Following treatment with the CYP3A4 inducer rifampicin, reductions in Cmax and AUC CBD (50% and 60% reduction, respectively), were observed.[9]

Concomitant treatment with the CYP2C19 inhibitor omeprazole resulted in no notable change in any of the pharmacokinetic parameters.[9]

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 drugs being substrates for p-glycoprotein.[10]

Abuse potential

Because of the non-psychoactive components of MediCabilis™, in particular the low THC content, there is low potential for substance abuse.

PRESENTATION AND STORAGE CONDITIONS

Presentation

MediCabilis™ *Cannabis sativa* 50 is a dark-green liquid.

The medical-grade amber glass bottle with stopper is supplied with 2 graduated syringes and child-proof polyethylene cap.

Pack Size

25mL and 50mL

Storage Conditions

Store below 25° C. Store upright. Keep away from heat and direct sunlight. Keep out of reach of children.

Special precautions for disposal

Any unused product or waste material should be returned to the pharmacy which supplied the prescription.

DOSAGE AND ADMINISTRATION

MediCabilis™ *Cannabis sativa* 50 is for oral use only.

Adults

Determining the optimal individualised dose of MediCabilis™ *Cannabis sativa* 50 may take some weeks, and side effects from either over- or under-dosing may cause temporary problems. If possible, the selected dosage should be maintained for a period of two weeks unless adverse effects such as fatigue are significant. Dosage reduction may be required in such circumstances.

Titration period:

A titration period may be required to reach the optimal dose. The number and timing of administration will vary between patients.

1. Start MediCabilis™ *Cannabis sativa* 50 at a dose of half a milliliter (mL) per day for two days.
2. Increase to three mL per day if relief is not achieved.
3. Increase after a two-day trial of each dosage to a maximum of 12mL per day.

The optimal dose is the lowest dose that achieves the highest benefit.

Children

No data specific to MediCabilis™ *Cannabis sativa* 50 is currently available. MediCabilis™ *Cannabis sativa* 50 should only be used in children and adolescents below 18 years of age at the discretion of a medical practitioner.

Elderly

No data specific to MediCabilis™ *Cannabis sativa* 50 is currently available. Cannabis extracts low in THC and high in CBD have been shown to be well-tolerated in the elderly.[7]

Patients with significant hepatic or renal impairment

No data specific to MediCabilis™ *Cannabis sativa* 50 is currently available. Phase 1 clinical trial on health volunteers showed no clinically abnormalities reported in vital signs, ECG, physical findings or safety laboratory tests. However effects in patients with significant hepatic or renal impairment has not been assessed. Effects in such patients may be exaggerated or prolonged. Frequent clinical evaluation and monitoring is recommended if prescribed (see PRECAUTIONS).

Method of administration

The oil should be administered with the enclosed syringe, with the oil placed under the tongue or taken orally.

OVERDOSAGE

There is no experience of deliberate overdose with MediCabilis™ *Cannabis sativa* 50 in patients. In the case of overdose, treatment should be symptomatic and supportive.

For information on the management of overdose, contact NHS 111 (England).

MANUFACTURED AND DISTRIBUTED BY

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Information prepared May 2020, UK Version 1.0

MediCabilis

Product information

MediCabilis™ *Cannabis sativa* 50
Full spectrum cannabis extract (Bod50)
50mg CBD/mL

MEDICINE SUMMARY

Name

MediCabilis™ *Cannabis sativa* 50 (50mg CBD/mL)

Extraction solvent

Medium Chain Triglyceride (MCT) oil sourced from coconut

Accessibility

MediCabilis™ *Cannabis sativa* 50 is available for clinical trial use and for patients via the TGA Approved Prescriber (AP) and Special Access Schemes (SAS). It is not a registered medicine.

Description

- Distinct and standardised full phytochemical *Cannabis sativa* extract (ECs315) in a Medium Chain Triglyceride MCT base.
- **Active ingredients:** *Cannabis sativa* L. oil extract delivering:

- **Cannabidiol (CBD+CBDA)**	**50mg/mL**
- Cannabigerol (CBG)	~1.5mg/mL
- Cannabichromene (CBC)	~2mg/mL
- Cannabidivarin (CBDV)	~1mg/mL
- delta-9-tetrahydrocannabinol	no more than 2mg/mL

- ECs315 is a distinct extract produced from a cloned and cultivated *Cannabis sativa* L. plant to ensure plant specificity. The plants have been specifically cultivated to produce specific chemotypes, expressed as cannabidiol.

Phytochemical composition:

Cannabinoids:

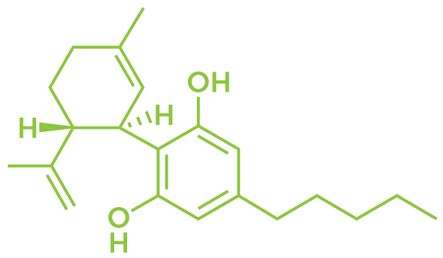
- CBD is the predominate cannabinoid in MediCabilis™ *Cannabis sativa* 50 with 95% present in it's decarboxylated form. CBDA is the acidic precursor to CBD. 50mg, as a combination of CBD and CBDA, is provided in each mL.
- MediCabilis™ *Cannabis sativa* 50 contains standardised and consistent phytochemical cannabinoid profile.

Terpenes:

- Terpenes are naturally present in most plant substances, providing some of the associated taste and aroma.[1] They are well tolerated and used widely in a number of applications including as natural food and cosmetic flavours.
- MediCabilis™ *Cannabis sativa* 50 is produced with strict and rigorously controlled processes ensuring the terpene, along with cannabinoids, phytochemical profile is always consistent.
- Full-spectrum cannabis extracts typically contain terpenes. However as terpene production in the cannabis plant is reactive to several factors terpene quantities and type will vary in the absence of strict and rigorous production.[2]

Chemical structure: Cannabidiol (CBD)

Molecular formula of CBD is $C_{21}H_{30}O_2$
Molecular weight: 314.5
CAS Number is 89958-21-4.



PHARMACOLOGY

Pharmacotherapeutic group: Other Analgesics and Antipyretics
ATC Code: N02BG10

Mechanism of Action and Pharmacodynamic Effects

The primary action is via the endogenous endocannabinoid system, described as "an ancient lipid network which mammals modulates neuronal functions, inflammatory processes and is involved in the etiology of certain human lifestyle diseases".

The endocannabinoid system downregulates stress-related signals involved in chronic inflammation and some types of pain.[3] The endocannabinoid system contains at least two types of cannabinoid (CB) receptors, CB1 and CB2:

- CB1 is found mainly in nerve terminals of the CNS where it modulates neurotransmitter release
- CB2 is found primarily in cells of the immune system, and thought to have pain, immune and inflammatory modulating properties[4]

Cannabidiol (CBD), the primary active constituent of MediCabilis™ *Cannabis sativa* 50), acts as a partial agonist at both CB1 and CB2 receptors.

The active constituents of MediCabilis™ *Cannabis sativa* 50 are non-psychotropic.

THC has not been shown to exert psychoactive effect at the negligible amount present in MediCabilis™ *Cannabis sativa* 50.

Pharmacokinetics

Absorption:

A clinical trial with healthy volunteers demonstrated MediCabilis™ *Cannabis sativa* 50[5] :

- CBD reached the blood stream in approximately 30 minutes
- Mean Tmax for CBD ranged between 2 to 5 hours and did not change with increasing doses

For further information please contact Dr Adele Hosseini (adele.hosseini@bodaustralia.com)

Distribution:

- The resultant maximum concentrations in the blood following oral administration of MediCabilis™ might be lower than those obtained by inhaling the same dose of CBD, due to a lower rate of absorption and redistribution into fatty tissues.
- Cannabinoids are highly lipophilic and can be stored in adipose tissue. This may result in CBD being slowly released at sub-therapeutic levels back into the blood stream, then metabolised and excreted via the urine and faeces.
- Preferential distribution to fat tissue raises the possibility of accumulation of depot in chronic administration, especially in patients with high levels of body fat.[6]

Metabolism:

- CBD is metabolised in the liver, and approximately one third of the parent drug and their metabolites are excreted in the urine (the remainder via the faeces). The P450-3A subfamily catalyses the formation of other hydroxylated minor metabolites.
- The metabolism of CBD is extensive, with more than 33 metabolites identified in urine.
- The major metabolic route is known to be carboxylation, hydroxylation and oxidation at C-7 followed by further hydroxylation in the pentyl and propenyl groups.

Elimination:

- Elimination half-life of CBD following single dose administration of MediCabilis™ *Cannabis sativa* 50 in healthy volunteers range from 2 to 9 hours (mean half-life 5.8 hours).

CLINICAL TRIALS

A Phase 1 safety and tolerability clinical trial on MediCabilis™ *Cannabis sativa* 50 is currently being finalised at the Nucleus Network research facility in Melbourne by Dr Jason Lickliter. For further information, contact Dr Adele Hosseini (adele.hosseini@bodaustralia.com).

INDICATIONS

MediCabilis™ *Cannabis sativa* 50 does not have approved indications. Use is at the discretion of the prescribing practitioner based on the individual needs of the patient and on the evidence for high CBD, full-spectrum, cannabis extracts. A number of conditions for the use of cannabis extracts have been documented, and are listed for consideration below. These include (but not limited to):

- Chemotherapy-Induced nausea and vomiting (CINV)
- Management of epileptic seizures and conditions
- Inflammatory bowel disease
- Inflammation related conditions
- Anxiety
- Multiple sclerosis (MS)
- Pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain

SAFETY AND POTENTIAL SIDE EFFECTS

Tolerability:

MediCabilis™ *Cannabis sativa* 50 has been shown to be well tolerated. A Phase 1 clinical trial in healthy volunteers demonstrated MediCabilis™ *Cannabis sativa* 50 is well tolerated:

- There were no serious adverse events
- Adverse events were mild and as expected
- There were no clinically abonormalities reported in vital signs, ECG, physical finidngs or safety laboratory tests

Potential side effects:

The most commonly experienced adverse effects are:

- drowsiness (8% or 8 in 100)
- nausea (8% or 8 in 100)
- sedation (8% or 8 in 100)
- altered sensory perception (8% or 8 in 100).

The amount of THC is less than 0.2%, hence psychiatric effects are not expected. However, should adverse effects occur the medicine should be adjusted by the prescribing practitioners. Patients should promptly report any exacerbation of psychiatric symptoms such as depression , disorientation, feeling over-excited or losing touch with reality, have difficulty speaking, eating (more or less than usual), or hallucinations.

CONTRAINDICATIONS

- Hypersensitivity to cannabinoids or to any of the excipients.
- Any known or 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.
- Pregnancy.
- Breast-feeding (in view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants) .

PRECAUTIONS

- Patients who commence MediCabilis™ *Cannabis sativa* 50 should be assessed by the prescribing doctor at least four weeks after treatment commences.
- Mild or moderate dizziness is commonly reported with the use of Cannabis products. This most frequently occurs in the first few weeks of treatment.
- The consumption of alcohol is not recommended when patients are treated with medicinal cannabis.
- Extra precautions are advised in managing any serious conditions, including severe CVD, liver or kidney disease.

Psychiatric adverse events

Phase 1 clinical trial indicated no psychiatric adverse effects should be expected with MediCabilis™ *Cannabis sativa* 50. The amount of THC, a psycho-active cannabinoid, is less than 0.2%, hence psychiatric effects are not expected. However, should adverse effects occur the medicine should be adjusted by the prescribing practitioners. Patients should promptly report any exacerbation of psychiatric symptoms such as depression, disorientation, feeling over-excited or losing touch with reality, have difficulty speaking, eating (more or less than usual), or hallucinations.
For further information, contact Dr Adele Hosseini (adele.hosseini@bodaustralia.com).

Genotoxicity

No data specific to MediCabilis™ *Cannabis sativa* 50 is currently available. As data becomes available from the ongoing clinical trial, information will be updated to reflect those findings.

Carcinogenicity

No data specific to MediCabilis™ *Cannabis sativa* 50 is currently available. As data becomes available from the ongoing clinical trial, information will be updated to reflect those findings.

Effects on Fertility

MediCabilis™ *Cannabis sativa* 50 is contraindicated for use in pregnancy. At present there is insufficient evidence to establish safety of MediCabilis™ *Cannabis sativa* 50 in pregnancy.

Paediatric Use

Use in children and adolescents below 18 years of age is at the discretion of the prescribing medical practitioner.

Geriatric Use

No data specific to MediCabilis™ *Cannabis sativa* 50 is currently available. However, cannabis extracts with high CBD and low THC have been shown to be well tolerated and suitable for use in the elderly.[7]

INTERACTION WITH OTHER MEDICINES

Cannabidiol (CBD) is metabolised by the cytochrome P450 enzyme system.

In vitro studies have shown that CBD is a potent inhibitor of multiple cytochrome P450 enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2D6 and CYP3A4. Consequently, it is likely that it will result in an interactive effect when used in conjunction with other pharmacological agents that are metabolised by these cytochromes, although this is yet to be investigated.[8]

Concomitant treatment with the CYP3A4 inhibitor ketoconazole produced an increase in Cmax and AUC of CBD 2-fold. Therefore, if concomitant drug treatment with CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin) is started or stopped during treatment with 1:1% (v/v) CBD, a new dose titration may be required.[9]