Ministry of Health, Welfare and Sport

Ministry of Health, Welfare and Sports
Office of Medicinal Cannabis
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The Netherlands

Medicinal Cannabis
Information for pharmacists and healthcare professionals

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1. Name of the Active Pharmaceutical Ingredient (API)

Cannabis, dried flowers (Cannabis flos)
There are five cannabis products:

Product	**Tetrahydrocannabinol THC**	**Cannabidiol CBD**
Bedrocan®	approx. 22%	<1%
Bedrobinol®	approx. 13,5%	<1%
Bediol® (granulate)	approx. 6,3%	approx. 8%
Bedica® (granulate)	approx. 14%	<1%
Bedrolite® (granulate)	<1%	approx. 7,5%

2. Qualitative and quantitative composition

Cannabis consists of the dried inflorescences of the female *Cannabis* sativa/indica L. plant, and is cultivated and processed under standardised conditions in order to obtain a consistent product. Cannabis contains several constituents including cannabinoid substances, such as tetrahydrocannabinol (delta-9-tetrahydrocannabinol, THC) and cannabidiol (CBD).

3. Pharmaceutical form

Dried female flowers (gamma-irradiated) for Bedrobinol® and Bedrocan®; granulated dried female flowers (gamma-irradiated) for Bediol®, Bedica® and Bedrolite®.

4. Clinical details

4.1 Therapeutic indications

Clinical studies are being performed with cannabis or cannabinoids. In many cases the results of these studies are inconclusive. However several studies show that cannabis can have a therapeutic effect in the treatment of:

- disorders that involve spasticity with pain (multiple sclerosis, spinal cord injuries);
- nausea and vomiting (resulting from chemotherapy, radiotherapy, and HIV combination therapy and medication for hepatitis C);
- chronic pain (in particular neurogenic pain);
- Tourette's syndrome;
- nausea, decreased appetite, weight loss and weakness related to cancer and AIDS;
- therapy resistant glaucoma;
- various forms of epilepsy

If treatment with registered medicines is unsatisfactory, medicinal cannabis can be considered.

Experiences of patients and doctors also include a significant number of other indications.

Medicinal Cannabis cannot cure the disorders mentioned above. Cannabis can ease the symptoms of the disorders or reduce the side-effects of medicines. A healthcare professional makes the decision regarding whether a patient can benefit from medicinal cannabis.

Inhaling cannabis with a high content of tetrahydrocannabinol increases the risk of psychological side-effects. This can be avoided by using a low dosage, by choosing a product with a low tetrahydrocannabinol content, a product with a combination of tetrahydrocannabinol and cannabidiol, or through oral administration (tea) when cannabis is used for the first time.

4.2 Posology and method of administration

The required amount of cannabis per day should be determined on an individual basis. The starting dosage must be low. The effective dosage is often different/lower than the dosage that causes psychological side-effects ('getting high'). If a patient benefits from a higher dose, the dose of cannabis can be increased slowly.

Two methods of administration are recommended: oral and inhalation. Inhaling cannabis leads to a stronger and more rapid therapeutic effect.

Oral administration: (see also 6.6)
Tea: Drink 1 cup (0.2 litre) of tea in the evening, hot or cold.
Using this method, it takes approximately two weeks before the maximum effect is achieved. If after roughly two weeks the result is unsatisfactory, the patient can drink one extra cup (0.2 litre) in the morning.
Oil suspension: A few Dutch pharmacies produce an oil suspension from the cannabis obtained from the OMC.

Inhalation (vaporizer): (see also 6.6.)
The recommended starting dose is 1-2 times a day. Inhale a few times until the desired effect is achieved or until psychological side-effects occur. Wait 5-15 minutes after the first inhalation and wait between inhalations. When using the inhalation method, it is important to consider the strength of the cannabis. Be careful about the dosage when you switch from one variety of cannabis to another, especially if you use cannabis with a higher content of tetrahydrocannabinol. With repeated administration of cannabis, it will take 2 weeks to achieve steady-state. This must be kept in mind when determining the drug efficacy.

4.3 Contra indications

Users with a tendency to experience psychotic disorders are advised strongly against the use of cannabis. Caution must be exercised with regard to patients with underlying psychological problems.

Patients with heart disease (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 the effects on the heart subside.

4.4 Special warnings and precautions

Inexperienced users may become alarmed by the psychological effects of cannabis. When administering cannabis for the first time, it is advisable to do so in quiet, familiar surroundings and in the presence of another person who can reassure the patient if necessary.

Smoking is not recommended. Cannabis smoke contains harmful substances, including carcinogens and carbon monoxide. As a result, frequent use of smoked cannabis over a long period of time is likely to expose users to the same health risks that are 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 using a vaporizer.

4.5 Interactions with other drugs and other forms of interaction

It is known that the use of cannabis at the same time as other tranquillizing substances such as alcohol, benzodiazepines and opiates leads to cumulative effects. If cannabis is combined with an opiate, the dose of the opiate can often be reduced. Provided that the analgesic effect improves or stays the same, the opiate may also produce fewer side-effects. There is insufficient evidence on the interaction of cannabis with other drugs and the consequent effects.

Because of the high first-pass effect in the liver, particularly when cannabis is administered orally, it is possible that pharmacokinetic interactions may occur with drugs that 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 tetrahydrocannabinol and thereby increase the likelihood of additional side-effects.

Drugs that accelerate the breakdown of tetrahydrocannabinol via the iso-enzymes mentioned are rifampicin, carbamazepine, phenobarbital, phenytoin, primidone, rifabutin, troglitazone and St John's Wort. If a patient stops taking one of these drugs, there may be an increase in the bioavailability of tetrahydrocannabinol.
Interactions are also possible with drugs which (like tetrahydrocannabinol) bind strongly to plasma proteins.

4.6 Pregnancy and breastfeeding

The use of cannabis during pregnancy and/or breastfeeding is not recommended. Regular or prolonged use of cannabis during pregnancy can affect the development of the unborn child. Components of cannabis can also find their way into breast milk.

4.7 Effects on ability to drive and operate machinery

The use of cannabis can lower the concentration and reduce reaction time. This may lead to problems in carrying out everyday activities. In the Netherlands, there is a legal limit for cannabis of 3.0 micrograms of THC/litre of blood for road users. THC remains in the body for a long time, so this limit can be exceeded very easily. Though the rules differ per country.

4.8 Side-effects

The psychological side-effects of cannabis can vary widely, and depend on a number of factors: the amount of cannabis used, the method of administration, and the patient's previous experience with cannabis and personal constitution (including the person's state of mind at the time of use and how sensitive the user is to the effects). A person may become "high" after using cannabis. This usually takes the form of a feeling of euphoria that slowly changes into a pleasant sensation of calmness and tranquillity. Users may also experience other effects while they are "high", such as sedation, cheerfulness with fits of laughter, hunger, heightened sensitivity to perceptions of colour and music, an altered sense of time and space, and lethargy. These altered perceptions can also 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 relationship between cannabis use and schizophrenia has been established, although it is not clear whether this relationship is causal.

Possible 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 bronchial tubes

These effects are temporary and subside a few hours after use. Long-term and intensive use of cannabis is presumed to have an effect on cognition, but this is reversible. In some cases, cannabis use can result in cannabis dependence and excessive usage. Chronic users who use high doses can experience physical withdrawal symptoms such as mild forms of restlessness, irritability, insomnia and nausea if they stop.

4.9 Overdose

An overdose of cannabis can cause depression, anxiety, panic and fainting. In general, these symptoms disappear spontaneously in a few hours. In the event of an overdose, benzodiazepines (diazepam IV) can be administered. 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 occurs peripherally, especially 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 within minutes via the lungs and are transported to the brain. The concentration of cannabinoids in the brain reaches a peak within 15 minutes, which coincides with the peak of the psychological and physiological effects. Absorption varies between individuals and depends on various factors, including the heating of the cannabis, the number of inhalations, the waiting time between two inhalations, the inhalation time and inhalation technique and lung capacity.

When cannabis is used *orally,* the absorption of cannabinoids into the blood is slower and less predictable. As a result, the psychoactive effect is delayed by between 30 and 90 minutes. The maximum effect is experienced two or three hours after consumption. The effect lasts between four and eight hours. The concentration of tetrahydrocannabinol in the blood with oral intake is 25-30% of the concentration achieved through inhalation. This is partly caused by the significant first-pass effect in the liver.

Distribution

After being absorbed, the constituents of the cannabis are distributed throughout the body. The concentration of cannabinoids rises the most rapidly in vital organs. A substantial portion of the tetrahydrocannabinol is stored in fatty tissue. Tetrahydrocannabinol and its metabolites are strongly bound to plasma proteins. The distribution volume of tetrahydrocannabinol is 10 litres per kilogram of body weight.

Elimination

In the liver, isoenzymes CYP2C9 and CYP3A4 of the cytochrome P450 system initially convert tetrahydrocannabinol to 11-hydroxy-THC (11-OH-THC), a metabolite that is biologically active. This conversion probably contributes to some of the effects of cannabis. The metabolite 11-OH-THC is then 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 tetrahydrocannabinol and 11-OH-THC is 25-36 hours. Tetrahydrocannabinol 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

Not applicable.

6.3 Shelf life

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

6.4 Special precautions for storage

Store 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 containers and 400 gram bags.

6.6 Instructions for use and processing

In cannabis, cannabinoids are primarily present as pharmacologically inactive acids (for example, THC acid). When heat is applied, the inactive compound (THC-A) is converted to the active compound (THC) via decarboxylation. Heating is therefore always required when administering.

Using a vaporizer

Always refer to the instructions provided with the device. The active ingredients of cannabis evaporate when the cannabis is heated. They can then be inhaled without the need for combustion. The right temperature has been reached when a light mist is visible, but no smoke has been formed. If the vaporizer has a thermostat, the temperature must be set at 190-210°C.

Tea preparation

Boil 500 ml of water in a covered pan. Add 0.5 grams (about 2 teaspoons) of medicinal cannabis. Turn the heat down and let the tea simmer for another 15 minutes with the lid on the pan. Remove the tea from the heat and strain it. Sweeten the tea as desired with honey or sugar. Keep any left-over tea in a thermos flask if you intend to drink it on the same day. When making tea for use over a few days, use 1 gram of medicinal cannabis in 1 litre of water. Add a sachet or teaspoon of coffee milk powder to the tea when it is still warm (this prevents the active ingredients from adhering to the flask or mug). After preparing as described above, let the tea cool and store the cooled tea in the refrigerator.

7. Particulars

In the Netherlands, cannabis is subject to the Opium Act (list II).

It is possible to cross the Dutch border with cannabis in the same way as other narcotic drugs:
1. If a Dutch citizen goes to a country that is a signatory to the Treaty of Schengen, the person can obtain a certificate from the Dutch Health Inspectorate.
2. If a Dutch citizen goes to a country outside the Schengen countries, the person must go to the embassy of that country for a certificate.

There is always a risk of prosecution when crossing an international border with cannabis without a certificate. Many countries provide for very severe penalties for the import of cannabis or the use/possession of cannabis.

Cannabis is marketed as Cannabis flos by the Office of Medicinal Cannabis (OMC). The OMC is part of CIBG, Ministry of Health, Welfare and Sports in the Netherlands.

Import

An overseas company or pharmacy can import medicinal cannabis.

The Office of Medicinal Cannabis requires the following official documents for the import procedure:

- two original import licences;
- a letter stating the amount of medicinal cannabis that is requested.

After the OMC has received those documents she will apply for an export licence from the Dutch Health Inspectorate. The OMC will draw up a contract and send the contract and an invoice to the applicant. When the signed contract, as well as the payment has been received, the OMC will export the medicinal cannabis to the applicant.