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MEMORANDUM

Medicinal use of *Cannabis*

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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 Medicines Agency (DKMA)[2] 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

During the past 20 years, the neurobiology of cannabinoids has been analysed. The first cannabinoid receptor, CB1, was identified in the brain in 1990.

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.

[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.

[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. However, on 8 October 2015, the Danish Medicines Agency was reestablished as an independent agency.

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. However, even though a number of studies of the harmful effects on humans have been made, only a limited number of studies are based on people who have only taken *Cannabis* for medicinal use.

The main intoxicating substance in *Cannabis* is THC (delta-9-tetrahydrocannabinol), but there are around 70 different 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 is also associated with 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 authorised medicine with active substances from *Cannabis* on the market is available in two pharmaceutical forms: Capsules and oromucosal spray.

You can read more about this topic and find references to published science about the harmful effects described in the Danish Health Authority's memo (in Danish): CANNABIS – current knowledge about intoxicating and harmful effects and prevalence. General knowledge about the topic is gathered in this memo.

You can also read about the general drug situation in Denmark and the efforts made:
The drug situation in Denmark 2014 – 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:

> **"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 regulations. 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 DKMA has given a special permission:

***2.** The euphoriant substances included on list A must not be found in Denmark, unless the Danish Medicines Agency 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 DKMA to give a marketing authorisation to medicines containing preparations of *Cannabis*:

Subsection 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 may be given to Sativex® 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 DKMA. The provision also requires that a physician has prescribed a medicinal product containing preparations of *Cannabis* (medicinal purposes).

According to section 5(1)(i) of the executive order, the physician's prescription must comply with the current rules, particularly the rules laid down in the Danish executive order on prescriptions. Pursuant to this section and section 60 of the Danish Medicines Act (pharmacy restriction), prescription-only medicinal products can only be dispensed by a pharmacy. According to the Danish Pharmacy Act, magistral medicinal products, that is medicines prepared in a pharmacy for an individual patient, may also be dispensed in accordance with a prescription from a physician.

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 and it has been legally dispensed. However, a company with appropriate authorisations and import and export certificates can lawfully import, stock and wholesale distribute medicines containing *Cannabis*, including Sativex®.

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 DKMA 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 DKMA may give authorisation in very special circumstances and on special conditions.

The concept 'preparation' is defined in section 1(2) of the executive order: *Subsection 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).

4.3. CBD – in pure form or in hemp products

The substance CBD in pure form is not covered by the Danish executive order on euphoriant substances.

The legislation on euphoriant substances contains no rule against the sale of products wholly or partially based on hemp, provided that the product has no measurable content of THC and that the distributor, upon request from the DKMA, can document that the product meets this requirement.

To determine whether a product has a measurable content of THC, an analytical method with the greatest possible sensitivity to THC should be used.

The fact that the legislation on euphoriant substances, under certain conditions, does not prevent the distribution of products wholly or partially based on hemp, does not necessarily mean that it is legal to distribute such products. Consequently, other legislation, such as legislation on medicinal products, food or the environment, may contain rules against or lay down further requirements for the distribution of hemp-based products.

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

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 limited medical research on the beneficial effects on humans, including efficacy, 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 (the control group was 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 DKMA has given authorisation to six clinical trials involving products containing cannabinoids, two of which were never started.

Three trials with Marinol® aimed at studying the effect on patients with anorexia, sclerosis, neuropathic pain and spasticity. These trials found 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.

A trial in Denmark aimed at studying the effect of Sativex® on neuropathic pain and spasticity in spinal cord injury patients was stopped prematurely. According to the researcher, it was impossible to recruit trial subjects. The reason was that the trial subjects were not allowed to drive a car under the influence of Sativex®, because of the zero tolerance for THC in traffic.

Before the trial was stopped, the then Danish Health and Medicines Authority examined[3] whether it was possible to exempt from the zero tolerance for specific trial subjects and discussed the matter with the Danish Ministry of Justice[4] that could grant the exemption. However, the Ministry of Justice referred to a reply to parliamentary question no. 581 (Ordinary part), which the Legal Affairs Committee of the Danish Parliament had addressed to the Minister for Justice on 14 February 2013. It appears from the reply that it is not possible to drive a car under the influence of Sativex®, because of the zero tolerance for THC in traffic.

According to the DKMA's clinical trial database, no research in medicinal use of *Cannabis* is currently taking place in Denmark.

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

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®.

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[3] As from 8 October 2015, the driving license area has moved from the Danish Health and Medicines Authority to the Danish Patient Safety Authority.

[4] This area has moved from the Ministry of Justice to the Danish Ministry of Transport and Building.

Recently, GW Pharmaceuticals initiated a clinical investigation of Epidiolex with a high CBD content in relation to pediatric epilepsy refractory to current treatments.

5.1. Other scientific evidence about Cannabis and cannabinoids

A few recent studies may be interesting in relation to our knowledge of medicinal use of *Cannabis*:

Various neurological disorders are described in Efficacy and safety of medical marijuana in selected neurologic disorders - Report of the Guideline Development Subcommittee of the American Academy of Neurology" The article focuses on 3 therapeutic areas: Multiple sclerosis (MS), epilepsy and movement disorders (e.g. Huntington's disease, Parkinson's disease and Tourette's Syndrome). The efficacy of 3 formulations of cannabinoids was studied: 1) Oral *Cannabis* extract (OCE, most often THC+CBD, but pure CBD formulations are available in the USA), 2) nabiximols (e.g. Sativex = THC+CBD) and 3) THC (e.g. Marinol).

Huntington's disease: Evidence-based guideline: Pharmacologic treatment of chorea in Huntington disease. Insufficient evidence.

Tourette's Syndrome from 2009: Cannabinoids for Tourette's Syndrome. The author does not find that a small reduction in tics justifies treatment.

Epilepsy: Cannabinoids for epilepsy from 2013 shows no reliable results and thus no clinical conclusions can be drawn.

The following article: Cannabinoids for Medical Use - A Systematic Review and Meta-analysis uses the same methodology as Cochrane which includes randomised clinical trials in particular. The following indications were assessed: nausea and vomiting caused by chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette's Syndrome. In addition, non-randomised studies, including at least 25 patients, were assessed. One strength of the article is the assessment of the safety of *Cannabis* across many indications, which included placebo control groups.

Adverse events are well described (figure 4 and table 3 in the article) and occur far more frequently with *Cannabis* compared with placebo. *Cannabis* treatment was associated with about 40% more serious adverse events, and the adverse events involve multiple organ systems. The following adverse events are mentioned with decreasing frequency: Disorientation, dizziness, euphoria, confusion, drowsiness, dry mouth, hallucination, nausea and vomiting. There are numerically, but not significantly more cases of paranoia, psychosis and anxiety among *Cannabis*-treated persons.

In the article Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems A Clinical Review the author reviewed

the medical literature from 1948 to March 2015 via MEDLINE. Out of 562 articles, 74 were carefully assessed, including 3 systematic survey articles and one treatment guide.

Focus is on controlled clinical trials related to indications that are not authorised by the FDA (currently only nausea and vomiting caused by chemotherapy and appetite stimulation in patients with AIDS wasting syndrome). The article has limited value, but does, however, give a good overview of the accepted indications in the 23 US states that have decriminalised *Cannabis* for medicinal use. The author has based his positive conclusions on often very small randomised clinical trials and no meta-analyses were made. According to the author, only medicinal use of *Cannabis* for spasticity due to multiple sclerosis, chronic pain and neuropathic pain is supported by high-quality evidence.

No documented effect on Crohn's disease, Parkinson's disease or amyotrophic lateral sclerosis. (See Systematic Review of Complementary and Alternative Medicine Treatments in Inflammatory Bowel Diseases.

There is a warning against the use of *Cannabis* for people with anxiety disorders, depression and psychosis, which may be aggravated by the treatment (see Cannabis use and mania symptoms: a systematic review and meta-analysis.

Dementia: Cannabinoids for the treatment of dementia, Cochrane Review from 2009 found no evidence of efficacy.

Schizophrenia: Cannabis and schizophrenia (Cochrane Review 2014) identified 8 randomised trials, involving 530 participants. Only one specifically assesses whether *Cannabis* can be used for symptom reduction in people with schizophrenia. CBD is compared with amisulpride. Results are inconclusive.

Fibromyalgia: Cannabinoids for fibromyalgia (Cochrane Review 2015). The report is still in the assessment phase. No results and no abstract.

Pain management of terminally ill patients experiencing inadequate analgesia despite chronic opioid dosing: There is some evidence that nabiximols (oral spray) administered by the patient has relieved symptoms. See the following two articles:
An Open-Label Extension Study to Investigate the Long-Term Safety and Tolerability of THC/CBD Oromucosal Spray and Oromucosal THC Spray in Patients With Terminal Cancer-Related Pain Refractory to Strong Opioid Analgesics

Nabiximols for Opioid-Treated Cancer Patients With Poorly-Controlled Chronic Pain: A Randomized, Placebo-Controlled, Graded-Dose Trial

The following article Turning Over a New Leaf: Cannabinoid and Endocannabinoid Modulation of Immune Function is an interesting survey article about potential use of cannabinoids for the treatment of

inflammatory and autoimmune diseases. However, no clinical evidence is available. CBD has been tested on graft-versus-host-disease in non-randomised studies. The effect is so remarkable that randomised studies are being considered. See the article: Cannabidiol for the Prevention of Graft-versus-Host-Disease after Allogeneic Hematopoietic Cell Transplantation: Results of a Phase II Study.

The article Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials reviews a number of published studies examining cannabinoids in the treatment of pain.

6. Rules about medicines requiring a 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 DKMA approves the summary after changes, if any.

It is important to underline that the DKMA does not actively seek to authorise certain types of medicine, nor does the DKMA 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 DKMA 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 CBD (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® from 2011 (when the product was authorised):

Year	No. of patients	Total sales in DDD	Number of packages sold	DDD per patient	No. of new patients
2011	16	911	27	57.0	16
2012	55	6,683	198	121.5	49
2013	59	7,796	231	132.1	34
2014	77	12,724	377	165.2	53
2015	61	8,168	132	133.9	30

2015 is updated until and including June
(Source: (Source: Statens Serums Institut – DDD: defined daily dose)

In 2014, 77 patients were prescribed Sativex®, of which 53 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 DKMA, including a technical description of the product and the indication.

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 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 DKMA 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 2011, 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.[5]

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

At present, the price of Sativex® is DKK 5,245.00 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 DKMA 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. It is presupposed that the medicine meets the good manufacturing practice for medicines (GMP).

We 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 permits).

When we have issued a compassionate use permit, the medicine can be bought at a pharmacy in Denmark. Read more about compassionate use permits

The DKMA 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 for the treatment of nausea and vomiting caused by chemotherapy. Later on, in 1992, the indication for Marinol® was extended to include loss of appetite and weight loss in patients with AIDS.

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[5] See the minutes of the Reimbursement Committee meeting of 25 October 2011 (in Danish). The Reimbursement Committee advises the DKMA in cases regarding reimbursement from the Danish regions - both general reimbursement and individual reimbursements for medicines.

The original authorised indications 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 issue compassionate use permits for Marinol® to treat individual patients with neurogenic pain caused by disseminated 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.

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

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, but compassionate use permits were also granted before then.

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 permits	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	222	9
2014	157	10
2015 until 26/9	125	11
Total	2,769	129

Nabilone

	Single permits	General permits
2004	2	1
2005	2	2
2006	2	2
2007-2010	0	0
2011	1	0
2012	1	0
2013	1	0
2014	1	0
2015 until 26/9	0	0
Total	10	5

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

7.2 Compassionate use permits for Dutch products from Bedrocan BV

In 2014, we received 2 applications for compassionate use permits for Bedrocan® and 2 applications for Bediol® from the Netherlands. The applications were rejected because the applicants did not provide sufficient reasons for the effect. In the matter about Bedrocan®, the application was rejected because the applicant wanted to make *Cannabis* oil from the product.

Since then, we have not received more applications for compassionate use permits for Bedrocan®. However, at present it is difficult to imagine that we can grant compassionate use permits for Bedrocan® or the other Dutch *Cannabis* products from Bedrocan BV. The reasons are:

1. Compassionate use permits can only be granted to medicinal products, see section 29(1) of the Danish Medicines Act. *Cannabis* products from Bedrocan BV are not ready-made medicinal products. The Netherlands has not issued marketing authorisations for the products, and Bedrocan BV only has registration as manufacturer of active substances for use in the manufacture of medicinal products. See the DKMA's memo on limitation of products with Cannabis submitted to the Danish Parliament.
2. As appears from Bedrocan BV's website, the Dutch products do not meet the requirements for Good Manufacturing Practice (GMP). They meet the requirements for Good Agricultural Practice (GAP).

8. Magistral manufacture of medicinal products containing active substances from *Cannabis*

Physicians can prescribe medicinal products manufactured in a pharmacy to a specific patient in special cases. A magistral medicinal product is a medicinal product manufactured in a pharmacy according to specific instructions of a physician. Magistral medicinal products are exempted from the general requirements that medicinal products must have a marketing authorisation, and this possibility should be used restrictively. We do not have the same knowledge about the quality, safety and efficacy of magistral medicinal products as we have about medicinal products authorised by the authorities. Nor do magistral medicinal products have an approved summary of product characteristics or package leaflet for the patient.

When a pharmacy manufactures the medicine, a number of rules for the manufacture of medicinal products must be followed, including good manufacturing practice (GMP) and Danish Drug Standards. In practice, we have two production pharmacies and a number of hospital pharmacies in Denmark handling the manufacture of magistral medicinal products.

According to the Danish Pharmacy Act, it is a condition for the manufacture of magistral medicinal products that the product cannot be replaced by another marketed medicinal product. If, in spite of this condition, the physician and the pharmacy find that there is a specific reason for manufacturing the product, the DKMA may give an authorisation. For example, if the patient is allergic to an active substance in the marketed medicinal product, there may be a need for a special dosage or other similar reasons.

Prescription of magistral medicinal products are subject to stricter reporting requirements for physicians who must inform the patient – particularly, if the medicine can produce a euphoriant effect and contains THC.

Due to the limited evidence for the efficacy of *Cannabis* on various symptoms and diseases, the DKMA cannot recommend prescription of magistral medicinal products containing active substances from *Cannabis*; consequently, the physician must take responsibility for the prescription.

Magistral medicinal products can also contain euphoriant substances, including active substances from *Cannabis*. This means that, in principle, Bedrocan BV's products can also be used as active substances in magistral medicinal products, because these products are considered to be active substances for the manufacture of medicinal products (see 7.2.).

Recently, the interdisciplinary pain management department at Rigshospitalet in Copenhagen has been in contact with a production pharmacy to discuss the possibility of manufacturing a number of magistral medicinal products containing THC and CBD, which the doctors in the department can prescribe to pain patients. Efforts are made to manufacture capsules and oral solution with dronabinol (synthetic THC, which is also found in Marinol®) and medicinal products with CBD. The department is working on a clinical trial involving pain management with magistral medicinal products containing active substances from *Cannabis* to chronic pain patients (60 persons).

9. Import of *Cannabis* for medicinal use from the Netherlands and other Schengen countries

If a person has lawfully obtained a prescription from a physician and preparations of *Cannabis* for medical use have been legally dispensed to cover a maximum of 30 days personal consumption from a pharmacy in the Netherlands, or another Schengen country[6], then the requirements for import to Denmark are met. This applies if a person has been prescribed Sativex® or Bedrocan® and the medicine has been dispensed, and if this person then imports the medicine to Denmark.

Citizens do not need a Schengen medical certificate issued by the authorities when travelling to Denmark with *Cannabis* for medicinal use, but it will facilitate the documentation in connection with imports to Denmark. The Schengen Agreement provides scope for travelling with narcotic drugs and psychotropic substances to the extent required for medical treatment and for personal use, corresponding to a supply sufficient for a maximum of 30 days. For example, if a person has a Schengen medical certificate issued in the Netherlands, then Denmark as a Schengen country must accept this as valid documentation.

The Dutch Office of Medicinal Cannabis (BMC) has announced that export of medicinal *Cannabis*, e.g. Bedrocan®, from the Netherlands can only take place with a valid Schengen Certificate issued by the Dutch Ministry of Health (CIBG). However, such certificate can only be issued to persons with a permanent address in the Netherlands. This is confirmed on their website.

[6] The formulation in the Schengen Agreement article 75(1): 1. As regards the movement of travellers to the territories of the Contracting Parties or their movement within these territories, persons may carry the narcotic drugs and psychotropic substances that are necessary for their medical treatment provided that, at any check, they produce a certificate issued or authenticated by a competent authority of their State of residence.

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).

10. 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 relatives because they believe that *Cannabis* has a beneficial effect and they have not found any other treatment that worked.

The DKMA 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 neuromedicine) 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 DKMA maintains that to date there is no evidence that *Cannabis* can treat cancer in humans[7].

[7] 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.

11. 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 in several cases we refer to statements of official authorities and pharmaceutical companies in international media and on the internet. Special focus is on the countries we normally compare ourselves with and countries having programmes for medicinal use of *Cannabis*, but the overview cannot be considered to be exhaustive.

11.1. 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.

In September 2015, Sweden informed us that they had assessed two applications for compassionate use permits for Bedrocan products from the Netherlands. The first application was rejected, because the documentation submitted did not provide a sufficient basis that the product is manufactured according to acceptable quality standards. Consequently, the Medical Products Agency could not assess the pharmaceutical quality of the medicinal product on the basis of the submitted documentation.

The latest application is from August 2015 about the dispensing of Bediol®. In November 2015, the Medical Products Agency announced that the application was rejected and that the decision was later brought before the administrative court.

11.2. 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.

In September 2015, the Norwegian authorities informed us that they had received six applications from physicians for compassionate use permits for Bedrocan products from the Netherlands. The Norwegian authorities have only issued one permit. The application was submitted by a specialist in neurology. The patient had previously been prescribed a Bedrocan product in the Netherlands, but was at the time hospitalised in a Norwegian hospital with a terminal disease. Following an overall assessment, a compassionate use permit for the Bedrocan product was given. Since *Cannabis* is considered an illegal euphoriant substance under Norwegian law, a requisition was also granted by the Norwegian Directorate of Health.

The Norwegian radio station, NRK P3, has produced a documentary programme: "Smuggling on prescription" about medicinal use of *Cannabis* and Norwegian citizens travelling to the Netherlands to get access to *Cannabis* via the Dutch programme. They also visit Bedrocan BV and the Dutch Office of Medicinal Cannabis.

In connection with the documentary, Cecilie Brein-Karlsen, State Secretary to the Minister for Health Bent Høie, was, according to NRK P3, quoted for the following statement (text on the website):
"*We want to make sure that Norwegian patients get the best possible treatment, but the treatment must also be of a high quality, be safe and have a documented effect. An application for a marketing authorisation for Bedrocan has not been submitted in Norway. We cannot use other rules for the authorisation of medicinal products containing Cannabis than those we use for other medicinal products*."

11.3. Finland

The Finnish medicines agency FIMEA authorised Sativex® as a prescription-only medicine in 2012.

Based on a parliamentary question, we asked FIMEA to provide information about the import of *Cannabis* products from the Netherlands. FIMEA informed us that three different *Cannabis* products for medicinal use (in the form of plant parts) have been imported to Finland. The brand names are Bedrocan®, Bediol® and Bedica®.

The yearly quotas for Finland's consumption of *Cannabis* are approved by the International Narcotics Control Board (INCB). Finland's quotas for *Cannabis* during the past 10 years are listed below (grams):

Year	Cannabis quotas
2005	1
2006	1,142
2007	602
2008	4,050
2009	20,047
2010	20,050
2011	20,050
2012	25,000
2013	35,000
2014	40,255

Moreover, FIMEA has informed us that the import is primarily related to the products mentioned above, all of them from the Netherlands. The current import has increased, but the quotas were never used. The imported *Cannabis* is dispensed on the basis of a special compassionate use permit issued to specific patients. The products are dispensed by a few Finnish pharmacies, and the control is carried out in the same way as for other medicinal products containing euphoriant substances.

In addition, the Finnish medicines agency has informed us that the special compassionate use permits for *Cannabis* were primarily given to reduce spasticity and pain in patients with multiple sclerosis or for other pain treatment purposes where other medicinal products have not been effective. In principle, the same indication as Sativex®.

Finally, FIMEA informed us that no new political measures have been initiated. A minor change was made to section 17 of an executive order

(490/2008), issued by the Ministry of Social Affairs and Health, making it possible to prescribe such euphoriant substances (UN 1961 convention, schedules I and IV) exclusively according to special compassionate use permits.

Subsequently, we received additional information in November 2015 from Finland, including the following overview of number of compassionate use permits:

2014: 149
2013: 94
2012: 83
2011: 47

According to FIMEA's practice, applications should be submitted by specialists in pain conditions. The Finnish authorities have found no basis for granting reimbursement for *Cannabis* products from Bedrocan BV.

11.4. 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[8] 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 6.5 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*.

Bedrocan BV has made two new products available:

- Bedrolite® with 9 per cent CBD and 0.4 per cent THC – available to patients and research. About to be standardised.
- Bedropuur® an indica variant with less than 1 per cent CBD. Until further notice, only available in Canada and for research.

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

[8] Bedrocan BV recently opened a business in Canada: Bedrocan Canada, bedrocan.ca.

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 BV.

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 use:

- 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
- Neuropathy (inflammation of nerves) 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

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

The 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 a 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.

Bedrocan BV does not have an authorisation to manufacture medicinal products, but has a registration from the Dutch authorities to manufacture active pharmaceutical ingredients for use in the manufacture of medicinal products. This registration appears from the European database EudraGMDP.

At present, scientific evidence appears to be insufficient to substantiate the effect of Bedrocan BV's products; in addition, they are not manufactured in compliance with the good manufacturing practice, which is a prerequisite for obtaining a marketing authorisation.

Against this background, the DKMA has assessed that the products are not medicinal products. See the DKMA's memo on limitation of products with Cannabis submitted to the Danish Parliament.

The BMC has previously informed us that 1,100 patients have been prescribed Bedrocan BV's *Cannabis* products in the Netherlands. They have not received any adverse reaction reports. In November 2015, the BMC announced that 1,500 patients take *Cannabis*, and they still have not received any adverse reaction reports. The main indications for the prescription is neuropathic pain, spasticity (MS patients) and appetite stimulation. Patients with fibromyalgia also use the products. The average daily dose is 700-750 mg.

Automatic reimbursement is not given to the dispensing of *Cannabis* in the Netherlands. It is up to the individual health insurance companies to set the criteria for reimbursement of expenses for *Cannabis* products. Some companies give no reimbursement at all, whereas some companies grant full reimbursement, and some companies only give reimbursement for the expenses if the policyholder is critically ill.

11.5. Germany

The German medicines agency, Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), has authorised Sativex® as a medicinal product.

In special cases, the BfArM gives authorisation to medicinal use of *Cannabis* via the authority "Bundesopiumstelle". The patient's physician applies via an application form for such authorisation so that the patient can buy *Cannabis* flowers or cannabis extract for self-treatment subject to medical supervision. With this authorisation, the patient can buy *Cannabis* products at a German pharmacy, which the pharmacy has imported from the Netherlands.

11.6. 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 use in the development and manufacture of medicinal products.

In 2009, the MHRA authorised Nabilone® capsules containing 1 mg nabilone (synthetic cannabinoid). You can read the package leaflet and the summary of product characteristics on the MHRA's website. The indication is 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.

11.7. France

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

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

11.8. 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 use. You can read the statement in English; it was last updated in 2009. The FDA underlined that medicines cannot be used by physicians and patients if the safety, efficacy and quality are not documented.

In 1985, the 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.

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

A number of states have presently decriminalised 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”), see 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 use of illicit drugs and pose significant health and safety risks to all Americans, especially young people.

11.8.1. US states allowing medicinal use of Cannabis

Since 1996, 23 US states and Washington, DC have passed local laws allowing patients in these states to use *Cannabis* for medicinal purposes without being punished. Two of these states have decriminalised *Cannabis* in general (Colorado and Washington State).

These state laws do not, however, impact on the federal laws (the 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 we highlight some of the general differences and similarities between the rules of the individual states governing the decriminalisation of *Cannabis* for medicinal use:

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 75,000 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 can 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 can 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 can 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.

11.9. Uruguay

According to the media, Uruguay was the first country to legalise *Cannabis* in December 2013. Products are sold at pharmacies. At the same time, Uruguay wanted to 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.

According to the media, it will, however, take a long time to implement the rules.

11.10. 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 the 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 general practitioners to prescribe *Cannabis* to their patients in future.

In that connection, the then Israeli Minister for Health, Yael German, said to the press that more research is needed on the effects of medicinal *Cannabis* before allowing general practitioners 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 beneficial effects on 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.

According to the media, efforts were made in 2015 to make *Cannabis* more accessible to patients, including dispensing at pharmacies.

11.11. 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[9].

Previously, Canada had a system with three possible permissions:

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

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

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[9] 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*.

Due to the increasing demand, Canada changed its rules considerably as at 1 April 2014. Consequently, patients could no longer grow *Cannabis*, and the state stopped its production and distribution. Licensed producers took over 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 by healthcare professionals e.g. at a hospital.

Licensed producers are 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.

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.

11.12. Slovakia

The SIDC has authorised Sativex® as a medicinal product.

11.13. Italy

The AIFA has authorised Sativex® as a medicinal product.

For a number of years, Italy has decriminalised medicinal use of *Cannabis*, so that physicians can prescribe *Cannabis* for patients via pharmacies. They have imported *Cannabis* from the Netherlands, but according to the media they consider making the products themselves.

11.14. Switzerland

Swissmedic has authorised Sativex® as a medicinal product.

Since 2011, Switzerland has, according to the media, made it possible for physicians to write a prescription for *Cannabis* products like Marinol® if the physician applied for permission from the federal health office.

Since 2008, a pharmacist in Bern has had an authorisation to manufacture a tincture of *Cannabis* synthesized in a laboratory. It contained large quantities of CBD, but no THC. According to the media, authorisation to develop a *Cannabis* product containing THC was granted in 2011. Pharmacies must have a special authorisation to dispense these products. This is still an experimental treatment, which requires a complex procedure.

12. The DKMA's comments on the international experiences

As appears from the above review of international experiences, Sativex® is about to be authorised as a medicinal 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 efficacy, safety and quality, including clinical trials on humans.

Some countries (e.g. the Netherlands, Israel and the state of California, USA) have for a number of years followed programmes offering *Cannabis* for medicinal use to certain patients despite the lack of evidence. Canada has 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.

Some countries have issued compassionate use permits in specific cases to patients subject to applications from physicians, for example Germany and Finland.

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 medicine 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 DKMA. 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, and new medicines containing active substances from *Cannabis* are being developed all the time. Recently, GW Pharmaceuticals initiated clinical investigation of Epidiolex with a high CBD content in relation to pediatric epilepsy refractory to current treatments.

We expect to see new evidence on an ongoing basis so that we can learn more about *Cannabis* as a medicinal product, and we also expect to see new medicinal products containing active substances from *Cannabis* in the market.

13. Parliamentary questions etc. about medicinal use of *Cannabis*
The following important parliamentary questions illustrate the political interest in this area:

Question no. 107 from 2002: Which countries allow the production and export of *Cannabis*/hash?

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

Appendix to discussion of parliamentary resolution 131 – Memo: CANNABIS – current knowledge about intoxicating and harmful effects and prevalence (in Danish) of 1 April 2009 from the Danish Health Authority.

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 initiated 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 DKMA 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 general practitioners' 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 applications for authorisation to manufacture, market and dispense medicinal products containing *Cannabis* in Denmark have been rejected?

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.

Consultation question W from 2014: About legalisation, production and use of medicinal *Cannabis* in Denmark. The following is available: Speech notes from the consultation and video from an open consultation meeting in the Health Committee on 18 March 2014.

Question from committee no. 597 (Ordinary part) from 2014: About the rules in the Netherlands.

Question from committee no. 598 (Ordinary part) from 2014: Content of THC in medicinal products.

Question from committee no. 599 (Ordinary part) from 2014: Question about an initiative to inform general practitioners that they can prescribe medicinal *Cannabis* off-label.

B84 – 2014 Parliamentary motion on medicinal use of *Cannabis* (The Red-Green Alliance, Danish political party).

Question from committee no. 329 (Ordinary part) from 2015: An account of the Finnish import of *Cannabis* from the Netherlands.

Question from committee no. 535 (Ordinary part) from 2015: Why are the experiences with medicinal *Cannabis* from Finland, Slovakia, Italy and Switzerland not included in the memo about medicinal use of *Cannabis*.

Question from committee no. 536 (Ordinary part) from 2015: A request that information from the answer to question 329 is included in the memo about medicinal use of *Cannabis*.

Question from committee no. 171 (Ordinary part) from 2015: A request that the memo about medicinal use of *Cannabis* is updated

Question from committee no. 172 (Ordinary part) from 2015: Question about the number of compassionate use permits for *Cannabis* in the period from 2010 to 2015.

Question from committee no. 173 (Ordinary part) from 2015: What kind of research into medicinal *Cannabis* takes place in Denmark?

Question from committee no. 174 (Ordinary part) from 2015: What are the barriers to implementing the Dutch programme in Denmark, based on import of *Cannabis* from the Netherlands. Appendix: The DKMA's memo on limitation of products with Cannabis

B5 – 2015 Parliamentary motion on medicinal use of *Cannabis* (The Alternative, Danish political party).