

Ministry of Health, Welfare and Sports
Office of Medicinal Cannabis
P.O. Box 16144
NL-2500 BC The Hague
The Netherlands

Medicinal Cannabis

Information for Health Care Professionals

version date: 11 December 2008

1. Name of drug

Cannabis, dried flowers (Cannabis flos)

Cannabis is supplied in three varieties:

<u>Variety</u>	<u>Dronabinol /THC</u>	<u>Cannabidiol/CBD</u>
Bedrocan	approx. 18%	< 1%
Bedrobinol	approx. 11%	< 1%
Bediol (granulate)	approx. 6%	approx. 7.5%

2. Qualitative and quantitative composition

Cannabis is made up of the dried inflorescences of the female *Cannabis sativa* L. plant, and is cultivated and processed under standardised conditions in order to obtain a consistent product. Cannabis contains several constituents including substances that belong to the cannabinoids, such as dronabinol (delta-9-tetrahydrocannabinol, THC) and cannabidiol (CBD). The content of cannabinoids depends on the type of cannabis.

3. Pharmaceutical form

Dried female flowers (gamma-irradiated)

4. Clinical information

4.1 Therapeutic indications

The efficacy of cannabis-components has been examined in various small and large scale clinical studies. Results from these studies indicate that medicinal cannabis may have a positive therapeutic effect on the symptomatic treatment of:

- disorders that involve spasticity with pain (multiple sclerosis, spinal chord injuries)
- nausea and vomiting (resulting from chemotherapy, radiotherapy and HIV combination therapy)
- chronic pain (in particular neurogenic pain)
- Gilles de la Tourette syndrome
- palliative treatment of cancer and AIDS

The use of cannabis is indicated only when the results with current treatment protocols are unsatisfactory or when too many side-effects occur.

Medical literature also mentions a significant number of other indications. However, the scientific basis for application in the case of these indications is still small, and more research is needed.

The variety of cannabis to be used must be established by experience. So far, no scientific evidence exists which point towards preference of one of the varieties for a certain indication. Recent data indicate that DRONABINOL and CBD in combination improve pain and spasm in MS-patients. Inhaling cannabis with a high content of dronabinol increases the risk of psychological side-effects. This can be avoided when using cannabis for the first few times, by choosing a variety with a low content of dronabinol or through oral administration in tea.

4.2 Dosage and method of administration

The required amount of cannabis per day should be determined on an individual basis. The initial dosage should be low and can be increased slowly as symptoms indicate. The dosage needed to achieve the desired effects is often different/ lower than the dosage at which psychological side-effects occur (become high).

Two methods of administration are recommended: orally or via inhalation. Inhaling cannabis exhibits a stronger and faster therapeutic effect compared to oral administration.

Oral (tea): (see also 6.6)

drink 1 cup (0.2 litre) of tea in the evening, hot or cold

When using this method, keep in mind that it takes an average of two weeks before the maximum effect is achieved; if after roughly two weeks the result is too limited or unsatisfactory, drink one extra cup (0.2 litre) in the morning.

Inhalation (vaporizer): (see also 6.6.)

1-2 times a day, inhale a few times until the desired effect is reached or until psychological side-effects occur. Wait 5-15 minutes after the first inhalation and between inhalations.

When using the inhalation method, the strength of the cannabis must be kept in mind. Be careful about the dosage when switching from one variety of cannabis to another, especially if cannabis with a lower content of dronabinol was used earlier.

With repeated administration of cannabis, it takes 2 weeks to arrive at steady-state concentrations of dronabinol. This must be kept in mind when evaluating the activity of the drug.

4.3 Contra-indications

The use of cannabis is not recommended for patients predisposed to psychotic disorders. Use cautiously in patients with underlying psychological problems.

4.4 Special warnings and precautions when using cannabis

Patients with heart diseases (heart arrhythmias, angina pectoris) should avoid high doses of cannabis because of the cardiovascular side-effects (in particular tachycardia). Tolerance to these effects develops within a few days to weeks. The dosage may only be increased slowly as indicated by the effects on the heart and only after consultation with the physician.

The psychological effects of cannabis can be disturbing for inexperienced users. It is advised to administer cannabis for the first time in a quiet and familiar setting, and in the presence of another person who can calm down the patient if necessary.

Smoking is not recommended. Cannabis smoke contains harmful combustion products, including carcinogens and carbon monoxide. As a result, frequent use of smoked cannabis over a long period of time presumably exposes users to health risks associated with smoking. Smoking cannabis can impair pulmonary function (histopathological changes in the mucous membranes) and reduce resistance to infection. Regular cannabis smokers can develop pharyngitis, rhinitis

and COPD (Chronic Obstructive Pulmonary Disease). To limit the damage caused by combustion products, cannabis can be inhaled by a vaporizer.

4.5 Interactions with other drugs and other forms of interaction

There are known cumulative effects when cannabis is used at the same time with other tranquillizing substances such as alcohol, benzodiazepines and opiates. *Basically there is only one research into interactions with other drugs. Finding was that there were no potential effects of medicinal cannabis on the pharmacokinetics of concomitantly administered irinotecan and docetaxel, or other (anticancer) drugs.*

The effective dosage of opiates was found to be significantly decreased in the case of combination of opiates with cannabis in animal studies.

Because of the high first-pass effect in the liver, particularly in the case of oral administration of cannabis, it is possible that pharmacokinetic interactions could occur with drugs, which are broken down by the isoenzymes CYP2C9 and CYP3A4 in the cytochrome P450 system. Drugs that inhibit these isoenzymes are macrolides (in particular claritromycin and erythromycin), antimycotics (itraconazole, fluconazole, ketoconazole and miconazole), calcium antagonists (in particular diltiazem and verapamil), HIV protease inhibitors (in particular ritonavir), amiodarone and isoniazid. Simultaneous use of the enzyme inhibitors mentioned above can increase the bioavailability of dronabinol and with that, the possibility of additional side-effects.

Drugs that accelerate the breakdown of dronabinol via the isoenzymes mentioned are rifampicin, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, troglitazone and Saint John's Wort. When a patient stops taking these drugs, an increase in the bioavailability of dronabinol may be expected.

Interactions are also possible with drugs which (like dronabinol) are strongly bound to plasma proteins.

4.6 Pregnancy and breastfeeding

Use of cannabis during pregnancy should be avoided. Dronabinol is known to reach the fetus via the umbilical cord. There are no indications that the use of cannabis during pregnancy causes deformities. Research has not shown any unequivocal effect on growth parameters. School-aged children who were exposed to cannabis while in utero have a normal overall IQ but score lower on certain aspects (in particular, in their ability for abstract-visual reasoning, memory function, and the executive function, which is the ability to demonstrate flexible, purposeful behaviour). Hyperactivity, concentration problems and impulsivity are also reported in 10-year olds. Dronabinol has been detected in breast milk. Therefore, the use of cannabis while breastfeeding is not recommended.

4.7 Effect on ability to drive and operate equipment

The use of cannabis can reduce reaction-time and lower concentration. This may create problems in carrying out everyday activities. Participating in traffic is forbidden in the Netherlands and operating equipment is not recommended.

4.8 Side-effects

The psychological side-effects of cannabis can vary widely, and depend on several factors: the amount of cannabis used, the method of administration, the user's experience with cannabis and personal constitution, such as the person's state of mind at the time of use and how open the user is to experiencing the effects. A person can become "high" after using cannabis. This is a feeling of euphoria that slowly changes into a pleasant sensation of calm and rest. Users can also experience other effects while "high", such as sedation, cheerfulness with fits of laughter, hunger, a heightened sensitivity to perceptions of colour and music, a disrupted sense of time and space, and lethargy. This altered perception can give rise to a sense of anxiety, panic and confusion. Restlessness and insomnia are also reported. Cannabis can sometimes provoke a psychotic reaction, characterized by delusions and hallucinations. A genetic relationship between cannabis use and schizophrenia has been established, although it is not clear whether the relationship is causal.

Physical side-effects of cannabis are:

- tachycardia
- orthostatic hypotension
- headache
- dizziness
- sense of hot or cold in hands and feet
- red burning eyes
- muscle weakness
- dry mouth
- in cannabis smokers (and after inhaling): irritation of the airways

These effects are temporary and disappear a few hours after use.

Long-standing, intensive use of cannabis is presumed to have an effect on cognition, but this is reversible. In some cases, cannabis use results in dependence and abuse. Chronic users who stop can experience physical withdrawal symptoms such as mild forms of restlessness, irritability, insomnia and nausea.

4.9 Overdose

An overdose of cannabis may cause depression or feelings of fear, to the point of panic and fainting. The symptoms should spontaneously disappear in a few hours. In case of overdose, benzodiazepines (diazepam IV) can be administered if needed. Tachycardia can be treated with a beta blocker (propranolol IV).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Cannabinoids act on the cannabinoid receptors. At least two different receptors (G-protein coupled receptors) have been identified: CB₁ and CB₂ receptors. CB₁ receptors are found particularly in the central nervous system, while the CB₂ type are peripheral and located mainly in the immune system and gastrointestinal tract.

5.2 Pharmacokinetic properties

Absorption

The absorption of cannabinoids in the body is determined by the method of administration. When cannabis is *inhaled*, the cannabinoids are absorbed into the blood within minutes via the lungs and transported to the brain. The concentration of cannabinoids in the brain reaches a maximum within 15 minutes, which coincides with the peak of the psychological and physiological effects.

Absorption varies greatly per individual and depends on various factors, including the heating of the cannabis, the number of inhalations, the waiting time between inhalations, the inhalation time and lung capacity.

When cannabis is taken *orally*, absorption of cannabinoids in the blood is slow and more unpredictable. This results in the psychoactive effect being delayed 30 to 90 minutes with the maximum effect being experienced two or three hours later, and then lasting four to eight hours. Dronabinol concentrations in the blood with oral intake are 25-30% of those seen after inhalation. This is caused, in part, by the large first-pass effect in the liver.

Distribution

After being absorbed, the cannabis constituents are distributed through-out the body. The concentration of cannabinoids rises most quickly in the tissues with the largest blood supply: the brain, lungs, liver and kidneys. A substantial portion of the dronabinol is stored in fatty tissue. Dronabinol and its metabolites are strongly bound to plasma proteins. The distribution volume of dronabinol is 10 liter per kilogram of body weight.

Elimination

In the liver, isoenzymes CYP2C9 and CYP3A4 of the cytochrome P450 system initially convert dronabinol to 11-hydroxy-THC (11-OH-THC), a metabolite that is biologically active. This connection probably contributes to some of the effects of cannabis. The metabolite 11-OH-THC is further converted to 9-carboxy-THC (THC-COOH), which is biologically inactive. A range of other inactive metabolites are also formed. The elimination half-time of dronabinol and 11-OH-THC is 25-36 hours. Dronabinol metabolites can be detected in the urine up to several weeks after the last use of cannabis.

6 Pharmaceutical information

6.1 List of excipients

Not applicable.

6.2 Cases of incompatibility

None.

6.3 Shelf life

Cannabis can decompose under the influence of light and moisture. Cannabis can be stored in the original packaging until the expiry date indicated on the package.

6.4 Special precautions for storage

The cannabis should be stored in the original packaging at room temperature (15-25 °C).

6.5 Type and content of the packaging

Cannabis is available for pharmacies in 5-gram packages.

6.6 Instructions for use and processing

In cannabis, the cannabinoids are primarily present as pharmacologically inactive acids (for example, THC acid). Heating gives rise to free molecules through decarboxylation. For this reason, a heating step must always be carried out before administration.

Use of vaporizer

See instructions for use enclosed with the device. The cannabis is heated, causing the active ingredients to evaporate. Subsequently, they can be inhaled without combustion. The right temperature has been reached when a vapour is just visible (a light mist) but no smoke has formed (thick clouds). For vaporizers with a thermostat, the temperature should be set at 180-195 °C. It is possible to re-use the same cannabis 2-3 times in the inhaler.

Making the tea

Boil half a gram of cannabis for 15 minutes in half a liter of water in a covered pan. Before using, strain the solid ingredients from the tea. Sweeten the tea as desired with honey or sugar. The leftover tea can be kept in a thermosflask when consumed the same day.

When the tea is made for several days it is possible to store it in the refrigerator for up to 5 days. A fatty substance such as milkpowder should be added to the tea in order to keep the active ingredients in solution.

7. Particulars

Import

Import of medicinal cannabis from the Netherlands by an foreign company/ pharmacy is possible through the OMC.

For this, the following documents are needed:

- 2 original duplicates of an import licence from the requesting country
- A letter with the amount of medicinal cannabis needed, and the indication of the patient.

After we have received those documents we will apply for an export licence with the Netherlands Health Care Inspectorate. Subsequently, we will draw up a contract and send this together with an invoice. When we have received the signed contract in return and the invoice is paid we can send the medicinal cannabis.