2.5mg, 5mg, 10mg capsules. Note 10mg dronabinol = 1mg nabilone.
Route of administrations	Oral
Dosage **(evidence base and other pharmacological considerations for dosages)**	The pharmacologic effects of Dronabinol (MARINOL®) capsules are dose-related and subject to considerable interpatient variability. Commence dosing at lowest recommended dose and increase slowly until treatment goal is achieved Maximum dose 20mg per day. When Dronabinol is used to increase appetite, it is usually taken two times a day, before lunch and supper, or once a day in the evening or at bedtime.

Sativex

Indication(s)	Use in spasticity associated with Multiple Sclerosis (Australia) Management of advanced cancer pain (Canada)
Product **(THC/CBD combination)**	Sativex® Oromucosal Spray, nabiximols 80 mg/mL pump actuated metered dose aerosol [ARTG ID: 181978] 2.7mg (THC): 2.5mg (CBD) Registered for use in a number of countries including Australia for use in spasticity associated with Multiple Sclerosis
Action	Onset of action 30 to 150 minutes Duration four to six hours
Adverse events	Dizziness, somnolence, anxiety, trouble with memory or concentration, disorientation—all symptoms are, generally, mild and settled after a few hours. Reducing the frequency of the sprays or the amount taken will improve side effect profile.
Drug-drug interactions	Both THC and CBD are metabolised via the cytochrome P450 system. Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures. Interactions may alter the levels of other drugs. Positive urine drug test for THC

Precautions	Sativex® is contraindicated in patients who: • have a hypersensitivity to cannabinoids or to any of the excipients • have a suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition • who are breastfeeding (in view of the considerable likely levels of cannabinoids in maternal breast milk and the potential adverse developmental effects in infants). Nabiximols are not recommended for use in children or adolescents under 18 years of age due to lack of safety and efficacy data. Contraindicated in any patient who has a history of hypersensitivity to any cannabinoid or sesame oil. Do not use Sativex during pregnancy or if breast-feeding. Do not drive. Caution should be taken when treating patients: • with a history of epilepsy, or recurrent seizures • who have liver or kidney problems • who have a serious heart problems such as angina, a previous heart attack, poorly controlled high blood pressure or a problem with heart rate or heartbeat • who are elderly, especially if they have problems doing everyday activities such as making hot food and drinks • who have previously misused any drug or substance.
Formulations	Oral spray 10 mL (90 actuations of 100µl)
Route of administrations	Oral
Dosage **(evidence base and other pharmacological considerations for dosages)**	Maximum of 16 sprays per day Only use Sativex in your mouth—on the inside of the cheek or under the tongue. Storage: Store unopened Sativex upright in its carton in a refrigerator (2^{o}C to 8^{o}C).

Nabilone

Indication(s)	Control of severe nausea and vomiting associated with cancer chemotherapy agents used in the treatment of cancer, in patients who have failed to respond adequately to conventional antiemetic treatments.
Product **(THC/CBD combination)**	Nabilone - Synthetic THC analogue. (also known as Cesamet®) 100% THC Registered for use in the USA and Canada for chemotherapy induced nausea and vomiting.
Action	Onset of action 60 to 90 minutes Duration of action eight to 12 hours
Adverse events	Dizziness, drowsiness, dry mouth, dysphoria, ataxia, euphoria
Drug-drug interactions	Both THC and CBD are metabolised via the cytochrome P450 system. Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures. Interactions may alter the levels of other drugs.

Precautions	This drug is not intended to be used on an as-needed basis or as a first-line antiemetic. Nabilone is contra-indicated in patients with a known allergy to cannabinoid agents and when the nausea and vomiting arises from any cause other than cancer chemotherapy. Do NOT use nabilone if patient is allergic to any ingredient in nabilone or to other cannabinoids (e.g. marijuana). Safety and efficacy have not been established in patients younger than 18 years. The benefit/risk ratio of Cesamet use should be carefully evaluated in patients with the following medical conditions because of individual variation in response and tolerance to the effects: • Use with caution in the elderly, and in patients with hypertension or heart disease. • Use with caution in patients with current or previous psychiatric disorders, (including manic depressive illness, depression and schizophrenia). • Use with caution in individuals receiving concomitant therapy with sedatives, hypnotics, or other psychoactive drugs because of the potential for additive or synergistic CNS effects. • Use with caution in patients with a history of substance abuse, including alcohol abuse or dependence and marijuana use. • The safety aspects of the effects of hepatic and renal impairment have not been investigated. • Nabilone is purportedly highly bound to plasma proteins and undergoes extensive first pass hepatic metabolism. Those properties have the potential to lead to drug-drug interactions affecting the pharmacokinetics of similar behaving co-administered drugs or of Cesamet itself. • The effects of QT prolongation potential by Cesamet have not been determined. • Cesamet should be used with caution in pregnant patients, nursing mothers or paediatric patients because it has not been studied in these patient populations. • Elderly people may find physiological and neuropsychological effects disturbing.
Formulations	Capsule 0.25mg, 0.5mg, 1mg Note 1mg nabilone = 10 mg dronabinol
Route of administrations	Oral

Dosage **(evidence base and other pharmacological considerations for dosages)**	**Recommended dose:** 1 mg or 2 mg orally 2 times a day **Initial dose:** The dose should be given 1 to 3 hours before the first dose of the chemotherapeutic agent is administered. The lower starting dose should be used to minimize side effects; the dose can be increased as necessary. **Maintenance dose:** This drug may be given 2 or 3 times a day during the entire course of each cycle of chemotherapy and, if needed, for 48 hours after the last dose of each cycle. **Maximum dose:** Maximum dose 6mg per day (2 mg orally 3 times a day). **Comments:** A dose of 1 mg or 2 mg orally the night before each cycle of chemotherapy may be useful.