PRODUCT MONOGRAPH

LGP CLASSIC oil range

medicinal cannabis

1 NAME OF THE MEDICINE

LGP CLASSIC 10:10
LGP CLASSIC 20:5

Medicinal grade cannabis oil as a human therapeutic good, which is unregistered on Australian Register of Therapeutic Goods (ARTG).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The LGP CLASSIC oil range, active ingredients are derived from cannabis full plant extract, containing tetrahydrocannabinol (THC) and cannabidiol (CBD), dissolved in medium chain triglycerides oil, derived from fractionated coconut oil.

Active ingredients:

LGP CLASSIC 10:10 medicinal cannabis oil. Each 1mL contains:

delta-9-tetrahydrocannabinol (THC)	10mg
cannabidiol (CBD)	10mg

LGP CLASSIC 20:5 medicinal cannabis oil. Each 1mL contains:

delta-9-tetrahydrocannabinol (THC)	20mg
cannabidiol (CBD)	5mg

Description of cannabinoids:

Delta-9-tetrahydrocannabinol (THC)

THC is a lipophilic phytocannabinoid derived from the cannabis plant. It is one of more than 114 cannabinoids identified in cannabis and is regarded as the principal intoxicating psychoactive constituent of cannabis.[1]

The chemical name is:	(−)-trans-Δ^9-tetrahydrocannabinol
Molecular Formula:	$C_{21}H_{30}O_2$
Molecular Weight:	314.469 g/mol
ATC Code:	A04AD10
CAS Number:	1972-08-3

Cannabidiol (CBD)

Cannabidiol, CBD, is a major phytocannabinoid derived from the cannabis plant. It is not regarded as being psychoactive to any significant extent. It can affect the activity of a significant number of other targets including ion channels, receptors, and enzymes. Results from pre-clinical studies suggest CBD has anti-inflammatory, analgesic, anti-emetic, anti-psychotic, anti-ischaemic, anxiolytic and anti-epileptiform effects.

The chemical name is:	cannabidiol
Molecular formula:	$C_{21}H_{30}O_2$
Molecular weight:	314.469 g/mol
ATC Code:	none
CAS Number	13956-29-1

Excipient:

Medium chain triglycerides oil, derived from fractionated coconut oil.

3 PHARMACEUTICAL FORM

The dosage form is an edible oil, presented as a pale green oil, which is supplied in a 50mL amber glass pharmaceutical grade bottle with tamper-evident seal and child-resistant cap.

4 CLINCAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

There is growing evidence that medicinal cannabis can benefit patients in a variety of clinical settings. Based on this, the LGP CLASSIC oil range, as medicinal cannabis products, may have a role in medical conditions including:

- Intractable chronic pain insufficiently responsive to other analgesics
- Pain associated with spasticity in multiple sclerosis
- Pain associated with cancer in palliative care
- Cancer treatment-induced nausea and vomiting
- Appetite loss
- Insomnia

- Post-traumatic stress disorder
- Cachexia

4.2 DOSE AND METHOD OF ADMINISTRATION

LGP has not yet conducted clinical trials to investigate dosing strategies. The general rule in prescribing medicinal cannabis is "start low, go slow" as described in the literature[2].

A suggested dose titration regimen will be provided to prescribers, based on the evidence in the literature.

Patients and the prescribing doctor will need to monitor the effects of LGP CLASSIC oil products, including side effects at each dose, until the minimum effective dose is reached with the least side effects.

Higher doses of LGP CLASSIC oils may result in an increased risk of undesirable side effects. If adverse or harmful effects are experienced, patients should be advised to stop their medicinal cannabis therapy.

Patients should take or be administered the medicine orally or via an enteral feeding tube, using the graduated 1mL oral syringe provided.

Dosing intervals should be at least six to eight hours apart, depending on product efficacy and side effects. This dosing interval allows time for absorption and distribution with peak effect between subsequent doses achieving steady state.

Stopping rules

Medicinal Cannabis should be ceased where:

- the desired effect is not apparent after 4–12 weeks[3] of continued therapy; or
- psychoactive or other intolerable side-effects are prohibitive, particularly for THC-containing preparations.

4.3 CONTRAINDICATIONS

The Australian Therapeutic Goods Administration (TGA) has advised that medicinal cannabis, which includes the LGP CLASSIC oil range, should not be used in patients who:

- have a history of hypersensitivity to any cannabinoid;
- have a history of psychotic disorders (especially schizophrenia); or
- are confirmed pregnant, likely to be pregnant or planning on becoming pregnant.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The LGP CLASSIC oil medicine should be used with caution in the following conditions and situations:

severe cardio-pulmonary disease because of occasional hypotension, hypertension, syncope, or tachycardia;

history of substance abuse, including alcohol abuse, because such individuals may be more prone to abuse cannabis and medical cannabis preparations;

ongoing chronic hepatitis C should be strongly advised to abstain from daily cannabis use, as this has been shown to be a predictor of steatosis severity in these individuals;

concomitant therapy with sedative-hypnotics or other psychoactive drugs because of the potential for additive or synergistic CNS depressant or psychoactive effects;

Use in hepatic and renal impairment. LGP CLASSIC 10:10 should be used with caution be used in patients with severe liver or renal disease;

Effects on laboratory tests. Medicinal cannabis including LGP CLASSIC 10:10 may cause a positive result in random drug testing as measurable concentrations of THC can be detected in urine for many days after the last dose. It may take up to five days for 80 to 90 per cent of the dose to be excreted; or

Patients must not drive while taking LGP CLASSIC oil. Patients are encouraged to seek advice from their prescriber when it is safe to drive **after treatment with LGP CLASSIC oil has ceased.**

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The most clinically significant interactions may occur when cannabis including LGP CLASSIC oil is taken with other CNS depressant drugs such as sedative-hypnotics or alcohol.

Patients taking fentanyl (or related opioids) and anti-psychotic medications (clozapine or olanzapine) may also be at risk of experiencing adverse effects if co-consuming medicinal cannabis or cannabinoids.

Data from clinical studies

A significant proportion of published clinical studies of medicinal cannabis medications have used patient populations that were taking concomitant medications for a variety of disorders such as neuropathic pain of various etiologies.

According to these clinical studies, concomitant use of medicinal cannabis medications with other medications was reported to be well tolerated.

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in pregnancy – Pregnancy Category Unknown

Medicinal Cannabis use during pregnancy is not recommended. Medicinal cannabis including the LGP CLASSIC oil range, does not have a pregnancy category.

Avoid taking LGP CLASSIC oil and other products containing cannabis if confirmed pregnant, likely to be pregnant or planning on becoming pregnant.

Use in lactation

Avoid taking LGP CLASSIC oil and other products containing cannabis while breastfeeding. Patients should be encouraged to seek medical advice if breastfeeding or planning to breastfeed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients MUST NOT drive or use machinery while taking products containing cannabis, including LGP CLASSIC oil because it is may cause drowsiness and sedation.

Patients are encouraged to seek advice from their prescriber when it is safe to drive after treatment with LGP CLASSIC oil has ceased.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse reactions after using a medicinal product is important as it allows continued monitoring of the risk-benefit balance. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems

The most frequently cited adverse events associated with the use of medicinal cannabis medications were:

Nervous system disorders: vertigo, fatigue and sedation.

Psychiatric disorders: euphoria, confusion, hallucination or paranoid delusions.

Gastrointestinal disorders: dry mouth, nausea and vomiting, diarrhoea, change in appetite – increase or decrease.

Vascular and cardiac disorders: tachycardia.

An additional consideration in the evaluation of adverse effects associated with medicinal cannabis use is the concomitant use of tobacco and alcohol as well as other drugs, whether they are non-prescription, prescription, or illicit drugs.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The endocannabinoid system is an ancient and evolutionarily conserved, signalling system found in all vertebrates, and which appears to have important regulatory functions throughout the human body. Most tissues contain a functional endocannabinoid system with the CB_1 and CB_2 receptors having distinct patterns of tissue expression.[4]

Cannabinoid type 1 (CB_1) receptors are abundant in brain tissue, similar in number to inhibitory gamma-aminobutyric acid (GABA) receptors.[4]

CB_1 receptors location (and action) are mainly in the hippocampus (memory), cerebellum (coordination), hypothalamus (appetite) and mesolimbic pathways (temperature control).[4]

CB_1 receptors are lower in number in the brain stem. Therefore, cannabinoids are less likely to cause respiratory and cardiovascular depression than opioids or alcohol.[4]

CB_1 receptors are G-protein-coupled receptors located in the pre-synaptic nerve terminals that controls neurotransmitter release.

CB_1 receptors when activated, inhibit adenylate cyclase production and increases concentration of mitogen-activated protein (MAP) kinase leading to a decrease in intracellular cAMP. This inhibits calcium ions influx via voltage dependent calcium channels and stimulates potassium channels influx that hyperpolarize the nerve terminal. The resulting effect is a reduction in neurotransmitter release.[4]

Cannabinoid type 2 (CB_2) receptors are present in the immune system tissues, such as lymphoid spleen, thymus and lymph nodes, including circulating lymphocytes, macrophages and microglia.[4]

CB_2 receptor function is not fully understood. CB_2 receptors are located in atherosclerotic lesions with anti-atherosclerotic effects.[4]

Cannabidiol (CBD) has analgesic, anticonvulsant, anti-psychotic, anxiolytic, muscle relaxant, and neuroprotective effects.[5]

Delta-9-tetrahydrocannabinol (THC or Δ9-THC) has psychoactive effects by its agonist effects on cannabinoid CB_1 receptors. THC has anticonvulsant, antiemetic, anti-inflammatory effects and also shown to be helpful in appetite stimulation and insomnia.[5]

Clinical trials

Australian clinical trials supporting the efficacy and safety use of medicinal cannabis are limited. In Australia, clinical trials are being prepared at major centres. The Australian Advisory Council on the Medicinal Use of Cannabis has been established to prepare systematic critical reviews of the available clinical evidence from clinical trials on the use of medicinal cannabis in palliative care, epilepsy, multiple sclerosis, chemotherapy-induced nausea and vomiting and chronic pain.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Oral administration of cannabis oil onset of action is 30 to 90 minutes. The lipophilic oil base slows onset of action. The advantage is a more steady pharmacokinetic and pharmacodynamic profile over longer periods of time, similar to the effect of slow release medicines.

Peak effect of CBD and THC in most patients occurs within 30 minutes to 3 hours after oral administration.[5,6]

Bioavailability of oral cannabinoids in oil formulation ranges from approximately 10% to 20% due to intestinal and first pass liver metabolism.[5]

Distribution

Distribution of Δ9-THC and CBD are time-dependent, which begins immediately after absorption. Cannabinoids are retained mostly by adipose and other lipophilic tissues, which are highly perfused into organs, such as the brain, heart, lungs, and liver.[6]

Metabolism

THC and CBD undergo hepatic first pass metabolism to 11-OH-THC and 7-OH-CBD their respective primary metabolites.[7] The THC metabolite 11-OH-THC is still psychoactive and is further oxidized to 11-nor-9-carboxy-THC (THC-COOH). In humans, more than 100 metabolites could be identified, but 11-OH-THC and THC-COOH are the main active metabolites.[7]

Metabolism occurs mostly in the liver by cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP3A4.[8]

Elimination

Following oral administration, THC, CBD and their metabolites are excreted in both the faeces and the urine. It may take up to 5 days for 80 to 90 per cent of the total dose to be excreted[6]. THC may be detectable in the urine, saliva and buccal mucosa for many days after ceasing administration. The implications of positive chemical tests and safe driving needs to be discussed with patients.

The majority of THC is excreted in the faeces (30% - 65%) and urine (20%).[9] The main active metabolites in urine is the ester of glucuronic acid and THC-COOH, and free THC-COOH.

The mean plasma elimination half-life of active metabolite THC-COOH were reported 5.2±0.8 days for frequent cannabis users and 6.2±6.7 days for infrequent cannabis users. There is no significant difference in half-life between frequent and infrequent administration of cannabis[6].

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Edible oil presented as medium chain triglycerides (53 MCT) derived from fractionated coconut oil.

6.2 SHELF LIFE

The expiry date can be found on the packaging.

6.3 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. If available, store at 2°C to 8°C (Refrigerate. Do not freeze).
Protect from light.

6.4 NATURE AND CONTENTS OF CONTAINER

The LGP CLASSIC oil range of products are each supplied in a 50mL pharmaceutical grade amber glass container with a tamper-evident seal and child-resistant cap.

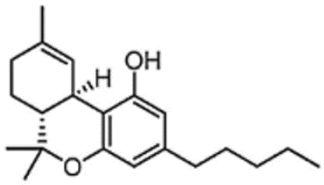
The LGP CLASSIC oil range of products are also each supplied with a plastic graduated 1 mL oral syringe. The syringe can be washed with warm soapy water, rinsed with clean water, drip-dried and re-used.

6.5 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be taken to a local pharmacy for safe and controlled disposal.

6.6 PHYSICOCHEMICAL PROPERTIES

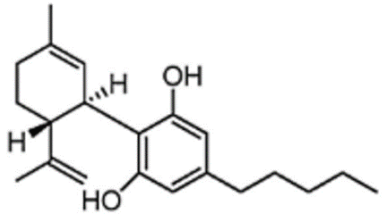
THC chemical structure delta-9-tetrahydrocannabinol



THC CAS Number: 1972-08-3

THC IUPAC Name: (6a*R*,10a*R*)-delta-9-tetrahydrocannabinol, (–)-*trans*-Δ^9-tetrahydrocannabinol

CBD Chemical structure cannabidiol



CBD CAS number: 13956-29-1

CBD IUPAC Name: 2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 8 Controlled Drug

8 SPONSOR

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9 DATE OF REVISION

Originally written 22 January 2019
Product Monograph code: LGPC-PM

Updated 12 March 2019
Version: Rev 1.1

Summary table of changes

Date	Section changed	Summary of new information
12 March 2019	6.3	• Store below 25°C. • If available, store at 2°C to 8°C (Refrigerate. Do not freeze).
12 March 2019	1	• Medicinal grade cannabis oil

10 REFERENCES

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2. MacCallum, C. A., & Russo, E. B. (2018). Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine*.

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8. Watanabe, K., Yamaori, S., Funahashi, T., Kimura, T., & Yamamoto, I. (2007). Cytochrome P450 enzymes involved in the metabolism of tetrahydrocannabinols and cannabinol by human hepatic microsomes. *Life Sciences*, *80*(15), 1415-1419.