

## PRESCRIBING GUIDANCE

# PRESCRIBING CANNABIS MEDICINES FOR CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

### About this document

This Prescribing Guidance has been developed to provide practical interim information to assist NSW medical practitioners in their decision-making around prescribing, managing and monitoring the use of cannabis medicines for the management of chemotherapy-induced nausea and vomiting (CINV). The Prescribing Guidance:

- Provides a summary of standard, registered therapeutic options in the management of CINV which should be used prior to considering the use of cannabis medicines.
- Details important considerations for prescribing cannabis medicines, including precautions and adverse events, drug interactions, dosing and monitoring outcomes.
- Presents information on delta-9-tetrahydrocannabinol (THC)-based cannabis medicines, as information on the use of other medicinal cannabinoids (other than THC) cannot be provided at this stage due to very limited evidence in the literature.
- Draws extensively on the [Therapeutic Goods Administration \(TGA\)](#) guidance documents and, as such, requires medical practitioners to review the TGA's guidance before making a decision to prescribe cannabis medicine products.

### Key Points

- The Australian Government's [Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia](#)<sup>1</sup> summarises the current evidence base for the use of cannabis products in the context of CINV. This review has shown that published evidence is of moderate quality at best. Further, interpretation of evidence should be done with the knowledge that the three most recently registered classes of anti-emetics for treatment of CINV have not been studied against medicinal cannabis. As these classes of drugs are significantly safer and more effective than earlier emesis agents, it is likely that medicinal cannabis products are inferior from an efficacy perspective to newer agents.
- It is important that all standard, registered therapeutic options are exhausted or deemed inappropriate (due to adverse effects or contraindications) prior to the consideration of a cannabis medicine for CINV.
- Medical practitioners should review the guidance advice made available by the [TGA](#) before making a decision to prescribe medicinal cannabis products for CINV.
- NSW-based medical practitioners can obtain further information and assistance with prescribing tailored to the patient-specific clinical context from the [NSW Cannabis](#)

[Medicines Advisory Service](#) by [email](#) or by telephone (02) 4923 6200.

### Current clinical trials

- **Cannabis Medicine Clinical Trial for Chemotherapy-Induced Nausea and Vomiting**  
A NSW Government funded [placebo controlled trial](#) evaluating an oral THC/CBD cannabis extract for secondary prevention of CINV in patients of any known malignancy receiving chemotherapy. See the [Australian New Zealand Clinical Trials Registry](#) for further information on the study.

### Use of evidence-based therapies for CINV in patients

Australian patients with CINV should first be treated according to the ASCO (2017)<sup>2</sup>, MASCC/ESMO (2016) clinical practice guidelines, nationally accepted guidelines (eviQ) and other recognised locally-accepted treatment guidelines.

Pharmacokinetic and pharmacodynamic interactions between medicinal cannabis and antineoplastic agents are predicted but not fully elucidated. THC and cannabidiol (CBD) are substrates of the P450 system with significant inhibitory and inducing effects on some enzymatic pathways, depending on the cannabinoid. From a pharmacodynamic perspective, there is evidence that cannabinoids that bind to the CB2 receptor (including THC) impact on T-cell function. Thus these drugs may be thus contraindicated in patients whose therapy involves immune modulation and activation of cytotoxic T-cells<sup>5</sup>.

### Summary of best practice in management of CINV in patients

**Antiemetic Guidelines for Chemotherapy-induced Nausea and Vomiting** (based on ASCO Clinical Practice Guideline, 2017<sup>2</sup>) - see over page.

## Summary of Best Practice in management of CINV in patients

### High-emetic risk antineoplastic agents: 4 drug combination of

- NK1 receptor antagonist
- 5HT3 receptor antagonist
- Dexamethasone
- Olanzapine

### Moderate-emetic risk antineoplastic agents:

Carboplatin AUC  $\geq$  4 mg/mL/min: 3 drug combination of

- NK1 receptor antagonist
- 5HT3 receptor antagonist
- Dexamethasone

All others: 2 drug combination of

- 5HT3 receptor antagonist
- Dexamethasone

High risk delayed nausea and vomiting:

- Continue dexamethasone

### Low-emetic risk anti-neoplastic agents:

- 5HT3 receptor antagonist OR
- Dexamethasone

### Minimal-emetic risk anti-neoplastic agents:

- Routine antiemetic prophylaxis not offered

### Breakthrough N&V:

- Re-evaluate emetic risk and ensure adequate prophylactic antiemetic prescribed
- Assess disease status, concurrent illness, other medications
- Add olanzapine
- Add NK1 receptor antagonist
- Add lorazepam

Then:

- Consider dronabinol or nabilone
- Evidence is insufficient for any other medical cannabis product

### High-emetic risk radiotherapy: both

- 5HT3 receptor antagonist
- Dexamethasone

### Moderate-emetic risk radiotherapy:

- 5HT3 receptor antagonist
- And/or dexamethasone

### Low-emetic risk radiotherapy – Rescue as needed with:

Brain RT: dexamethasone

Head/neck/thorax/pelvis RT:

- 5HT3 receptor antagonist
- OR dexamethasone
- OR dopamine receptor antagonist

### Chemotherapy + radiotherapy:

Antiemetic regimen as per highest chemotherapy emetic risk until chemo completed, then as per highest RT emetic risk

## PRACTICE POINTS

### Antineoplastic combinations:

Prescribe antiemetics based on the antineoplastic component with the highest emetic risk

### Multi-day regimens:

Prescribe antiemetics appropriate for risk on every day of the cycle and for 2 days post cycle

### Anticipatory nausea and vomiting:

- Prevention is better than cure
- Lorazepam
- Behavioural therapy with systematic desensitisation

## Prescribing medicinal cannabis for the management of CINV in patients

If the decision to proceed to cannabis prescription is made, please consider the following information.

Working through the following information will assist medical practitioners in completing the regulatory paperwork required to prescribe medicinal cannabis.

### The Prescriber

The prescriber should have a key involvement in provision of care. The prescriber may be an oncologist, a specialist in palliative and supportive care, or a general physician/general practitioner in liaison with the patient's oncologist. It is important that all members of the treating team are aware of the decision to prescribe a cannabis medicine. It is also important that this information is communicated to other members of the care team in writing.

The prescriber should have an ongoing therapeutic relationship with the patient. Follow up, assessment of efficacy, side effects, and pharmacovigilance is essential.

Given the current status of cannabis medicines as unregistered medicines, prescribers should consider seeking advice from their medical indemnity insurers prior to prescribing.

### The Patient

The patient must give informed consent to treatment. The consent process should include:

- This is an unregistered medicine (and costs may reflect this).
- The efficacy of this experimental therapy is still being researched.
- Awareness of the likely effects and side effects of treatment.
- There will be restrictions on driving and operating heavy machinery.
- The patient should also be given clear information about therapeutic goals and likely stopping criteria.
- Potential for dependence or withdrawal.

**Patients should be advised that they are not able to drive while treated with medicinal cannabis.**

Patients should be informed that measurable concentrations of THC can be detected in saliva for significant periods of time after administration. Further information is available from the [Transport for NSW Centre for Road Safety](#) and in [NSW Health's Prescribed Cannabis Medicines and Fitness to Drive Factsheet](#).

## Prescribing a cannabis medicine: important considerations

The following has been adapted from the TGA's [Guidance for the use of medicinal cannabis in Australia: Patient information](#)<sup>3</sup>.

### Cannabis products

- A variety of products are available.
- There are up to 100 cannabinoids (chemical compounds) in the cannabis plant.
- Many of the studies described in the medical literature have used either smoked cannabis (which is not recommended on health grounds), purified tetrahydrocannabinol (THC) or cannabidiol (CBD).
- THC is responsible for the psychoactive effects of cannabis and is the main reason cannabis is used recreationally. THC may contribute to reduction of nausea, vomiting, pain and muscle spasms as well as improvements in sleep and appetite. However it may also worsen these symptoms.
- CBD is psychoactive and causes sedation, but it appears non

intoxicating. It may be useful in the management of seizures, pain, and may have anxiolytic and antipsychotic effects. Adding CBD to a THC product in a patient with toxicity to reduce toxicity is unproven. It is more appropriate to reduce the dose and/or frequency of THC.

- Different cannabis products contain different CBD components, and different ratios of THC to CBD.
- There are other cannabinoids under research for CINV including cannabigerol (CBG), tetrahydrocannabivarin (THCV), cannabiol (CBN) and cannabichromene (CBC).

### Route of administration

#### Smoking

- Rapid onset of action, usually within minutes.
- High levels of blood THC with shorter duration of effect.
- Peak concentration in 30 minutes, effects last 2-4 hours.
- Significant individual variability due to unknown quantity of THC in product and loss of active agent in "side stream" or combustion during smoking.
- Smoking is well known to be harmful and not recommended on health grounds.

#### Vaporising

- Rapid absorption and high blood concentrations.
- Fewer contaminants and reduced "side stream" (when vaporised).
- Peak concentration in 15-30 minutes, effects last 2-4 hours.
- Useful for symptoms requiring rapid relief.
- Titration of dosing may be easier with oro-mucosal sprays than oral formulations.
- Sprays may be easier for those with difficulty swallowing.

#### Oral administration and oro-mucosal sprays

- Oils or liquid capsules are available.
- Slow onset of action with first effects at 30-90 minutes, peak effect at 2-4 hours.
- Effects can last 8-24 hours.
- Useful for symptoms requiring relief over longer periods of time (similar to controlled release medications).

#### Topical

- Cannabinoids are highly lipophilic compounds and this may facilitate permeation into the skin. However, the degree of water solubility (or polarity) of these compounds will also influence the rate and extent of transfer across the skin.
- Cannabidiol and Cannabinol are better absorbed topically and more likely to be available in topical preparations.
- Time of onset and duration of action are unknown and therefore would not be recommended for first line use.

### Evidence for use

The following has been adapted from the [Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia](#)<sup>1</sup>.

There is an absence of reliable evidence of the efficacy of medicinal cannabis in the treatment of CINV according to relative emetogenicity of chemotherapeutic regimens, or against currently available anti-emetic regimens.

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SEE NEXT PAGE FOR 'SUMMARY OF EVIDENCE FOR CANNABIS AND CANNABINOIDS FOR THE TREATMENT OF NAUSEA AND VOMITING' TABLE.

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Cannabinoid product	Condition	Preparation	Administration	Standardised
Dronabinol	CINV*	Capsule	Oral	Yes
	Cancer-associated N&V	Capsule	Oral	Yes
	CINV*	Capsule	Oral	Yes
Nabilone	Cancer-associated N&V*	Capsule	Oral	Yes
	CINV*	Capsule	Oral	Yes
	CINV*	Dissolved formula	Intramuscular injection	Yes
THC	CINV*	Liquid	Oromucosal spray	Yes
Nabiximols/THC:CBD	CINV*	Cigarette	Inhalation	Not specified

**Table 1. Summary of evidence for cannabis and cannabinoids for the treatment of nausea and vomiting.**  
See [Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia](#)<sup>1</sup>.

\*No studies of these medicinal cannabis products have been performed against the most recently approved antiemetics, considered the most efficacious available in adequately designed and performed randomised clinical trials.

The TGA's *Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia*<sup>1</sup> notes a single study using nabiximols (Sativex®) showing a positive effect, however the study was at high risk of bias.

The Australian product information for nabiximols (Sativex®) notes some patients experience nausea and vomiting when administered this product.

Nausea is noted as a common side effect from dronabinol (Marinol®).

## Precautions

The following has been adapted from the TGA's [Guidance for the use of medicinal cannabis in Australia: Overview](#)<sup>4</sup>.

Cannabis medicine products containing THC are generally **not appropriate** for patients who:

- Have a previous psychotic or concurrent active mood or anxiety disorder.
- Are pregnant, planning on becoming pregnant, or breastfeeding.
- Have unstable cardiovascular disease.

Any allergies to potential carrier oils (e.g. sesame, canola, sunflower) should be noted as products available in Australia often contain oils. This may influence product selection.

Consider concomitant medication use and potential for pharmacokinetic and pharmacodynamic drug interactions (see below)

## Adverse effects

The following has been adapted from the [Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia](#)<sup>1</sup>.

Patients and prescribing clinicians should be aware of possible adverse events such as somnolence, nausea and dizziness from cannabinoid products. Common adverse events such as confusion, pain, diarrhoea or hallucinations may impact the therapeutic goal (control of nausea) and reduce quality of life, and should be evaluated on a case-by-case basis.

Serious adverse events have been described clinically, such as psychosis and cognitive distortion requiring external assistance, but the severity, time course and further details are not recorded.

Details of the incidence and severity of adverse events with most

cannabis medicine products are lacking, as reported in the literature.

Based on the available studies, the most commonly reported adverse events in the use of cannabis medicines in nausea and vomiting include in order of frequency:

- dysphoria and or depression (13% of patients)
- hallucinations (6% of patients)
- paranoid delusions (5% of patients)
- drowsiness (proportion not reported)
- dry mouth (proportion not reported).

The cessation of long-term (of more than several months) use of THC-based medicines may also be associated with the experience of discontinuation effects.

## Drug Interactions

The current available information on drug interactions with cannabinoids is mainly sourced from the product information on Marinol® (THC) and Sativex® (THC and CBD combination)<sup>7,8</sup>.

Ongoing reports of potential interactions to the TGA are vital to improve the data in this area.

## Pharmacokinetic interactions

- delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolised by the cytochrome P450 enzyme system.
- In vitro studies have shown Sativex® has CYP450 enzyme inhibition effects, however this occurred at concentrations significantly higher than the maximum observed in clinical trials.
- In patients on clobazam, increased active metabolite N-desmethyloclobazam (nCLB) concentrations were noted<sup>11</sup> likely due to CYP2C19 and CYP3A4 inhibition by CBD<sup>12</sup>. Higher nCLB concentrations were associated with a higher frequency of reports of sedation<sup>11</sup>.
- If concomitant drug treatment with CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin) is started or stopped, a new dose titration will be required. If concomitant drug treatment with strong enzyme inducers (e.g. rifampicin, carbamazepine, St John's wort) is started or stopped, a new dose titration will be required.
- Monitor for potentially increased delta-9-THC -related adverse reactions when co-administered with inhibitors of CYP2C9 (e.g. amiodarone, fluconazole) and inhibitors of CYP3A4 enzymes (e.g. ketoconazole, itraconazole, clarithromycin, ritonavir, erythromycin, grapefruit juice).
- delta-9-THC is highly bound to plasma proteins and might displace and increase the free fraction of other concomitantly administered protein-bound drugs. Although this displacement has not been

confirmed *in vivo*, monitor patients for increased adverse reactions to narrow therapeutic index drugs that are highly protein-bound (e.g. warfarin, ciclosporin, amphotericin B) when initiating treatment or increasing the dosage of delta-9-THC.

- Based on *in vitro* data, an inhibition of P-glycoprotein at the intestinal level by CBD cannot be excluded. Therefore, caution is recommended upon concomitant treatment with digoxin and other substrates for P-glycoprotein.

## Pharmacodynamic interactions

### Sedation

- Care should be taken with hypnotics, sedatives, opioids, benzodiazepines, anticholinergics and antihistamines as there may be an additive effect on sedation and muscle relaxing effects.
- Cannabis medications may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly. In general, alcoholic beverages should be avoided.

### Cardiac toxicity

- Additive hypertension, tachycardia, possibly cardiotoxicity with amphetamines, cocaine, atropine or other sympathomimetic agents.

### Psychiatric effects

- Case reports of hypomania when cannabis is co-administered with fluoxetine and also disulfiram.

### Musculoskeletal

- Care should be taken when co-administering Sativex® with antispasmodic agents since a reduction in muscle tone and power may occur, leading to a greater risk of falls.

## Dosing

In general:

- Start at low dose and frequency.
- Titrate to effect whilst monitoring for side effects.
- Patient response to these medications varies widely.
- Favour lower doses in the elderly who may be at higher risk of CNS and cardiac adverse effects.

**The following are examples only – doses should be individualised for patient and indication. Dosing advice can only be provided on THC-based cannabis medicines. Information on the use of other medicinal cannabinoids (other than THC) cannot be provided at this stage due to limited evidence in the literature.**

Please refer to Table 1 of the TGA [Guidance for the use of medicinal cannabis for the prevention or management of nausea and vomiting in Australia](#)<sup>1</sup> for a summary of existing evidence for cannabis and cannabinoids.

**Example for THC** – adapted from Dronabinol (Marinol®) product information (for treatment of chemotherapy-induced nausea and vomiting)<sup>7</sup>:

- Starting dose 2.5 mg/m<sup>2</sup> once daily, given 1-3 hours prior to chemotherapy.
- Monitor for side effects.
- The dosage can be titrated to clinical response based upon initial response, as tolerated, in increments of 2.5 mg/m<sup>2</sup>.
- In light of current evidence, generally there should be a maximum dose of 30 mg of tetrahydrocannabinol per day. Beyond this dose, the risk of adverse effects may increase.

**Example of dosing for THC:CBD product** — using Sativex® oromucosal spray in chemotherapy induced nausea and vomiting<sup>8</sup>.

- Slow titration over two weeks, initially one spray per day.
- The mean number of sprays required for symptom relief was 4.81 per day (i.e. THC 12.5 mg/CBD 12.98 mg in divided doses daily).

## Monitoring Outcomes

Monitoring should initially involve reviewing the patient weekly in person, and via phone if required in the interim between clinical reviews.

There are three areas of outcomes that should be considered:

### 1. Symptom control

A pre-defined measure of success should be negotiated with the patient prior to commencement of therapy. This can be measured by using a validated tool, for example by the [Palliative Care Symptom Assessment Scale](#).

### 2. Drug adverse events

Careful monitoring of patients for adverse events and the need for a change in dosage is important. Adverse events may become apparent after commencement or after change in dose.

Adverse events may be related to other concurrent medications. Doses of these medicines should be adjusted as appropriate.

Significant adverse events observed with unregistered medicines must be reported to the TGA (including dependence and withdrawal symptoms). Although some of the adverse events are well known (e.g. psychosis, anxiety) it is still important to notify the TGA when these events occur to enable patterns of toxicity and contributing factors to be elucidated, to support future prescribing information.

### 3. Pathology monitoring

Drug concentrations of drugs where there is a potential or actual drug-drug interaction may be important.

Cannabidiol may cause hepatocellular injury. Patient's liver function biochemistry should be monitored prior to initiation and periodically as clinically indicated.

## Cessation and withdrawal

The cessation of long-term (of more than several months) use of THC based medicines may be associated with the experience of discontinuation effects. These can be categorised as relapse and/or withdrawal effects.

Relapse refers to a worsening of the underlying condition (e.g. CINV) for which THC is being prescribed.

The cessation of heavy (e.g. daily or almost daily) and prolonged (of several months or more) cannabis use can be associated with a withdrawal syndrome in up to 15 to 40% of long term cannabis users<sup>13,14</sup>. The features of cannabis withdrawal as defined in DSM5 are shown in Table 2 (see over page), with sleep problems (e.g. vivid dreams, insomnia), depressed mood and irritability/anxiety most commonly reported. Symptoms tend to emerge within 2-3 days of last THC use, peak within 4 to 14 days, with some residual symptoms persisting for 2-6 weeks<sup>15</sup>.

For those looking to discontinue THC based medication, a gradual dose taper over 4 to 8 weeks is generally recommended to minimise the severity of cannabis withdrawal symptoms.

There is no effective pharmacotherapy for managing cannabis withdrawal at this time, and supportive care is recommended. Consider a referral to Alcohol and Drug Service or Addiction Medicine specialist for patients experiencing difficulties with withdrawal.

It should be noted that there is no recognised withdrawal syndrome associated with cessation of CBD.

<b>Criterion A</b>	Cessation of cannabis use that has been heavy and prolonged
<b>Criterion B</b>	3 or more of the following seven symptoms develop within several days of Criterion A: 1. Irritability, anger or aggression 2. Nervousness or anxiety 3. Sleep difficulty (insomnia) 4. Decreased appetite or weight loss 5. Restlessness 6. Depressed mood 7. Physical symptoms causing significant discomfort from at least one of the following: stomach pain, shakiness/tremors, sweating, fever, chills, headache
<b>Criterion C</b>	The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
<b>Criterion D</b>	The symptoms are not due to a general medical condition and are not better accounted for by another disorder

Table 2. DSM-5 Diagnostic Criteria for Cannabis Withdrawal Syndrome<sup>16</sup>

## Further Information

- NSW-based medical practitioners can obtain further information and assistance with prescribing tailored to the patient-specific clinical context from the [NSW Cannabis Medicines Advisory Service](#) by [email](#) or by telephone (02) 4923 6200.
- Information on the NSW Prescribing Pathways for unregistered cannabis medicines is available from the NSW Government's [Centre for Medicinal Cannabis Research and Innovation](#).
- Information on NSW-based regulatory requirements around applying for and supplying Schedule 8 cannabis medicines, including requirements of the prescriber, dispensing and storage is available from the NSW Government's [Pharmaceutical Services](#) page on Cannabis Medicines.

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