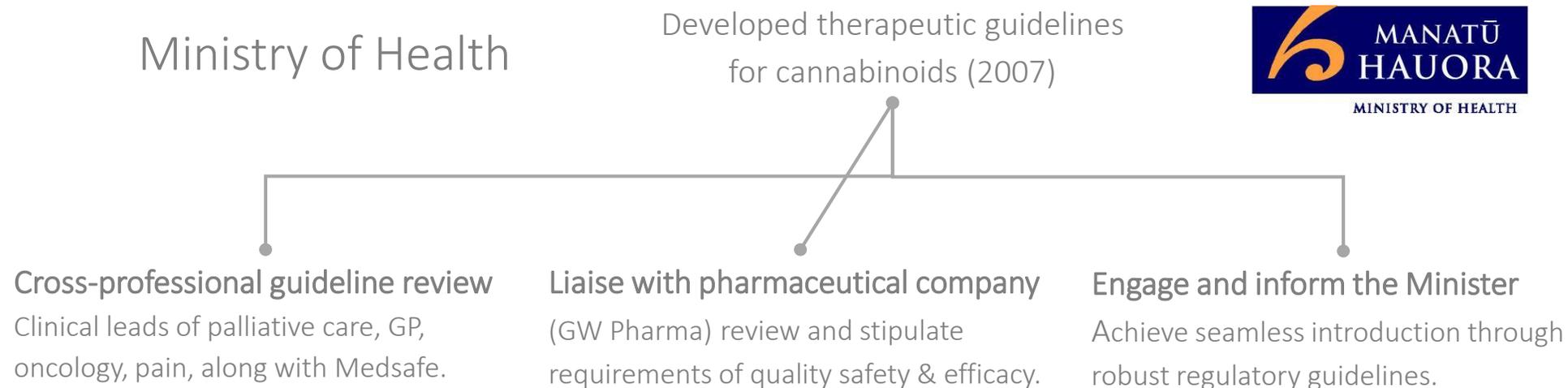




Use of cannabinoids in symptom management

Why cannabinoid therapeutics?

A need, evidence and a therapeutic product existed



Why?

Further need exists, now with greater supporting evidence and therapeutic options

Palliative care setting (example)

Therapeutic option exist

Pharmaceutical quality (GMP) in various administration formats.

Clinical insight and clinical research

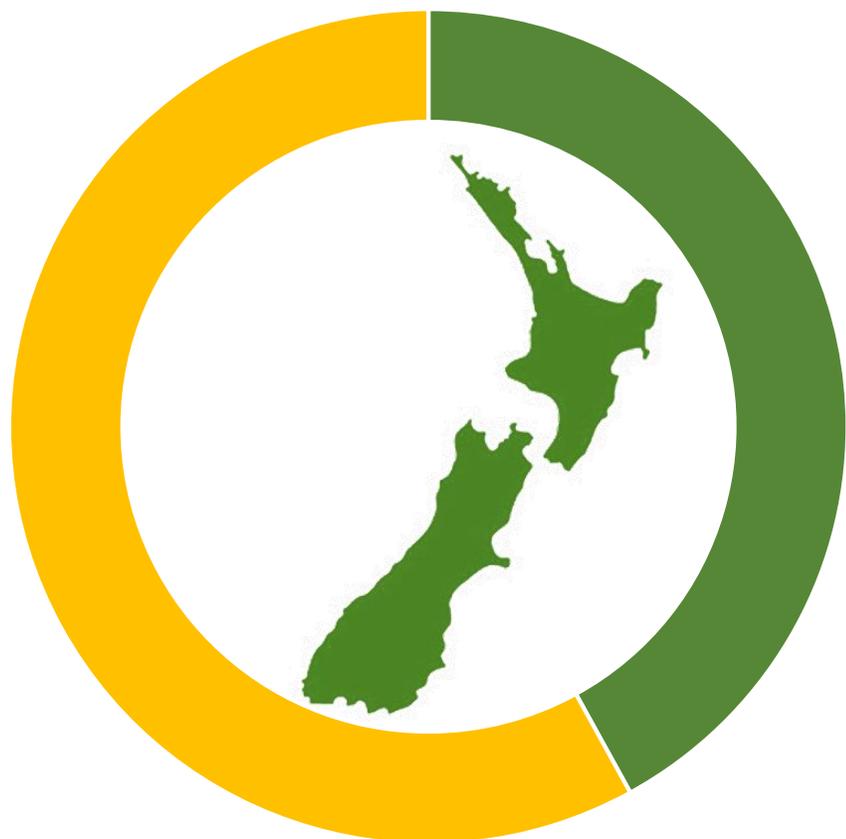
Trials (RCT) relevant to symptom management. Patient use worldwide.

A decade of use in New Zealand

Cannabis therapeutics now used a community setting since 2008.



Patient use



Despite its illegality, 42% of cannabis users reported using it medicinally in the last 12 months to treat pain, anxiety/nerves, depression, nausea

Reference: Cannabis Use 2012/13: New Zealand Health Survey



Patients use



The problem with unregulated products – ‘illegal cannabis’

Cannabis, as a botanical substance, can vary greatly in cannabinoid content, from one plant to the next, and batch-to-batch.

This can lead to inconsistent and unpredictable effects.

Often illegal cannabis contains pesticides, heavy metals, and toxic moulds and fungus.



Patient use

New Zealand



104 applications to prescribe
Sativex now approved (at January 2016)

Mainly prescribed off-label, that is for conditions other than MS.



Patient use

The Netherlands



The utilisation of medicinal-cannabis among the Dutch population who receive prescriptions for medicinal-cannabis suggest:

- Half of patients use another form of pain medication, 46 % used psycholeptics, 44 % used analgesics, 40% used anti-ulcer agents and 31% used NSAIDs.
- Medicinal-cannabis relieves patients' pain, stimulates their appetite, reduces nausea and improves their sleep.
- On average, these patients use 0.7 grams of standardised cannabis flos per day, divided over multiple portions, for about 250 days in total.

Since 2003 the Dutch medicinal cannabis programme has delivered standardised cannabis flos, prescribed by doctors and dispensed by pharmacists



Pharmacology

ligands and receptors

Endocannabinoid system

Essential role in homeostasis of bodily functions. Involved in regulation of appetite, sleep, pain, inflammation.

Cannabinoid receptors

CB1: CNS, heart, intestines, bladder. CB1 is one of the most prominent receptors in the brain.

CB2: immune system, spleen, tonsils

Exogenous ligands (phyto-cannabinoids).

THC and CBD identified and isolated



Cannabis plant -
cannabinoids

Exogenous ligand –
cannabinoids

Cannabinoid *G protein-*
coupled receptors



Opium poppy –
opium derivatives

Exogenous ligand –
opioids

Opioid *G protein-coupled*
receptors

Reference:

- Pertwee. 2006. The pharmacology of cannabinoid receptors and their ligands: an overview. *International Journal of Obesity*. 30, S13–S18.
- Pertwee. 2006. Cannabinoid pharmacology: the first 66 years. *British Journal of Pharmacology*. 147, S163–S171



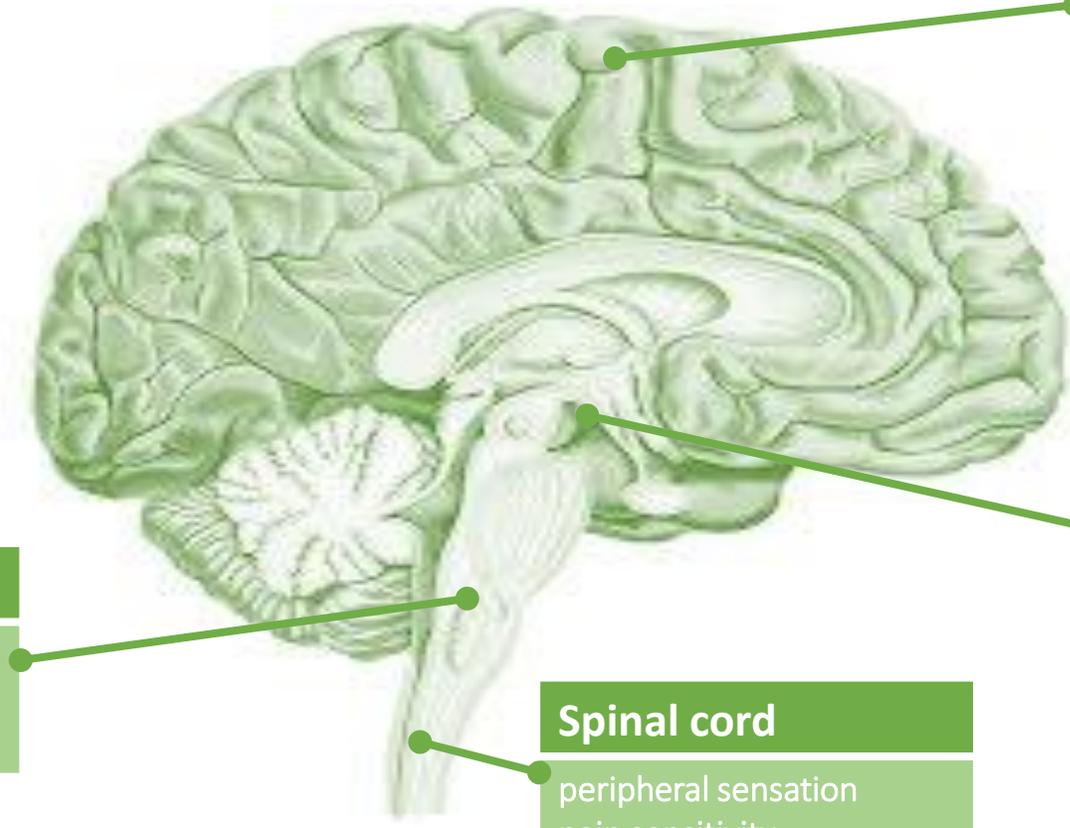
CB1 receptor

concentrated areas

nausea, appetite, pain, emotion

Medulla oblongata

nausea/vomiting centre
chemoreceptor trigger
zone



Cerebral cortex

Higher cognitive and
emotional functions

Hypothalamus

appetite

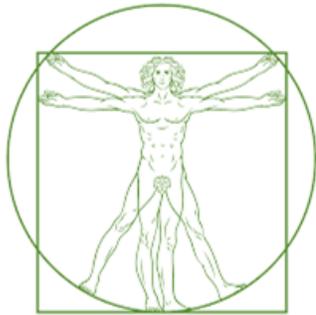
Spinal cord

peripheral sensation
pain sensitivity

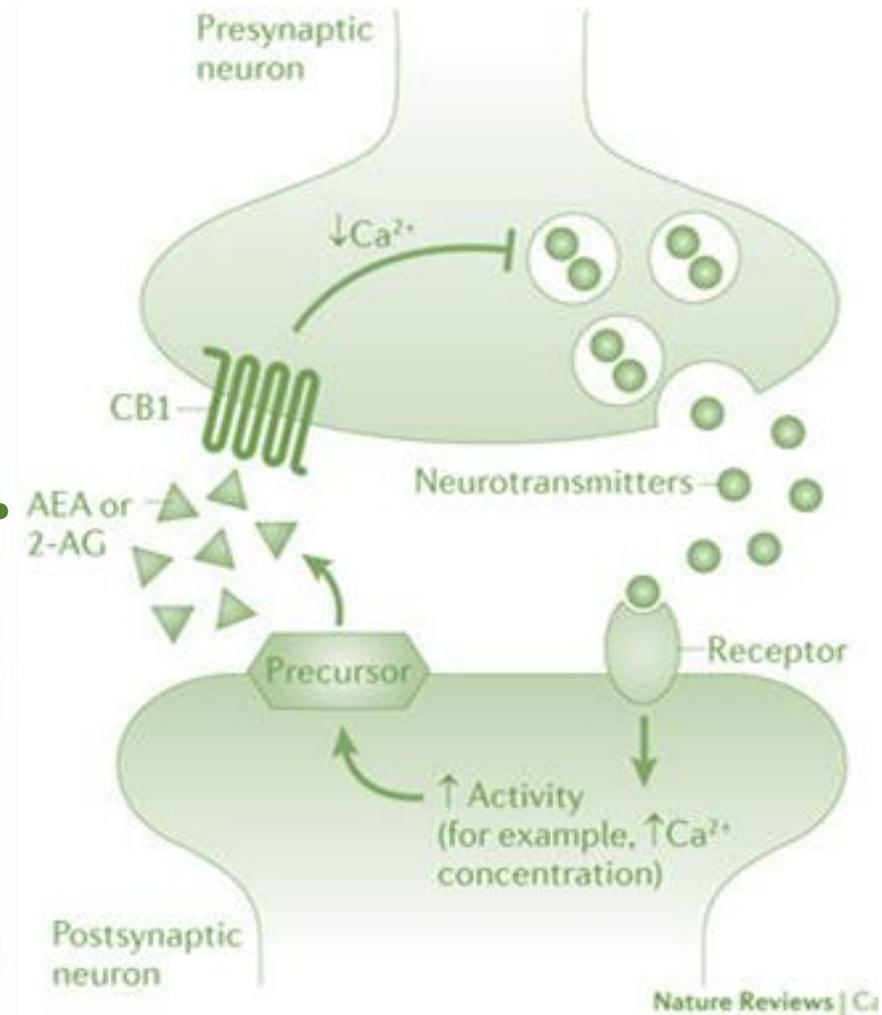
Pharmacology



Phyto-cannabinoids



Endo-cannabinoids



Clinical trials

review of data

Chronic pain

Between
2005 – 2015

- 69 studies
- 5860 patients

Spasms (MS & epilepsy)

Palliative (sleep, appetite, relaxation)

Appetite, vomiting & nausea

- Patient use surveys indicate pain as the main indication for medicinal cannabis use.
- The effects of cannabinoids on chronic pain is the most researched topic.

Reference:

- Hazekamp & Grotenhermen. 2010. Review on clinical studies with cannabis and cannabinoids 2005-2009. *Cannabinoids*; 5: 1-21
- Kowal, Hazekamp, Grotenhermen. 2016. Review on clinical studies with cannabis and cannabinoids 2010-2014. *Cannabinoids*; 11 (special issue):1-18.



Palliative care



Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.



In particular, palliative care:

- provides relief from pain and other distressing symptoms
- will enhance quality of life, and may also positively influence the course of illness



WHO Definition of Palliative Care: www.who.int/cancer/palliative/definition/en/



Palliative care setting

Compared to most other patients

- The doctor-patient relationship is more intensive and structured
- Prescribing is very well planned and monitored
- The risk of medicine diversion for misuse use may be less
- Adverse drug reactions are, possibly, more readily identified and resolved (and reported).

Types of palliative care-related prescriptions by category

- **analgesics**
- anti-emetics and anti-nauseants
- **anti-epileptics**
- anti-inflammatory & anti-rheumatics
- drugs for functional GI disorders
- **laxatives**
- **psycholeptics**
- stomatological preparations

analgesics



anti-emetics &
anti-nauseants



Reverence: Palliative Care Services Australia 2014.
www.aihw.gov.au



Wellbeing

appetite, nausea

In terms of palliative care, better understanding is needed of how cannabinoids might relieve nausea, or increase appetite, without side effects.

There is a lack of evidence about the efficacy and safety of cannabis-based therapies.

In particular, more is needed to know

- how to optimise the dose
- the best mode of administration
- the time that peak levels occur
- the length of time they are active



Clinical trials

wellbeing

The first of its kind in Australia, a double-blind randomised controlled trial (led by Professor Meera Agar, a NSW palliative care specialist) will explore whether vaporized medicinal cannabis flos can promote appetite and improve quality of life among cancer patients.

Vaporised cannabis flos

- Eliminates the respiratory risks of smoking
- Allows reliable dosage
- Is suitable for patients finding swallowing difficult.

Study protocol

- Delivers therapeutic concentrations of cannabinoids before meal times
- Profiles cannabinoids in the blood stream after the dose
- Examines the impact on appetite and related symptoms
- Examines impact on quality of life.

For people with cancer, the pathways that promote appetite are disrupted.

Their quality of life is reduced due to fatigue, low mood, nausea and insomnia – aspects critical to health and wellbeing.

Refer to:

www.medicinalcannabis.nsw.gov.au/__data/assets/pdf_file/0017/755/medicinal_cannabis_palliative_practitioner.pdf



Pain

clinical data

- THC * /CBD * is effective in chronic cancer pain relief alone and when added to standard opioid therapy.
- THC may target the affective quality of pain, instead of simply reducing pain intensity. CBD may modulate the effects of THC.
- The interactions between THC and CBD highlights the complexity of studies on cannabinoid-based drugs.
- For cannabis flos, specifically, the potential synergy of the cannabis terpene compounds define the final effect of the drug.
- Specific concentrations of THC or CBD, alongside subtle differences in plant composition may significantly affect the drug's ability to treat specific medical conditions.

* THC delta-9-tetrahydrocannabinol;

* CBD: cannabidiol

Reference:

- Hazekamp & Grotenhermen. 2010. Review on clinical studies with cannabis and cannabinoids 2005-2009. *Cannabinoids*; 5: 1-21
- Kowal, Hazekamp, Grotenhermen. 2016. Review on clinical studies with cannabis and cannabinoids 2010-2014. *Cannabinoids*; 11 (special issue):1-18.



Pain ladder

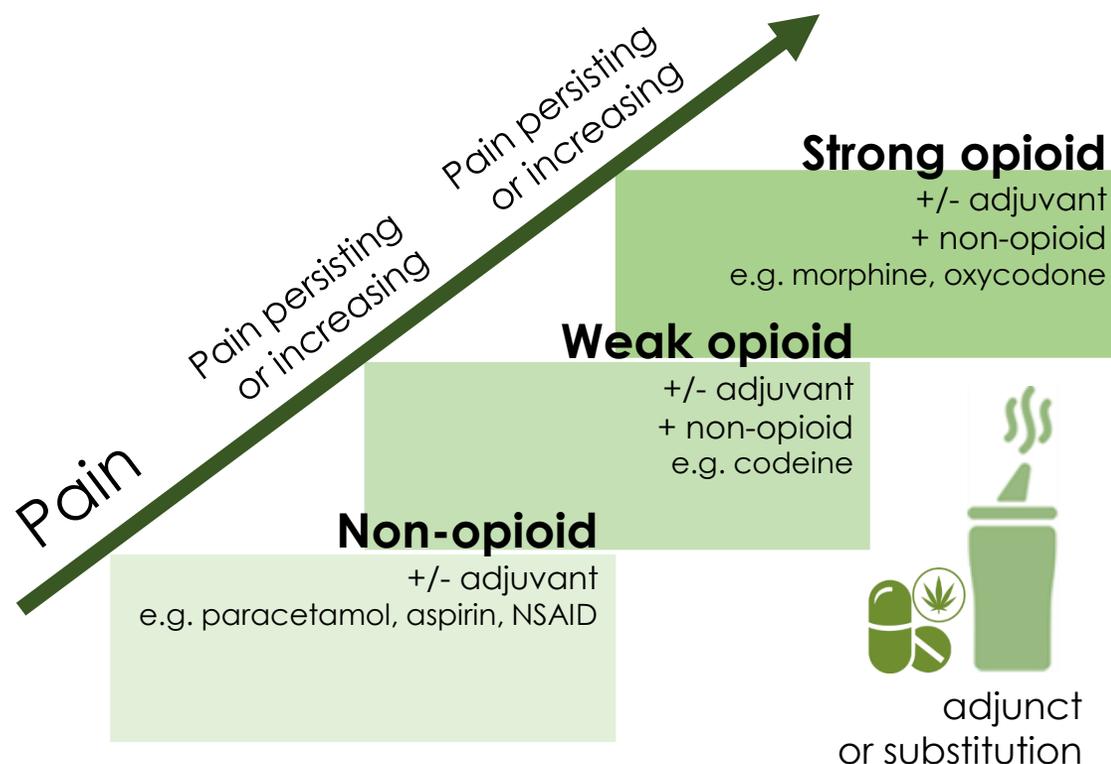
extending therapeutic option

According to WHO, if cancer pain occurs, there should be prompt oral administration of drugs in the following order:

- non-opioids (aspirin and paracetamol);
- then, as necessary, mild opioids (codeine);
- then strong opioids such as morphine, until the patient is free of pain.

Is it appropriate and justified to add cannabinoids?

It is appropriate and justified to substitute with cannabinoids?



Reference: www.who.int/cancer/palliative/painladder/en/



Pharmaceutical quality

Cultivation (GAP and GMP)

GAP: good agricultural practice | GMP: good manufacturing practice

Production – finished dose manufacture (GMP)

Quality specifications

- certificate of analysis from accredited lab
- consistent API content batch-to-batch
- no heavy metals or pesticides
- microbial content at acceptable levels

Dose forms

- vaporization (via medical device)
- oral

References:

- Gieringer, Hazekamp. 2011. How accurate is potency testing? O'Shaughnessy's. Autumn: 17.
- Hazekamp. 2006. An evaluation of the quality of medicinal grade cannabis in the Netherlands. Cannabinoids; 1(1):1-9

Internationally, the quality of medicinal-cannabis products can vary greatly

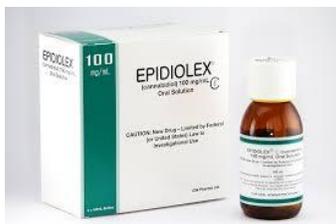


Pharmaceutical quality

GW Pharmaceuticals (UK)



Sativex: THC:CBD extract
Prescription medicine
Admin: sublingual spray



Epidiolex: CBD
Admin: oral dose

Bedrocan BV (NT)



Bedrocan: GMP cannabis flos
Prescribed medicine (NL)
Admin: vaporization
(oral dose forms also available)

AbbVie Inc. (USA)



Marinol: synthetic THC (Dronabinol)
Prescription medicine
Admin: oral dose

Valeant Pharma. Int. (USA)

Cesamet: synthetic THC (Nabilone)
Prescription medicine
Admin: oral dose



Administration

Smoking

Inhalation of smoke



Oral ingestion

Taken by mouth (swallowed)



The four most common ways medicinal-cannabis is taken by patients across the world.

Hazekamp, A., Ware, M., Muller-Vahl, K., Abrams, D., Grotenhermen, F. (2013). The medicinal use of cannabis and cannabinoids - An international cross-sectional survey on administration forms. *Journal of Psychoactive Drugs*. 45(3):199-210.

Vaporization

Converted into a vapour - inhaled



Tea (infusion)

Taken by mouth/swallowed



Vaporization



The most efficient route of administration is inhalation

The use of a vaporizer medical device avoids the respiratory disadvantages of smoking



Vaporization



Administration

Absorption via the lungs may reduce total daily intake.



Dose type

Cannabis flos is used in granulated (ground up) form. A vapour of therapeutic cannabinoids and terpenes is inhaled



Onset

First effects can be noticed within minutes.



Duration

Typically between 2 - 4 hours.



Safety

Harmful compounds are virtually absent.

Fully standardised, pharmaceutical-quality cannabis flos provides an optimal medicinal product for vaporization and inhalation into the lungs.

The vapour of cannabis flos contains therapeutic levels of cannabinoids and terpenes. Harmful compounds are virtually absent, making it suitable for use by immune-compromised patients.

The vapour content is rapidly absorbed by the lungs, improving the ability to adjust dose and therefore minimize side effects. There are no pyrolytic compounds that constitute a risk for second-hand exposure.



Vaporization

developments



Raw Cannabis



Constant Cannabinoid Levels
Pharmaceutical-Grade

Structural Modification



No Chemical Alteration
No Added Excipients

Preloaded Cartridges



Uniquely Identified
Child Proof

Metered-Dosed Delivery



100 Microgram Resolution
Selective Dosing

www.syqemedical.com



Access

Where New Zealand is at:

- Guidelines for access and use – see Ministry of Health website
- Case-by-case basis
- Sativex™ registered for MS spasticity – predominantly prescribed off-label
- Other pharmaceutically derived products will be accessible

New Zealand is
taking a
measured,
cautious
approach

www.health.govt.nz/our-work/regulation-health-and-disability-system/medicines-control/prescribing-cannabis-based-products



Not a panacea

A long human experience with cannabis

Among others, the following are widely believed, but are they right?

- “It is safe ...no one has ever died!”
- “People should just grow their own medicine!”

This is a new class of medicines

- There is evidence to suggest that medicinal cannabis has a role in palliative care.
- There is still more to understand – particularly use in very young children.
- There exists a risk of drug-drug interactions – especially within complex disease states employing a range of medications.
- Caution advised with a familial history of psychosis, and those with heart disease.



Further reading

Administration

- Eisenberg, Ogintz, & Almog. 2014. The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: A phase 1a study. *Journal of Pain and Palliative Care Pharmacotherapy*; 28:216–225.

Patient use surveys

- Pledger, Martin, Cumming. 2016. New Zealand Health Survey 2012/13: Characteristics of medicinal cannabis users. *New Zealand Medical Journal*; 129 (1433).
- Hazekamp & Heerdink. 2013. The prevalence and incidence of medicinal cannabis on prescription in The Netherlands. *European Journal Clinical Pharmacology*; 69(8):1575-80

Clinical reviews

- Hazekamp & Grotenhermen. 2010. Review on clinical studies with cannabis and cannabinoids 2005-2009. *Cannabinoids*; 5: 1-21
- Kowal, Hazekamp, Grotenhermen. 2016. Review on clinical studies with cannabis and cannabinoids 2010-2014. *Cannabinoids*; 11 (special issue):1-18.