Sundhedsstyrelsen
Danish Health and Medicines Authority

MEMORANDUM

Medicinal use of *Cannabis*

2nd edition

2014

26-02-2014
File no.2013113424/

Frank Bøgh Wendelbo-Madsen
fwm@dkma.dk

Laboratory & Inspection
Axel Heides Gade 1
Denmark

Email sst@sst.dk
Web sst.dk

Contents

1. Introduction

Hash, pot, marijuana, skunk and hash oil are some of the many terms used for a number of illicit products extracted from the *Cannabis sativa* plant.

Cannabis sativa, also known as ordinary hemp, is a plant of the genus *Cannabis* in the hemp family. Other types of *Cannabis* include *Cannabis indica* and *Cannabis ruderalis*.[1]

Since the 1960s, *Cannabis* has been the most commonly used illicit drug, but some of the active substances found in *Cannabis* are also used legally in some types of medicine.

Some of the active substances found in *Cannabis* (cannabinoids) can be manufactured synthetically, just like cannabinoids not occurring naturally. Such active substances can be used in medicines.

In this memo, the Danish Health and Medicines Authority (DHMA) will provide information about the Danish rules and experience in this field and to some extent about the rules applicable and the experience gained in other countries.

2. The body's own cannabinoids and receptors

Within the past 20 years, the neurobiology of cannabinoids has been analysed. The first cannabinoid receptor, CB1, was identified in the brain in 1988.

A second cannabinoid receptor, CB2, was identified in 1993. The highest concentration of CB2 receptors is located in natural killer cells, suggesting a possible role in immunity.

In addition, endogenous cannabinoids (endocannabinoids) have been identified in the body. They appear to have a role in pain modulation, control of movement, feeding behaviour, and memory.

3. Knowledge about intoxicating and harmful effects and the prevalence of *Cannabis*

As we describe different aspects of *Cannabis* for medicinal use in this memo, it is also relevant to look at the general experience with harmful effects on humans. It should be mentioned, however, that even though a number of studies of the harmful effects on humans have been made, not that many studies are based on people who have only taken *Cannabis* for medicinal use.

---

[1] Other botanical terms for the plants are ”*Cannabis sativa* L.”, ”*Cannabis indica* Lam.” and ”*Cannabis ruderalis* Janisch.” The last letters after the name are abbreviations referring to the botanist who classified the plant. ”L.” stands for the Swedish botanist Carl von Linné. ”Lam.” stands for the French botanist Jean-Baptiste Lamarck. Janish refers to the Russian botanist Dmitrij E. Janischewsky. In the field of botany, the scientific classification of the plant name is written in italics, and the generic name (*Cannabis*) is capitalised, whereas the species (*sativa*) is written in small letters.

The main intoxicating substance in *Cannabis* is THC (delta-9-tetrahydrocannabinol), but there are around 70 different psychoactive cannabinoids in *Cannabis*, including cannabidiol (CBD).

The potential harmful effects of *Cannabis* intoxication include the risk of anxiety and panic reactions as well as psychotic reactions, reduced learning abilities and an increasing risk of traffic accidents etc.

The harmful effects of long-term use include a risk of addiction. *Cannabis* smoking also involves an increased risk of smoker's lungs and probably also respiratory tract cancer. To this should be added an increased risk of psychiatric disorders. Moreover, intellectual and functional abilities will be constantly reduced when using *Cannabis* daily or almost daily, and high doses over several years can impair memory and concentration.

Impaired concentration, memory and coordinated movement may have a negative effect on education, complex tasks and traffic safety.

Daily or almost daily use may also have far-reaching consequences – even after having stopped using the drug. Young people, especially socially vulnerable young people, and mentally vulnerable persons, are particularly vulnerable to the harmful effects.

Cannabis can be consumed in a variety of ways, including by eating, by drinking in the form of tea, by inhaling through a vaporiser or by smoking. Smoking is the most common method of consuming *Cannabis* as smoking gives the fastest and best controlled intoxicating effect. The approved medicine with active substances from *Cannabis* on the market is available in two pharmaceutical forms: Tablets and oromucosal spray.

You can read more about this topic and find references to published science about the harmful effects described in this memo, which is also available on our website (in Danish): CANNABIS – current knowledge about intoxicating and harmful effects and prevalence. Here we have gathered our general knowledge about the topic.

You can also read about the general drug situation in Denmark and the efforts made:
The drug situation in Denmark 2013 – National report to the European Monitoring Centre for Drugs and Drug Addiction, EMCDDA.

3.1. The Dutch Ministry of Health's brochure about side effects of medicinal use of Cannabis

The information for patients prepared by the Dutch Ministry of Health (CIBG) about medicinal use of *Cannabis* has the following description about side effects:

Patients generally tolerate medicinal *Cannabis* well. A low dosage often provides sufficient relief, so that side effects rarely occur. When they do,

it is usually the result of a high dosage or combined use with a substance such as alcohol that intensifies the side effects.

Known side effects of medicinal *Cannabis* are mood-altering effects, insomnia and heart palpitations. Other effects are: relaxation, fits of laughter, feeling hungry, heightened sensitivity to the perception of e.g. colour and music, lethargy and distorted temporal and spatial awareness. Your reaction time may also be slower, especially during the first hours after use.

If you take a large dose, you can get 'high'. This is a feeling of euphoria which slowly subsides into feeling satisfied, peaceful and calm. The altered perception may cause you to feel confused. These effects usually disappear after a few hours. If you have a genetic predisposition to psychosis (like schizophrenia) or other mental health problems, please consult your specialist before using medicinal *Cannabis*. You should also consult your doctor if you are a cardiac patient.

Continuous use of *Cannabis* during pregnancy can affect the foetus. Also, certain components of *Cannabis* – like THC – end up in breast milk. That is why the use of medicinal *Cannabis* is not advisable during pregnancy and while breastfeeding. For more information, consult your doctor or pharmacist.

Smoking
Smoking *Cannabis* regularly is bad for your health. Smoke damages the lungs and could lead to infections of the nose, throat and lungs. For this reason, smoking medicinal *Cannabis* is not recommended. Instead, inhaling *Cannabis* using a reliable vaporiser is a more suitable method.

Addiction
Addiction is unlikely with *Cannabis* used as a medicine. The recommended dose is usually lower than that for recreational use. You should take particular care, however, if you have been addicted in the past. High dosages of medicinal *Cannabis* taken over a longer period may lead to addiction. Quitting may then cause withdrawal symptoms, such as mild forms of restlessness, irritability, insomnia and nausea.

4. Rules about *Cannabis* as a euphoriant substance
In Denmark, euphoriant substances are governed by the Danish Act on Euphoriant Substances (in Danish) and the Danish executive order on euphoriant substances (in Danish). The executive order divides euphoriant substances into lists A-E that are subject to different provisions. New substances are regularly added to these lists.

4.1. List A – Cannabis

Cannabis is included on list A, no. 1:

1. Cannabis (meaning all above-ground parts of plants belonging to the genus Cannabis, from which the resin has not been removed. Exceptions are fruits of the hemp plant (hemp seeds) and hemp fibres in isolated form).

This means that hemp seeds and hemp fibres (fibres used e.g. for hemp ropes) are not comprised by the provision.

According to section 2 of the executive order, euphoriant substances included on list A, including *Cannabis*, must not be found in Denmark, unless the DHMA has given a special permission:

***2.** The euphoriant substances included on list A must not be found in Denmark, unless the Danish Medicines Agency [2] in very special circumstances and on special conditions gives permission to such substances.*

Section 2(3) has a special provision about preparations of *Cannabis* that makes it possible for the DHMA to give marketing authorisation to medicines containing preparations of *Cannabis*:

(3) Preparations of the euphoriant substance included on list A as no. 1 can, notwithstanding subsection (1), be imported and exported, sold, bought, dispensed, received, manufactured, processed, possessed and used for medicinal purposes.

This provision was introduced in 2011 so that a marketing authorisation could be given to Sativex® (see chapter 3) and similar medicines.

The provision does not give free access to the manufacture, possession, import or use of *Cannabis* generally as a number of other rules also apply, including the requirements laid down in the executive order on euphoriant substances and the provisions of the Danish Medicines Act stipulating that medicines in Denmark must be approved with a marketing authorisation or a compassionate use permit from the DHMA. The provision also requires that a physician has prescribed a medicinal product containing preparations of *Cannabis* (medicinal purposes).

Thus, it is an offence to possess, buy, sell, import and export, process, use and dispense products containing preparations of *Cannabis*, unless a physician has prescribed the medicine. However, a company with appropriate authorisations and import and export certificates can lawfully import, stock and distribute medicines containing *Cannabis*, including Sativex®.

[2] On 1 March 2012, the Danish Health and Medicines Authority was formed through the merger of the Danish Medicines Agency and the National Board of Health.

Cannabis that has not been prepared is not comprised by the exception set out in section 2(3). So it would require an amendment of the executive order for the DHMA to be able to give a marketing authorisation to the sale of *Cannabis* without preparation in Denmark. Consequently, it is illegal to possess, buy, sell, import and export, process, use and dispense *Cannabis* without preparation – whether prescribed by a physician or not. According to section 2(1), the DHMA may give authorisation in very special circumstances and on special conditions.

In section 1(2) of the executive order, preparation means:

(2) Preparations mean: Solutions, dilutions, extracts, concentrates, tinctures, any pharmaceutical preparations and all in all any processing of the substances and herbal substances concerned, to the effect that no chemical changes of the substances have taken place.

4.2. List B – THC in pure form and other cannabinoids

List B includes a number of substances that must only be used for medicinal and scientific purposes.

The active substance THC in pure form (for example dronabinol which is found in Marinol®) is comprised by list B, item 223:

223. Tetrahydrocannabinol (all isomers of tetrahydro-6, 6,9-trimethyl-3-pentyl-6H-dibenzo(b,d)-pyran-l-ol).

A number of chemical groups of synthetic cannabinoids were added to list B in 2012. The groups are:

- Benzoylindole (item 236)
- Cyclohexylphenol (item 238)
- Naphthoylindole (item 239)
- Naphthoylpyrrole (item 240)
- Naphthylmethylindene (item 241)
- Naphthylmethylindole (item 242)
- Phenylacetylindole (item 244)

Read more in amending executive order no. 778 from 2012 (in Danish).

5. Positive effects of medicines containing active substances from *Cannabis*

A great deal of published medical research shows that the use of *Cannabis* has many negative effects – particularly when used for long periods. In contrast, there is very little medical research on the beneficial effects on humans, including effect, quality and safety.

In connection with the authorisation of the extended indication for Marinol® in the USA, a double-blind, placebo-controlled trial was conducted involving 139 patients with AIDS-related anorexia with weight loss. Patients were treated with 5 mg/day. Side effects occurred in 13 of 72 patients and the dosage was reduced to 2.5 mg/day. As

compared to placebo, patients experienced a significant improvement in appetite and trends towards improved body weight and mood, and decreases in nausea were also seen.

In connection with the authorisation of Sativex®, three clinical trials (in Danish) were conducted which showed that patients with multiple sclerosis experienced less spasms. In one of the trials, which was placebo-controlled (control group is given placebo oromucosal spray) and double-blind (physician and patient do not know who is given Sativex® or placebo), around half of the patients experienced a certain reduction in spasticity.

A review of scientific articles in 2009 showed that six studies had examined the treatment of spasticity associated with multiple sclerosis with an extract of *Cannabis* containing a combination of THC and CBD. The variation in the effect was large, but showed a tendency towards reduced spasticity.

The Dutch experiences with *Cannabis* for medicinal use are still not considered to be relevant medical research because double-blind, placebo-controlled trials have not yet been conducted.

Over a period of 17 years, the DHMA has given authorisation to six clinical trials involving products containing cannabinoids, two of which have never been started. Three trials with Marinol aimed at studying the effect on patients with anorexia, sclerosis, neuropathic pain and spasticity. The only ongoing trial is studying the effect of Sativex® on neuropathic pain and spasticity in spinal cord injury patients.

The conclusion of three completed trials was a limited, but statistically significant, effect on weight increase in anorexic patients and neuropathic pain in patients with multiple sclerosis. No conclusion was made in relation to the effect on spasticity because there was not enough subjects participating in the trial.

In Denmark, clinical trials must be approved by both the Danish Health and Medicines Authority and a research ethics committee. The DHMA monitors whether trials comply with the Good Clinical Practice (GCP). Read more about general clinical trials.

UK-based GW Pharmaceuticals has developed and manufactures Sativex® and writes on its website that they have a pipeline of additional cannabinoid drug candidates in development and that they work to expand the indication for Sativex®. GW Pharmaceuticals is currently conducting phase 3 clinical trials of Sativex® with a view to being able to treat pain in patients with advanced cancer. Depending on the outcome of this trial, the result may be a potential extension of the indication for Sativex®.

6. Rules about medicines requiring marketing authorisation (Sativex®)

To obtain authorisation to market a medicine in Denmark the applicant must show that the beneficial effects of the medicine are greater than the side effects, that the medicine is safe to use and that the medicine is of a sufficiently high and consistent quality. To prove these facts, clinical trials in humans must be conducted. It is a very comprehensive process to obtain authorisation of a medicine, and usually only pharmaceutical companies have the resources to apply for a marketing authorisation of a medicine.

In connection with the authorisation, the company should also prepare a summary of product characteristics that forms the basis for a package leaflet aimed at consumers and informing about the indication for use of the medicine, contraindications and known adverse reactions. The DHMA approves the summary after changes, if any.

It is important to underline that the DHMA does not actively seek to authorise certain types of medicine, nor does the DHMA conduct clinical trials or medical research to market a medicine. Thus, new medicines are developed by pharmaceutical companies and public and private researchers.

Generally, the DHMA does not consider intoxication to be a desirable effect of a medicine. We normally consider this to be an unwanted side effect. If such side effect is greater than the effect of a medicine containing active substances from *Cannabis*, we would probably not authorise the medicine if we received an application for a marketing authorisation.

At the time when we received an application for a marketing authorisation of Sativex®, the Danish rules prevented an authorisation. Therefore, the executive order on euphoriant substances was amended in 2011 so that medicines containing preparations of *Cannabis* could be granted an authorisation.

Sativex® Oromucosal Spray is an authorised medicine based on an extract of *Cannabis* containing THC and cannabidiol. The wording of the approved indication is as follows:

> ”Sativex® is indicated as treatment for symptom improvement in adult patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.”

Sativex® is available as prescription-only from specialists in neurology or neuromedicine.

The table below gives an overview of the prescription of Sativex® in the years from 2011 (when the product was authorised) up to and including 2013:

Year	No. of patients	DDD	Number of packets	DDD per patient	No. of new patients
2011	**16**	911.25	27	56.95	16
2012	**55**	6,682.50	198	121.50	49
2013	**59**	7,830.00	232	132.71	34

(Source: Statens Serums Institut – DDD: defined daily dose)

In 2013, 59 patients were prescribed Sativex®, of which 34 were new patients.

You can read the Sativex® package leaflet at indlaegsseddel.dk (in Danish) and you can read the summary of product characteristics (in Danish) authorised by the DHMA, including a technical description of the product and the indication. There is no reimbursement for Sativex®.

So far, we have not received any other applications for the marketing of medicines containing preparations of *Cannabis* or cannabinoids as active substances.

Physicians in Denmark may use the medicine outside its approved indication (known as ”off-label” use). This requires that the physician thoroughly and professionally considers the available evidence, the benefits and risks associated with the medicine and provides specific information to the patient. This also applies to specialists in neurology in relation to Sativex®, but the DHMA has no knowledge of how often this happens or for which diseases.

Sativex® has been authorised as a medicinal product in the countries appearing from the website of GW Pharmaceuticals, which has developed and manufactures the medicine.

6.1. Reimbursement for the purchase of Sativex®

In the autumn of 2001, we received an application for general reimbursement for Sativex®. We refused to grant the medicinal product general reimbursement or general conditional reimbursement on the grounds that there is an obvious risk that the medicine may be used outside the approved indication and the medicine may be the subject of abuse.

The physician can apply for single reimbursement for a patient's purchase of Sativex®, and generally single reimbursement for Sativex® is granted to patients suffering from sclerosis with severe spasticity, who have had insufficient response to the optimal treatment with Baclofen and/or Tizanidine.

At present, the price of Sativex® is DKK 5,551.55 for a package of 3 x 10 ml oromucosal spray.

7. Rules about compassionate use permits (Marinol® and Nabilone)
It is possible for physicians in Denmark to prescribe medicines with no marketing authorisation in Denmark. In that case the physician applies to the DHMA for a compassionate use permit (section 29 of the Danish Medicines Act). We give authorisation to sale and dispensing in special cases and to a limited extent, provided that the physician has given an adequate reason and has submitted material showing that the desired medicine may have a beneficial effect on the relevant patient/indication.

The DHMA can give an authorisation for treatment of an individual patient (single compassionate use permit), but we can also give a general permission for the treatment of several patients with the same indication (general compassionate use permit).

When we have given a compassionate use permit, the medicine should be bought at a pharmacy in Denmark. You can read more about compassionate use permits here.

The DHMA has given a number of compassionate use permits for Marinol® (dronabinol – capsules) and for Nabilone (nabilone – capsules).

The two older medicines Marinol® (dronabinol – capsules) and Cesamet® (nabilone – capsules) were both authorised in the USA in 1985 and used to treat nausea and vomiting caused by chemotherapy. Later on, in 1992, the indication area for Marinol® was extended to include loss of appetite and weight loss in patients with AIDS. (See chapter 10.8.)

The originally authorised indication areas of Marinol® and Cesamet® are almost out-of-date, because new medicines for the treatment of nausea have become more efficient, and the AIDS wasting syndrome (wasting, severe weight loss) is almost non-existent in the western world after the introduction of modern antiviral therapy.

Marinol® can still be used when applied for by a physician, if the modern medicines do not work, and a number of highly specialised Danish hospital departments (haematological and oncological departments) have been granted general compassionate use permits and can therefore use the medicine if they estimate that there are medicinal reasons for such use. Following application, we also give compassionate use permits for the treatment of individual patients with Marinol® that is used to treat neurogenic pain in connection with multiple sclerosis.

In 2009, the British authorities authorised Nabilone capsules containing 1 mg nabilone (a synthetically manufactured cannabinoid). The indication is control of nausea and vomiting caused by chemotherapeutic agents used for the treatment of cancer in patients who have not responded adequately to conventional antinauseants. (See chapter 10.6.)

The DHMA also gave compassionate use permits for Sativex® before it was authorised as a medicine in Denmark in 2011.

We recently received an application for authorisation to the dispensing of Bedrocan. We are awaiting more information about the matter.

7.1. The scope of compassionate use permits

The two tables below show the number of compassionate use permits for Marinol® and Nabilone from 2002 to December 2013, but compassionate use permits were also granted before then. We do not know how much medicine has been prescribed to the individual patient or how many patients have been treated, because the general compassionate use permits may be used for several patients with the same indication, and maybe a compassionate use permit for a single patient (single permit) is not used due to death or lack of effect.

We typically grant compassionate use permits to individual patients valid for either three months or one year, and general compassionate use permits valid for five years. So the below figures may include compassionate use permits granted on the basis of reapplications of single permits and general permits where the compassionate use permit has been renewed.

Marinol®

	Single permit	General permits
2002	23	0
2003	421	1
2004	490	22
2005	224	10
2006	141	3
2007	114	2
2008	130	9
2009	140	18
2010	188	10
2011	177	6
2012	217	18
2013 until 6/12.	212	9
Total	2,477	108

Nabilone

	Single permit	General permits
2004	2	1
2005	2	2
2006	2	2
2007-2010	0	0
2011	1	0
2012	1	0
2013	1	0

(With validity for one year, reapplications may also be included)

8. Import of medicines containing *Cannabis* from the Netherlands and other countries

If a person has lawfully obtained a prescription from a physician and medicine with preparations of *Cannabis* for medicinal use has been dispensed to cover a maximum of 30 days personal consumption in the Netherlands, or another Schengen country, then the legal requirements for import to Denmark are met. The same applies if a person has been prescribed Marinol® and the medicine has been dispensed.

Citizens do not need a Schengen medical certificate issued by the authorities when travelling with *Cannabis* for medicinal use, but it will facilitate the documentation in connection with imports to Denmark. The Schengen Convention provides scope for travelling with medicines containing euphoriant substances for personal use, corresponding to a supply sufficient for a maximum of 30 days. For example, if a Dutch citizen has a prescription from a physician and a Schengen medical certificate issued in the Netherlands, then Denmark as a Schengen country must accept this as valid documentation.

In Denmark, pharmacies issue Schengen medical certificates.

If you import *Cannabis* without having a prescription from a physician, the customs authorities may report the matter to the police for violation of the rules on euphoriant substances.

Read more about travelling with euphoriant substances (in Danish).

9. Self-medication with *Cannabis* for medicinal use

The media have published a number of articles about individuals who buy or grow *Cannabis* illegally for the purpose of self-medication or for their children because they believe that *Cannabis* has a beneficial effect and they have not found any other treatment that worked.

The DHMA strongly warns against taking *Cannabis* or products with *Cannabis* without having a prescription from a physician. Possession of *Cannabis* is illegal, but the use of *Cannabis* also involves a significant risk of serious side effects (see chapter 3 above about intoxicating and harmful effects). Even if you only consume small amounts of *Cannabis* over time, it may have harmful effects. If you have bought *Cannabis*

illegally or grown the plant illegally, the contents of active substances in *Cannabis* will vary, and the quality is not necessarily as good as the quality of authorised medicine.

You should consult your physician about the possibilities for treatment, and if no other treatment is available, then ask your physician about treatment with Sativex® (can only be prescribed by specialists in neurology) or Marinol®. If your physician does not find that these products are relevant for your treatment, then you should not take *Cannabis* illegally.

On the internet, you may find people who claim that they have cured everything from cancer to diabetes by using for example *Cannabis* oil, but there is no scientific basis for such statements.

You may also find statements that scientific research shows that active substances in *Cannabis* have a curing effect on cancer. It is correct that some in vitro studies and animal testing show certain promising signs of potential beneficial effects in relation to cancer, but no scientific studies to date show that active substances of *Cannabis* have a positive effect on cancer in humans. Against this background, the DHMA maintains that to date there is no evidence that *Cannabis* can treat cancer in humans[3].

10. Rules in other countries about medicinal use of *Cannabis*

The below review is based on research of the websites of authorities in a number of countries. In some cases we have received information from the authorities and refer to statements of official authorities and pharmaceutical companies in international media.

10.1. Sweden

Like Denmark, Sweden has not legalised *Cannabis* for medicinal use. The Swedish Medical Products Agency also authorised Sativex® as a prescription-only medicine in 2011.

10.2. Norway

Like Denmark, Norway has not legalised *Cannabis* for medicinal use. The Norwegian Medicines Agency also authorised Sativex® as a prescription-only medicine in 2012.

The Norwegian authorities have informed us that they have received two applications from Norwegian physicians for compassionate use permits for Bedrocan from the Netherlands. The Norwegian authorities turned down one of the applications, but the other application from a specialist in neurology was given authorisation.

[3] At Cancer Research UK you can read the answers to a number of questions about *Cannabis* and cancer, including that there is no evidence that *Cannabis* can treat cancer in humans, even though some interesting trials have been made involving, for example cell cultures.

10.3. Finland

Like Denmark, Finland has not legalised *Cannabis* for medicinal use. The Finnish Medicines Agency also authorised Sativex® as a prescription-only medicine in 2012.

10.4. The Netherlands

Regarding *Cannabis* for medicinal use, the Netherlands has for more than ten years had a special arrangement allowing physicians to prescribe preparations of *Cannabis* in various forms to their patients.

The Dutch state has asked the Dutch company Bedrocan BV to manufacture a number of products based on *Cannabis* that physicians can prescribe to patients who can buy the products at a pharmacy in the Netherlands. The *Cannabis* products with various contents of the two cannabinoids THC and CBD are:

- Bedrocan® (or the variety *Cannabis* Flos) – THC of 22 per cent and less than 1 per cent cannabidiol (CBD)
- Bedrobinol® – THC of around 13.5 per cent and less than 1 per cent cannabidiol (CBD)
- Bediol® – THC of 6.3 per cent and cannabidiol (CBD) of around 8 per cent – the plant is granulated
- Bedica® THC of 14 per cent and less than 1 per cent cannabidiol (CBD). This product is based on *Cannabis Indica*, whereas the other products are based on *Cannabis Sativa*.

According to the description of the products, the DHMA finds that the products are preparations of *Cannabis* (cf. sections 1(2) and 2(3) of the Danish executive order on euphoriant substances).

The company grows the *Cannabis* plants used to manufacture these products. No pesticides are used and any microorganisms are removed from the plants. They are grown according to the Good Agricultural Practice - GAP. The administration forms include tea and *Cannabis* vaporisation – smoking of *Cannabis* is not recommended. The distributor is the Dutch-based company Fagron Pharmaceuticals.

The Office for Medicinal *Cannabis* (Bureau voor Medicinale Cannabis – BMC), under the Dutch Ministry of Health (CIBG), has prepared information and a list of symptoms aimed at physicians prescribing *Cannabis* for medicinal purposes:

- Pain and muscle spasms or cramps associated with multiple sclerosis or spinal cord damage
- Nausea, reduced appetite, weight loss and debilitation associated with cancer and AIDS
- Nausea and vomiting caused by medication or radiotherapy for cancer and HIV/AIDS
- Neurogenic pain (neuropathy) caused by, for example, nerve damage, phantom limb pain, facial neuralgia or chronic pain following an attack of shingles
- Tics associated with Tourette's syndrome

- Therapy resistant glaucoma

BMC underlines in its information that this list is not a result of major clinical research, but rather the result of observations by individual physicians and patients who have experienced good results and not too many side effects. A Dutch physician can only prescribe *Cannabis* for medicinal use in the Netherlands if the standard treatment and registered medicines do not work or have too many side effects.

BMC also underlines that *Cannabis* for medicinal use cannot cure the mentioned diseases, but only relieve the symptoms or reduce the side effects of other medicines. The list is not exhaustive, because the physicians decide under which circumstances *Cannabis* for medicinal use can be prescribed.

None of Bedrocan BV's products have obtained marketing authorisation – not even in the Netherlands – which means that they are not authorised as medicinal products. Bedrocan BV has not applied for authorisation to market its products in Denmark. At present, scientific evidence appears to be insufficient to substantiate that the effect of Bedrocan BV's products is greater than the many known side effects of *Cannabis*, and likewise they are not manufactured in compliance with the good manufacturing practice, which is a prerequisite for obtaining a marketing authorisation.

10.5. Germany

The German authority responsible for the authorisation of medicines, The Federal Institute for Drugs and Medical Devices, gives authorisation to the medicinal use of *Cannabis* in special cases. This is handled by the Federal Opium Agency (Bundesopiumstelle). The patient's physician applies for permission via an application form. Then the patient can buy *Cannabis* products at a German pharmacy, which has imported the products from the Netherlands (see section 10.4.).

Read the information to physicians and patients (in German).

10.6. England

Like Denmark, England has not legalised *Cannabis* for medicinal use. The British MHRA (Medicines and Healthcare Products Regulatory Agency) also authorised Sativex® as a prescription-only medicine in 2010.

The company behind Sativex®, GW Pharmaceuticals, was founded in 1998 and is based in England, where the company has obtained a licence to grow *Cannabis* plants at an undisclosed location for the development and manufacture of medicinal products.

In 2009, MHRA authorised Nabilone® capsules containing 1 mg nabilone (synthetic cannabinoid). You can read the package leaflet and the summary of product characteristics on the website of MHRA. The product is indicated for the control of nausea and vomiting caused by

chemotherapeutic agents used for the treatment of cancer in patients who have not responded adequately to conventional antinauseants.

10.7. France

In June 2013, France changed its rules and permitted the manufacturing, transportation, export, possession, offers, purchase and use of special medicines containing *Cannabis* or derivatives hereof. Medicines must be authorised by ANSM (Agence nationale de sécurité du médicament).

Thus, France will also have the possibility of authorising the marketing of Sativex®.

10.8. USA

In 2004, the US Food and Drug Administration, FDA, gave a statement to a US congressional subcommittee about the potential merits of cannabinoids for medicinal uses. You can read the statement in English; it was last updated in 2009. FDA underlined that medicines cannot be used by physicians and patients if the safety, effect and quality are not documented.

In 1985, FDA authorised two types of medicine containing synthetic cannabinoids – not extracts of *Cannabis*, but synthetically manufactured substances. Marinol® contains a synthetically manufactured cannabinoid that corresponds to THC, and Cesamet® contains nabilone, which is a synthetically manufactured cannabinoid that does not occur naturally and is not found in the *Cannabis* plant.

The indication was treatment of nausea and vomiting caused by chemotherapy. Later on, in 1992, the indication area for Marinol® was extended to include loss of appetite and weight loss in patients with AIDS. Cesamet® has not been marketed in the USA.

FDA wants to be open towards medicinal use of cannabinoids to the extent that the safety, effect and quality are demonstrated by scientific evidence. Research will probably not be focused on smoking parts of the plant, but rather on examining the effect of certain active substances in *Cannabis*.

A number of states have presently legalised the medicinal use of *Cannabis*. However, according to US federal law, it is illegal to possess, use, buy, sell or grow *Cannabis* (here termed ”marihuana”), cf. the Controlled Substance Act, in which *Cannabis* is listed as a ”Schedule I drug”, meaning that it has a high potential for abuse and has no currently accepted medicinal use.

According to the website of the White House, the US Administration opposes legalisation of *Cannabis* in the USA because legalisation would increase the availability and the use of illicit drugs and pose significant health and safety risks to all Americans, particularly young people.

10.8.1. US states allowing medicinal use of Cannabis

On its website, the White House has published a number of links to US state laws about the use of *Cannabis*:
http://www.whitehouse.gov/ondcp/state-laws-related-to-marijuana

Since 1996, 20 US states and Washington, DC have passed laws allowing patients in these states to use *Cannabis* for medicinal use without being punished. Most recently, the New York Times wrote that the governor of New York state would announce an amendment of the state laws that will allow medicinal use of *Cannabis*.

These state laws do not, however, change the federal laws (Controlled Substance Act) issued by the US federal government according to which it is illegal to possess, use, buy, sell and grow *Cannabis*.

The Deputy Attorney General of the US Department of Justice has issued guidance to all US attorneys regarding *Cannabis* enforcement. It appears from the guidance that the US Congress has determined that *Cannabis* is a dangerous drug and that the illegal distribution and sale of *Cannabis* is a serious crime that provides a significant source of revenue to large-scale criminal enterprises, gangs and cartels. Due to its limited prosecutorial resources and as several states have enacted laws relating to the medicinal use of *Cannabis*, the Department of Justice has focused its efforts on certain enforcement priorities, such as preventing:

- the distribution of *Cannabis* to minors
- revenue from the sale of *Cannabis* from going to criminal enterprises
- the diversion of *Cannabis* across the states
- violence and the use of firearms in the cultivation and distribution of *Cannabis*
- drugged driving due to *Cannabis*
- the growing of *Cannabis* on public lands.

Below some of the general differences and similarities between the programmes are highlighted:

General similarities of the programmes:

- Physicians cannot prescribe *Cannabis* for medicinal use, because the FDA has not authorised *Cannabis* as a medicinal product and because it is a ”Schedule I drug” according to the Controlled Substance Act.

- Physicians can recommend the use of *Cannabis* to a specific patient if they believe that it will have a beneficial effect.

- Programmes with *Cannabis* identification cards are common.

- Caregivers are often given special rights to help a patient, who wishes to take *Cannabis* for medicinal use.

General differences of the programmes:

- There are **legal differences** in relation to regulation, including whether the rules are applicable for the state, for a county or a city. In several places, counties and cities of a specific state can regulate medicinal use of *Cannabis* locally.

- **Physicians' recommendation** to a specific patient for use of *Cannabis* can be either oral or written. In California the recommendation can be both written and oral. In Alaska, a physician must issue a written statement that meets a number of requirements and states that the physician has personally examined the patient, that the patient has been diagnosed with a debilitating medical condition, and that the physician has considered other treatments but has concluded that the patient might benefit from the medicinal use of *Cannabis*.

- There are different programmes involving ***Cannabis* identification cards**. In some places it is voluntary to use identification cards to document that *Cannabis* is for medicinal use (e.g. in California where more than 70,000 ID cards have been issued). In other states, an ID card is required to get access to medicinal *Cannabis* (e.g. in Alaska). In some places, a caregiver (defined differently by the states) can also be registered and get an ID card and grow *Cannabis* on behalf of the patient (e.g. in California). A distinction is also made between a primary caregiver and an alternative caregiver. In the state of Illinois, a caregiver can serve only one patient whereas in California a caregiver can serve several patients.

- It varies how much *Cannabis* a patient or his/her caregiver is allowed to **grow** to the patient. For example, in California a patient is entitled to maintain six mature or 12 immature *Cannabis* plants. A caregiver can grow this number of plants per patient. In Illinois cultivation and distribution of *Cannabis* for medicinal use require special permissions aimed at companies.

- It varies how much *Cannabis* a patient or a patient's caregiver can **possess**. In California, the patient may possess no more than eight ounces (around 237 ml) of dried *Cannabis*, and a caregiver may possess this amount per patient. In Illinois a patient may possess 2.5 ounces (around 74 ml) over a period of 14 days, unless the patient has a special permission to possess larger amounts. The patient's designated caregiver and the patient may only possess up to a total of 2.5 ounces.

- Typically, there are also different rules for when a patient **must not possess or use *Cannabis*** anyway. In Illinois it is prohibited to possess or use *Cannabis* for medicinal purposes on a school bus, at schools, in any prison, in a car, in any public place and near minors. In California it is prohibited to smoke *Cannabis* for medicinal use within 1,000 feet of the grounds of a school,

recreation centre, or youth centre, unless the medicinal use occurs within a residence. It is also prohibited to smoke *Cannabis* on a school bus, in a car that is being operated or while operating a boat or being on probation.

- Different **diseases** are defined as a debilitating medical condition. For example, the list from Illinois includes Crohn's disease, Sjogren's syndrome, Parkinson's disease, Tourette's syndrome, severe fibromyalgia and a number of other diseases. The list is exhaustive and may be updated subject to application from a physician. In California it is up to the physician to assess whether *Cannabis* may be beneficial to the specific patient.

- There are differences between the regulation of **sales outlets** selling *Cannabis* ("marijuana dispensaries") and where they can be located.

- There are differences between the **taxation and fees** of medicinal *Cannabis*. For example, some counties and cities in California have chosen to tax the sale of medicinal *Cannabis*. The city of Oakland in Alameda County in California was one of the first cities to impose a special tax in California on the sale of *Cannabis* for medicinal use. In Illinois the profits from the medicinal *Cannabis* programme are allocated to a fund for the purpose of preventing crimes.

10.9. Uruguay

It has for a long time been legal to use *Cannabis* in Uruguay, but recently the head of Uruguay's National Drugs Board, Julio Calzada, said to the press that efforts are made for the government to manufacture *Cannabis* and set the price of government-controlled *Cannabis* at around USD 1 a gram. The purpose is to counter illegal sale of *Cannabis* from Paraguay, the quality of which is poor and which is also sold at around USD 1 in the streets. *Cannabis* will be sold from pharmacies.

President of Uruguay, José Mujica, has said to the press that this is not about being free and open. It is a logical step, and they want to take users away from clandestine business. They do not defend *Cannabis* or any other addiction, but to them trafficking is worse than any drug.

At the same time, Uruguay will make it easier to do research on medicinal use of *Cannabis*.

In a press release from December 2013 the president of the INCB, Raymond Yans criticised Uruguay's changed rules and considered them a break of the UN treaty. He emphasised that *Cannabis* is not only addictive but may also affect some fundamental brain functions, IQ potential, and academic and job performance and impair driving skills. And smoking *Cannabis* is more carcinogenic than smoking tobacco.

10.10. Israel

For a number of years, patients in Israel have had the opportunity to request a special permission from the state to use medicinal *Cannabis*. The request for permission must be submitted by a specialist to IMCA (Israeli Medical Cannabis Agency) under the Israeli Ministry of Health. *Cannabis* is grown by eight different suppliers in Israel, the largest being Tikun Olam which provides approximately 25 per cent of the supply. Patients pay about USD 100 per month for a licence, regardless of the amount of *Cannabis* prescribed.

In 2012, around 10,000 patients were approved for legal use of *Cannabis*, which increased to 13,000 patients in 2013.

At the end of 2013, the Knesset discussed whether to change the rules and allow physicians to prescribe *Cannabis* to their patients in future.

In that connection, the Israeli Minister for Health, Yael German, said to the press that more research is needed on the effects of medicinal *Cannabis* before allowing physicians to prescribe it to patients.

German has consulted with physicians and researchers in the field of psychiatry, pain, clinical pharmacology, gastroenterology and AIDS. The experts agree that *Cannabis* is not a recognised drug and there are no standards about doses and treatment methods. There is also little scientific information on side effects, contraindications and drug interactions or controlled studies on efficacy and damage from medicinal *Cannabis*. The experts also stated that while some patient groups report an improvement of their symptoms, including sleep and appetite, overuse of *Cannabis* can lead to anxiety, outbreaks of anger and psychotic situations. The use of *Cannabis* can also interfere with driving and lead to road accidents.

German's spokeswoman said to the press that a number of changes to the existing system will soon be made, bringing about more efficiency and transparency, including faster assessment of applications for the use of medicinal *Cannabis* and more information on the website of the Ministry of Health about the criteria for obtaining medical permission. Moreover, it is expected that the distribution of *Cannabis* for medicinal use will be transferred from the suppliers to pharmacies.

10.11. Canada

Canada's policy on *Cannabis* for medicinal use is to a large extent impacted by the courts which have several times overruled the applicable law because it was in conflict with the Canadian human rights[4]. Pursuant to the applicable rules, Canada has made a system with three possible permissions:

1. Possession as a patient.
2. Private cultivation for a patient.
3. Cultivation for a designated person.

Canada has cultivated *Cannabis* and sent it by mail to patients who had been granted a permission.

Due to the increasing demand, Canada changed its rules considerably as at 1 April 2014. Consequently, patients can no longer grow *Cannabis*, and the state will stop its production and distribution. In future, licensed producers will handle the production. It is prohibited to maintain shops selling *Cannabis*. Patients must receive *Cannabis* from the licensed producers.

Possession no longer requires permission, but only medical documentation or dispensing from healthcare professionals e.g. at a hospital.

Licensed producers will be subject to detailed requirements for the production, including compliance with good manufacturing practice covering premises, equipment, safety, quality assurance, recall procedures, quality assurance person etc. Not more than 30 g of dried *Cannabis* can be packaged in a container, and detailed labelling rules must be followed. Detailed rules for the safe shipping of dried *Cannabis* exist. A licensed producer may import and export *Cannabis*.

A licensed producer must report serious adverse reactions of dried *Cannabis* to the state within 15 days. A licensed producer must annually prepare a summary report of all adverse reactions, including analyses, and provide the state with a copy.

---

[4] In 1982, Canada adopted its own special human rights Canadian Charter of Rights and Freedoms, which give the courts extensive possibilities for overruling the laws of the state if the courts find that the rules are in conflict with these rights, including the "right to life, liberty and security of the person and the right not to be deprived of those rights except in accordance with the principles of fundamental justice".

In 2000, the Canadian courts of Ontario overruled the state rules on prohibition on possession of *Cannabis* in the case *R. v. Parker* for one year. The case was about a man who suffered from epilepsy and reduced his symptoms by smoking *Cannabis* which he grew himself. Because the legislation did not provide for an exemption for medicinal use of *Cannabis*, the courts found that it was in conflict with the Canadian human rights.

Since then a number of cases have influenced the Canadian rules about medicinal use of *Cannabis*.

Patients or caregivers can possess a maximum of 150 g dried *Cannabis* or less if the physician has fixed a lower daily quantity – in that case 30 times the daily quantity.

Before a patient can buy dried *Cannabis* from a licensed producer, the producer needs some information about the patient, including the original medical document about the use of *Cannabis*. The producer must check the validity of the medical document and that the physician is authorised.

The patient can only apply for *Cannabis* from one source at a time on the basis of the same medical document.

A medical document must indicate the period of use that must not exceed one year, and the daily quantity of dried *Cannabis* to be used by the patient, expressed in grams.

11. The DHMA's comments on the international experiences

As appears from the above review of international experiences, Sativex® is about to be authorised as a medical product in a large number of European and western countries. These countries have authorised a medicinal product containing an extract from cultivated *Cannabis*.

However, no countries in the world have authorised raw *Cannabis* as a medicinal product. There is still no medical evidence for the effect, safety and quality, including clinical trials on humans.

Some countries (e.g. the Netherlands, Israel and the state of California) have for a number of years followed programmes offering *Cannabis* for medicinal use to certain patients despite the lack of evidence. Countries like Canada and Germany have subsequently introduced similar programmes. The countries have very different programmes regarding which physicians can prescribe or recommend medicinal use of *Cannabis* and for which symptoms and diseases it can be prescribed. However, the experience gained in these countries has not provided new scientific evidence about *Cannabis*.

At the moment, some states in the USA tend to go towards offering *Cannabis* for medicinal use. This is not in compliance with the federal laws, but violations are largely ignored when the individual states have permitted *Cannabis*.

The decision to offer *Cannabis* for medicinal use in various countries and US states is not based on new research into the beneficial or harmful effects on humans, but is rather a matter of politics.

At present, we see no healthcare basis for recommending that Denmark should offer raw *Cannabis* for medicinal use, including via a recommendation or prescription from a physician. We see no reason to depart from the general rules for the authorisation of medicines. Distributors of *Cannabis* must prove that the drug can meet the requirements for authorisation, just like any other medicine.

In our opinion, Denmark has the medicinal products with active substances from *Cannabis* that can be justified by the evidence available. The synthetically manufactured cannabinoids Marinol® and Nabilone (previously Cesamet®) have been on the market for a number of years, and Danish patients have had access to them via their physician who can apply for a compassionate use permit from the Danish Health and Medicines Authority. In 2011, Sativex® was authorised in Denmark, so that we now have a medicine containing extracts from cultivated *Cannabis*.

A number of clinical trials of Sativex® are currently being conducted, also in Denmark, and new medicines containing active substances from *Cannabis* are being developed all the time. We expect to see new evidence on an ongoing basis so that we can learn more about *Cannabis* as a medicinal product.

12. Parliamentary questions about medicinal use of *Cannabis*
Particularly in the period from 2012-13 a number of parliamentary questions have been answered which illustrates the political interest in this area:

Question no. 256 (Ordinary part) from 2003: Can experiences from the Netherlands be transferred to Denmark?

Question from committee no. 86 (Ordinary part) from 2012: Reference to an article in a Norwegian magazine and questions about the import of *Cannabis* for medicinal use from the Netherlands.

Question from committee no. 188 (Ordinary part) from 2012: Import of Bedrocan to Denmark.

Question from committee no. 189 (Ordinary part) from 2012: Why is *Cannabis* Flos from a Dutch company not available by prescription in Denmark?

Question from committee no. 767 (Ordinary part) from 2012: Legislation about *Cannabis* for medicinal use, indications and right to prescribe.

Question from committee no. 596 (Ordinary part) from 2013: Question about medicinal use of *Cannabis* in Germany following an article in Bild.

Question no. S 2135 from 2013: Can research into medicinal use of *Cannabis* be conducted in Denmark?

Question from committee no. 810 (Ordinary part) from 2013: Will the minister permit medicinal use of *Cannabis* for epilepsy or controlled trials of epilepsy?

Question from committee no. 811 (Ordinary part) from 2013: The Danish Health and Medicines Authority collects knowledge and experience gained abroad about *Cannabis* for medicinal use.

Question from committee no. 212 (Ordinary part) from 2013: Amendments of the rules governing physicians' prescription of *Cannabis* for medicinal use.

Question from committee no. 213 (Ordinary part) from 2013: Possibility of obtaining a marketing authorisation for medicinal products containing *Cannabis*.

Question from committee no. 214 (Ordinary part) from 2013: Authorisation to do research on Sativex®.

Question from committee no. 215 (Ordinary part) from 2013: Reimbursement for *Cannabis* oil.

Question from committee no. 291 (Ordinary part) from 2013: International experiences with *Cannabis* for medicinal use, for use in children and in patients with epilepsy.

Question from committee no. 292 (Ordinary part) from 2013: Medicinal products containing *Cannabis* in Denmark.

Question from committee no. 293 (Ordinary part) from 2013: Barriers to the manufacture of *Cannabis* for medicinal use in Denmark.

Question from committee no. 294 (Ordinary part) from 2013: How many people have received a rejection of an application for authorisation to manufacture, market and dispense medicinal products containing *Cannabis* in Denmark?

Question from committee no. 336 (Ordinary part) from 2013: The differences of US states' laws on medicinal use of *Cannabis.*

Oral question S299 from 2013: About legalisation of *Cannabis* oil for medicinal use.