MINISTRY OF HEALTH

Medical Grade Cannabis

Clinical Guide

IMC-GCP – Israeli Medical Cannabis – Good Clinical Practices

Written and edited by:

Mgr. Yuval Landschaft, Boaz Albo (M.Sc.), Prof. Rafael Mechoulam, Prof. Arnon Afek

IMCA – Israeli Medical Cannabis Agency

The Israeli Medical Cannabis Agency (IMCA), Office of the Associated Director General, Ministry of Health

Draft edition 1.1 – January 2017

Dear physicians, fellow healthcare practitioners,

In recent years, there has been an increase in the use of medical grade cannabis in many countries in the world, including the State of Israel, while at the same time there has been significant progress throughout the world in scientific research in the field of cannabis, which has led to the clinical consolidation of the use of the cannabis plant as one that contains compounds that have beneficial medical effect for a variety of symptoms.

While cannabis is not registered as a drug or medicinal product, the Ministry of Health believes that its medicinal products used for medical purposes should be treated, to the extent possible, in the same way as a registered drug or medicinal product containing a substance defined as a narcotic drug and requiring control and regulation for securing the public's health and safety is treated. This also considers the substantiated special character of the plant rather than raw materials manufactured in a laboratory or factory in a reproducible manner.

The constant increase in the extent of applications for approval of the use of cannabis for medical and research purposes alike, along with the absence of global standards, has increased more than ever the need to establish appropriate standards for quality and the need for orderly, clear medical methodology.

It is my pleasure to welcome the initiative and present to you "Medical Grade Cannabis– Clinical Guide", the first guide of its type, and one of significant importance, which forms a coherent, uniform medical practice for treatment using cannabis, on which we worked with consultation from and in cooperation with leading experts and professionals. This clinical guide will expand and render accessible the knowledge base and will help physicians provide their patients the best possible treatment.

I wish to thank the Minister of Health, Rabbi Yaakov Litzman and the Director General of the Ministry of Health Mr. Moshe Bar Siman Tov, for their support in providing direction for and advancing the field of medical grade cannabis and drawing lines of action, and of course my co-workers: first and foremost my fellow clinical guide writers – Mgr. Yuval Landschaft and Boaz Albo (M.Sc.) and of course Prof. Rafael Mechoulam –international experts in the field of cannabis, the scientist who first characterized the endocannabinoid mechanism, whose active scientific contribution to writing this clinical guide was invaluable. I am very grateful for the difficult, demanding and devoted work in creating, writing and editing this clinical guide.

I also wish to express my gratitude to those who helped them in consultation, scientific and clinical editing and publishing the clinical guide, the scientific advisors, the chapter editors, the workers and managers of the Israeli Medical Cannabis Agency (IMCA), the advisory committees on medical grade cannabis and all employees of the Ministry of Health who helped with their wonderful, devoted work.

Thank you all for your great effort and contribution to this important goal.

Wishing the best of health and productive work in the future,

Prof. Arnon Afek

Associate Director General

Dear physicians, fellow healthcare practitioners,

In recent years, there has been an increase in the use of medical grade cannabis in many countries in the world, including the State of Israel, while at the same time there has been significant progress throughout the world in scientific research in the field of cannabis, which has led to the clinical consolidation of the use of the cannabis plant as one that contains compounds that have beneficial medical effect for a variety of symptoms.

While cannabis is not registered as a drug or medicinal product, the Ministry of Health believes that its medicinal products used for medical purposes should be treated, to the extent possible, in the same way as a registered drug or medicinal product containing a substance defined as a narcotic drug and requiring control and regulation for securing the public's health and safety is treated. This also considers the substantiated special character of the plant rather than raw materials manufactured in a laboratory or factory in a reproducible manner.

The constant increase in the extent of applications for approval of the use of cannabis for medical and research purposes alike, along with the absence of global standards, has increased more than ever the need to establish appropriate standards for quality and the need for orderly, clear medical methodology.

It is my pleasure to welcome the initiative and present to you "Medical Grade Cannabis– Clinical Guide", the first guide of its type, and one of significant importance, which forms a coherent, uniform medical practice for treatment using cannabis, on which we worked with consultation from and in cooperation with leading experts and professionals. This clinical guide will expand and render accessible the knowledge base and will help physicians provide their patients the best possible treatment.

I wish to thank the Minister of Health, Rabbi Yaakov Litzman and the Director General of the Ministry of Health Mr. Moshe Bar Siman Tov, for their support in providing direction for and advancing the field of medical grade cannabis and drawing lines of action, and of course my co-workers: first and foremost my fellow clinical guide writers – Mgr. Yuval Landschaft and Boaz Albo (M.Sc.) and of course Prof. Rafael Mechoulam –international experts in the field of cannabis, the scientist who first characterized the endocannabinoid mechanism, whose active scientific contribution to writing this clinical guide was invaluable. I am very grateful for the difficult, demanding and devoted work in creating, writing and editing this clinical guide.

I also wish to express my gratitude to those who helped them in consultation, scientific and clinical editing and publishing the clinical guide, the scientific advisors, the chapter editors, the workers and managers of the Israeli Medical Cannabis Agency (IMCA), the advisory committees on medical grade cannabis and all employees of the Ministry of Health who helped with their wonderful, devoted work.

Thank you all for your great effort and contribution to this important goal.

Wishing the best of health and productive work in the future,

Prof. Arnon Afek

Associate Director General

Contents

1. Foreword 9

2. Medical grade cannabis – the way to "medicalization" 13

3. The cannabis plant 17

4. The endocannabinoid system 19

5. Cannabinoids 21

6. The mechanism of action of the phyto-cannabinoids at the cellular level 27

7. Pharmacokinetics – routes of administration of medical cannabis and absorption, distribution, metabolism and clearance of THC 31

8. Main side effects and interactions 43

9. Approved medical indications for treatment with medical cannabis 45

10. Medical grade cannabis products 49

11. Matching the appropriate treatment type to the patient 57

12. Adjusting the monthly quantity of cannabis to the patient 65

13. Recommendation for dosage and consumption times adjustment during the day using a titration model 71

14. Guidelines and recommendations for effective use of medical grade cannabis 75

15. Cannabis abuse and addiction (dependence) 79

16. General warnings and directions in treatment using medical grade cannabis 87

17. Appendices 91

18. Bibliography and recommended reading 119

1. Foreword

In recent years, there has been an increase in the medical use of cannabis in many countries in the world, including in the State of Israel. At the same time, there has been significant progress in scientific research in the field of cannabis, which has led to clinical consolidation of the cannabis plant as a plant that contains compounds that have beneficial medical effect for a variety of symptoms.

Cannabis is a "narcotic drug" as defined by law, but the global medical establishment does recognize that cannabis has medical uses that may help patients with certain diseases. The use of medical grade cannabis is a developing, dynamic field and the regulation of its medical use is going through stabilization and organization in many countries in the world. While cannabis is not registered as a drug or medicinal product, the Ministry of Health believes that its products used for medical purposes should be treated, to the extent possible, in the same manner as a registered drug or medicinal product containing a substance defined as a narcotic drug and requiring control and regulation for securing the public's health and safety. This also considers the substantiated special character of the plant rather than raw materials manufactured in a laboratory or factory in a reproducible manner.

In any arrangement pertaining to the use of medical grade cannabis, the State of Israel is bound to the provisions of the international **Single Convention on Narcotic Drugs, 1961,** and exacting observance of the provisions of the ordinance and regulations in **the Dangerous Drugs Ordinance [New Version] 1973.** The Ministry of Health serves as a "governmental agency" in accordance with the provisions of the Convention in all matters relating to the control and regulation of cannabis treatment for medical and research applications, for which purpose the Israeli Medical Cannabis Agency (IMCA) has been established at the Ministry of Health.

The State of Israel is one of the world's leading countries in the extent of use of medical grade cannabis, and recently a regulation outline has formed for the field of medical grade cannabis, which ensures access to and supply of cannabis of medical grade on the one hand and control of a medicinal product that is defined as a "narcotic drug" on the other. The regulation outline, including this clinical guide, is intended to set appropriate standards in the field of cannabis for medical and research use – **"medicalization"**, which in contrast to legalization or decriminalization, are fundamentally legal or moral decisions rather than medical ones.

Medicalization is based on principles:

1. **Establishing clinical practice methodology and indications for approval of cannabis for medical use** – determination and control by professional medical agencies in each individual medical aspect and training of physicians using a medical practice methodology.
2. **Standardization of cannabis products** – as generic medicinal products that have fixed concentrations that can be as regulated as possible, which will be permitted for a specific medical indication, and be purchased, at pharmacies, using:
    - Farms for growing cannabis of IMC-GAP level – for growing strains in ranges whose concentration is dictated, known and controlled.
    - Factories that will produce generic, uniform medical grade cannabis products at IMC-GMP level – in efflorescence and oil form only.
    - Distribution to pharmacies at IMC-GDP level.
    - Readily available, standardize medical grade cannabis products at pharmacies – pharmacies in the dispensing network will undergo suitable training in the field of maintenance, registration, dispensing and pharmaceutical and clinical instructing on cannabis products.

"**Medicalization**" is an important, critical objective for allowing appropriate medical use of cannabis and in order to allow for the availability of valid, quality cannabis products in a manner that is as similar as possible to that existing for medicinal products. In order to ensure this, all links of practice and workers in the "supply chain" of medical grade cannabis products will work according to the strictest criteria and quality conditions in accordance with the **IMC – Good Practices** procedures of the Ministry of Health – IMCA, from the stage of plant reproductive material to the finalized "cannabis product" that is dispensed at the pharmacy. This will allow patients to have an appropriate source of supply of medical grade cannabis that is produced under the highest quality conditions, thus ensuring safeguarding of public health, wellbeing and safety and prevention of the misuse of the drug.

Cannabis products that the attending physician will prescribe will be of medical grade. Each link of the cannabis product supply chain will be required to follow a very high level of quality, in accordance with the procedures for good quality conditions of the IMCA: IMC-GAP, IMC-GMP, IMC-GDP, IMC-GSP, which deal, respectively, with growing, production, distribution and securing of appropriate conditions, which define the lines of activity and criteria to which the links of the supply chain are committed.

The world of "**medicalization**" of cannabis consists of three main fields, which rely on each other in order to create a stable medical regulatory system that is characterized by quality and reproducibility, producing appropriate medical treatment and maintaining high medical professionalism in the following fields:

A. <u>The clinical field</u>

1. **"The clinical practice methodology" for treatment using medical grade cannabis products –** according to the **"Medical Grade Cannabis – Clinical Guide"**
   The clinical guide ("the green book") is intended to concentrate and make available the existing information, lay down a uniform pathway of medical methodology to serve as a tool for physicians for recommendation, building a treatment plan, establishing doses, the type and quantity of medical grade cannabis products.

2. **"The medical indications"** that are approved for providing medical care using cannabis products.
   Medical indications that are determined by the professional agencies and updated from time to time, which examine the medical indications required for permitting the use of cannabis, the target population for receiving usage licenses and the medically appropriate cases for issuing such licenses.

3. "**Training of physicians**" in administering cannabis products according to the recommended medical methodology. The introduction of the **"physician training seminar – for administering medical grade cannabis"** - A seminar consisting of lectures in which the physician will be provided the existing basic scientific knowledge and that will present the medical practice methodology for providing medical care using cannabis products based on the clinical guide. After training, the physicians will be able to prescribe cannabis products to their patients subject to the drug prescribing procedures covering "narcotic drugs".

4. **"Affording access to patients":**
   - Advancing the transition from a license regime to a prescription one.
   - Work using a remote interface based on a central computer database by physicians who will be trained for the purpose of making the service accessible, improving the efficiency of processing applications for issuing prescriptions, issuing reports and statistics.
   - Instructing – setting up a pharmaceutical instructing network for using medical grade cannabis – for improving the theoretical and practical professional infrastructure that will allow the attending physician to make an educated medical decision to recommend the use of cannabis products and conduct the necessary medical follow up during treatment, and for the patient to use the various products correctly and effectively.

B. <u>The manufacturing field and the supply chain</u>

1. "**Medical grade cannabis products**" and their standardization conditions as valid generic products.
   According to the "**table of medical grade cannabis products**" approved by the IMCA.
   Generic products that fulfill professional criteria that the Ministry of Health has formed, in defined configurations and active substance concentrations.

2. The "**supply chain**" of medical grade cannabis products and its main links in its practice.
   According to "**Government Resolution 1587 – Use of cannabis for medical and research purposes**".
   A "value chain" that is parallel to that of the pharmaceutical system (medicinal products: manufacturing of raw materials – pharmaceutical factory – pharmaceutical warehouse – pharmacy // medical cannabis: growing of efflorescence – cannabis product factory – cannabis warehouse – pharmacy), defining the threshold conditions and also defining requirements of a business venture asking to work in the cannabis field and defining the activity fields and main practice links in the supply chain:
   - Reproduction farms and growing farms – growing of defined plant lines with uniform genetics.
   - Factories for producing and packaging of medical grade cannabis products – processing of raw plant material, production and packaging.
   - Cannabis product warehouses – distribution and storage of cannabis products.
   - Pharmacies – dispensing cannabis like any medicinal product containing a narcotic drug.

3. The "**quality assurance**" of the supply chain links.
   According to the conditions appearing in the IMC good practice procedures, which define the main lines of activity of the chain's links and the criteria that they are required to meet:
   - **IMC-GAP (Israel medical cannabis – good agricultural practice)**: growing under appropriate conditions of cannabis for medical use – directions, quality requirements and required criteria
   - **IMC-GMP (Israel medical cannabis – good manufacturing practice)**: production under appropriate conditions of medical grade cannabis products
   - **IMC-GDP (Israel medical cannabis – good distribution practice)**: distribution under appropriate conditions of medical grade cannabis products
   - **IMC-GSP (Israel medical cannabis – good security practice)**: securing the supply chain for medical grade cannabis under appropriate conditions – guidelines, quality requirements and required criteria

C. <u>The research and development field</u> - for advancing scientific research of the cannabis field:

1. Advancing the formation of a common basic pharmacological – regulatory field alongside coherent, defined medical practice, in laying down the way to a regulated medical field that includes products that have research based medical benefit – evidence based medicine.
2. Advancing and encouraging research and study proposals, for multidisciplinary studies, for advancing innovation of practical goal oriented agricultural research and for advancing current research of the cannabis plant (active components, physiological, pharmacological and biochemical effects), the advantages of using it alongside the risk that it poses.

3. Study applications will be examined according to a "cannabis research procedure", by leading experts from scientific fields from the clinical and academic institutions and from the Ministries of Health and Agriculture within a cannabis R&D committee. The committee is divided into sub-teams:
   - For the field of clinical research – clinical, pre-clinical, pharmacological, chemical, biochemical, physiological and molecular studies of man, etc., under the influence of administration of cannabis from plant sources.
   - For the field of technological and medical devices research – studies on the development of cannabis based devices for industrial use and for medical administration, creating alternatives to smoking, etc.
   - For the agricultural research field – studies for agronomic cultivation, agrotechnical development, biochemical, physiological and molecular development of the cannabis plant, etc.
4. Periodical update of medical practice methodology and official document set according to current studies and current medical literature.

In conclusion, the Ministry of Health is acting to make treatment with medical grade cannabis more accessible, while ensuring safety and quality. The "medicalization" process detailed in the regulation outline is intended to ensure correct, medical practice and to ensure that the quality of the supply chain of medical grade cannabis, including growing, production, distribution and dispensing of medical grade cannabis products, will be of the highest quality level.

The combination of the "Green book" and the quality procedures IMC-GAP, IMC-GMP, IMC-GDP, IMC-GSP for the supply chain of medical grade cannabis products constitute the Israeli pharmacopeia for medical grade cannabis. Accordingly, combining coherent, well defined medical practice with cannabis products that fulfill quality standards constitutes the first foundation on the way to a regulated, research based medical field – evidence based medicine.

This is the first publication of its type in the world, which compiles existing knowledge and which has been published as a draft in order to serve as a tool for physicians. If research fact based knowledge is gathered and added alongside medical opinions, they may be updated.

I hope that this book will be used by practitioners of the field and will contribute to the health of the patients who are our chief concern.

Best regards,

Mgr. Yuval Landschaft

Director of the IMCA,

The Ministry of Health

2. Medical grade cannabis – the way to "medicalization"

Evidence found in the tombs of kings in India, Egypt and ancient Assyria all showed that even 5,000 years ago cannabis was used for medical purposes. Evidence of religious Indian ceremonies held 2,700 years ago probably indicates the use of a mixture of wine and cannabis for surgical anesthesia purposes, whereas in China, evidence dating back 2,000 years of the use of cannabis for pain relief has been found.

The cannabis plant probably arrived in Europe in the 13th century, but only in the 17th century was it first used for agriculture, clothing, sailmaking, extracting oils and food products, as well as being smoked as an intoxicating agent and medicinal narcotic.

After the spread of the cannabis plant throughout the world in the 18th century, physicians in the United States started to recommend medical cannabis for use against urinary incontinence, venereal diseases and skin infections, whereas in England cannabis was used for treating arthritis and for relieving the nausea and discomfort of tetanus, rabies and cholera.

In 1914, laws restricting the uses of the cannabis plant started to be passed in the United States, and in 1937, cannabis was outlawed by the American authorities. This declaration led the rest of the world to accept the American position, and in the 1950s cannabis was banned in all western countries and the medical use of cannabis products came to a complete halt.

In 1961, the **Single Convention on Narcotic Drugs** was ratified, amended in 1972 (hereinafter "the Convention") containing rules on the control of the use of narcotic drugs. The Single Convention on Narcotic Drugs establishes the unique regime of control and regulation of this drug, including the existence of a governmental agency responsible for its regulation.

In the last decade, the demand for using medical grade cannabis has gained popularity in certain countries in the world, following which various solutions have been offered in order to allow access to treatment using it. At this time, in most countries, cannabis is illegal, but it would seem that its use for medical purposes is gaining popular opinions both from the public and from the medical establishment, and in many countries in the world, more studies are being published, which on the one hand confirm the positive effects of cannabis and on the other indicate its risks and harm.

In Israel, the **Dangerous Drugs Ordinance [New Version] 1973** (hereinafter "the Ordinance") was published in 1973, and in 1979 regulations were promulgated under the Ordinance "**Dangerous Drugs Regulations – 1979".** According to the Provisions of the Dangerous Drugs Ordinance, Cannabis is a substance that is defined as a "narcotic drug" whose use is prohibited unless duly licensed. The authority under the Ordinance concerning a "narcotic drug" is conferred to the Director General of the Ministry of Health or a person authorized thereby on this matter (hereinafter "director"). The "director" has the power to permit the use of cannabis in accordance with the provisions of the Ordinance, the regulations thereunder, the relevant procedures and guidelines. It should be emphasized that in order to receive a license

for using medical grade cannabis, medical recommendations alone are not enough – a license signed by the person authorized as a "director" must be obtained. The regulatory policy in Israel relies, inter alia, on the commitment of the state to uphold the provisions of the Convention, in addition to observing the Dangerous Drugs Ordinance.

Since the early 1990s, there has been incipient use of medical grade cannabis in Israel. As long as the phenomenon was uncommon, the Ministry of Health permitted, after examining each application on its merits, the use of medical grade cannabis under its power pursuant to Section 7 of the Dangerous Drugs Ordinance, without any guiding rules having been prescribed on this matter or concerning the supply of the drug to its licensed users. As the trend of using medical grade cannabis expanded and the number of licensed cannabis users increased, it was found necessary to regulate the field in a comprehensive manner, from forming guidelines for approving the use of cannabis, regulating its supply, to the manner of its dispensation to patients. Over the years, a number of attempts to regulate the field were made, until a comprehensive Government resolution on this issue was passed. The thorough work that led to the regulation model that was laid down in the Government resolution was conducted by the Ministry of Health in arrangement with other Government ministries, after holding regular contacts with practitioners in the field with the assistance and consultation of a number of committees that were established for examining the issue.

In 2011, Government Resolution No. 3609 was passed, stating that the Ministry of Health would serve as a "governmental agency", in accordance with the provisions of the said Convention, to which end the Israeli Medical Cannabis Agency (IMCA) was established within the Ministry of Health. Pursuant to that resolution, an inter-ministerial steering committee consisting of representatives of Government ministries, governmental authorities and other agencies for tracking and coordinating the issue was also established. In 2013, Government Resolution No. 1050 was passed, establishing principles for regulation and lines of activity.

In 2016, Government Resolution 1587 was passed, prescribing the "**medicalization**" model – the outline for regulating the field of cannabis for medical and research use. The State of Israel is one of the world's leading countries today in the extent of use of medical grade cannabis and examining the subject of advancing regulation of the use of medical grade cannabis. The regulation outline for the field of medical and research use of cannabis that was prescribed by the Government of Israel establishes appropriate standards for quality in order to allow for good medical use of cannabis, to form a regulated source of supply of cannabis, and in order to provide for the availability of valid, high quality cannabis products, in much the same manner as for medicinal products.

The regulation outline prescribes the action of all of the links in the occupation and the practitioners in the "supply chain" of medical grade cannabis products, according to very strict criteria and quality conditions in accordance with **IMC – Good Practices** procedures of the Ministry of Health – the IMCA. The outline will afford patients an appropriate source of supply of cannabis for medical purposes, while safeguarding public health and safety and prevention of the misuse of the drug, and regulating a new market that is aligned with the laws of the State of Israel and whose practice follows the highest quality conditions required for protecting public safety.

The Ministry of Health – the Israeli Medical Cannabis Agency (IMCA) is in charge of regulating the field of cannabis for medical and research use and is the agency responsible for establishing the professional – medical criteria pertaining to the various cannabis products, with the assistance of a list of professionals, including physicians, biologists, chemists, pharmacists, agronomists, and coordination with relevant Government ministries (the Ministries of Agriculture, Public Security, etc.). In addition, the IMCA is responsible for updating these criteria from time to time and as necessary and is the agency authorized by the Ministry of Health for examining, approving and issuing appropriate licenses to all practitioners in the fields of cannabis and to the various researchers and research bodies interested in conducting studies involving the use of or contact with cannabis, cannabinoids or other compounds extracted from the plant.

The principles by which the IMCA operates are:

- Cannabis, is to be treated, to the extent possible, like any other medicinal product that requires control and regulation for protecting public health and safety, considering its special character – a plant rather than a product manufactured in a laboratory or factory.
- Given the classification of cannabis as a narcotic drug, any arrangement pertaining to the medical use of cannabis in Israel must be as close as possible to an arrangement pertaining to the use of narcotic drugs.
- The commitment of the Ministry of Health in all matters relating to the supply of cannabis to patients is not different to its commitment concerning any other medicinal product that is not vital in an emergency or that is not included in the health basket.
- The Ministry of Health is interested in removing barriers concerning the supply of the drug to patients who can gain medical benefit from it.
- The state is responsible for and committed to protecting public safety and health and is entrusted with the prevention of misuse and criminal use related to narcotic drugs, including cannabis.
- It is the duty of the state to oversee the cannabis market, using the various governmental agencies (health, police, customs, agriculture), issue licenses when required and take any action necessary for protecting public health and safety or for preventing misuse and criminal use related to the drug.

Due to the absence of global standards for the use of the drug and in view of the increase in the number of applications for approval of use of medical grade cannabis, the Ministry of Health – IMCA has established medical and professional committees whose purpose is to advise the policy making in the various fields of growing, production and supply of medical grade cannabis for patients.

The advisory committees to the unit and to the field of medical grade cannabis and their activity fields:

- Inter-ministerial steering committee: for tracking and coordinating the subject, constituting a steering forum and recommendation of action strategies.
  The committee has representatives of the following ministries and agencies: the Ministry of Health, Ministry of Finance, Ministry of Justice, Ministry of Public Security, Ministry of Agriculture, the Israel Police, the Tax Authority – Customs, the Anti-Drug Authority.
- Indications committee: examines the expansion / reduction of the spectrum of indications, clinical recommendations, examination of ethics rules and pharmacolegal rules.
- Appellate / exceptions committee: for examining and recommendation of urgent care, compassionate care, appeals against decisions.
- Quality control committee: for examining and providing recommendations for quality requirements for the entire supply chain of medical grade cannabis.
- Security committee: for examining and recommending security standards for growing, for growers / workers, conveying, production, supply, prescribing.
- R&D committee: (medical, medical devices, agriculture) for advancing research in the field of cannabis, recommendation for approval of research applications, examination of professional standards.

Additional information, which is updated from time to time, may also be found on the website of the Ministry of Health / units / the Israeli Medical Cannabis Agency – at the address: http://www.health.gov.il/UnitsOffice/HD/cannabis/Pages/default.aspx

Within the regulation outline, the IMCA has prepared this clinical guide "Medical Grade Cannabis - Clinical Guide" ("the green book"), whose purpose is to lay down the initial line of the information base. This clinical

guide concentrates and renders accessible information for physicians, and primarily constitutes a uniform, central and clear axis of medical methodology that will serve as a tool for physicians for recommendation for building a treatment plan and considerations for setting dosing, type and quantity of cannabis per month. The clinical guide covers information that has been accumulated and published in scientific literature and by professionals practicing the field concerning the cannabis plant, the active substances in the plant and their effect, the endocannabinoid system, the pharmacokinetic processes and the side effects and main drug interactions. This clinical guide represents a large amount of work that has included, inter alia, concentration of dozens of knowledge sources dealing with cannabis from the fields of botany, pharmacology, chemistry and biochemistry, and following them the determination of a "therapeutic methodology" based on the dosing paradigm for a product containing THC and approved by the FDA.

At the beginning of the field of use of cannabis for medical purposes, there was no clear deliberation of the indications for use, the therapeutic methodology or medical examination methods. In addition to this, there is a wide range of "cannabis strains", knowledge on which is based mostly on the physiological effect on users, based on observations of people engaged in the field rather than medical professionals or pharmacological research. Within the wide range of strains there is variance in growing and production processes, and therefore in the composition of active substances in the plant too. This variance exists not only between strains, but also in between growing cycles of a given strain, and also between

plants of the same growing cycle of that strain. In view of the scope of the uncertainty stemming from the state of such great variance, and in view of the absence of a pharmacological common denominator and reproducibility in therapeutic sequence, the need for a regulatory outline establishing strict criteria and quality rules is greater than ever before, along with a regulatory deliberation for a therapeutic "protocol" for cannabis in medical applications. Such a deliberation should rely, to the extent possible, on currently established scientific information, defining inter alia the quantity of use, daily dose, frequency of use and most importantly the characterization of the product and its chemical composition – as commonly practiced in medicine.

The information in this clinical guide is intended to assist in the examination of the possibility of treatment using cannabis and serve as an accessory in accompanying the process of matching the treatment and the dosage and developing the therapeutic plan and medical follow up. The clinical guide shows the approved indications for receiving a cannabis usage license, the guidelines and recommendations for developing a treatment plan, for effective use and adjusting the quantity and dosage of medical grade cannabis. The attending physician assumes the responsibility for matching the appropriate treatment with regard to product type, monthly quantity, potency and daily cannabis dose per patient.

This clinical guide probably covers only part of the desired and undesired effects that stem from the use of cannabis. In order to expand the evidence based knowledge, an effort must be made to advance studies in the field and to the extent that knowledge based on empiric facts accumulates, modifications / additions / reductions may be made and medical treatment with cannabis as described in this clinical guide may be improved, for the benefit, wellbeing and health of the public.

Best regards,

The Management of the Israeli Medical Cannabis Agency (IMCA)

3. The cannabis plant

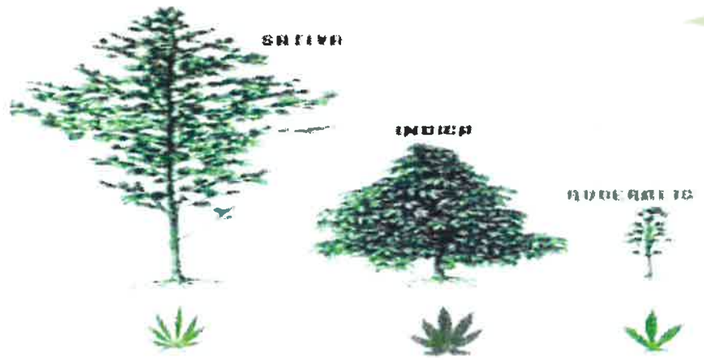
The cannabis plant is the best known genus of 11 genera of plants of the cannabis family. Cannabis consists of 3 primary species that differ in plant morphology, ratio and quantity of substances:

- *Cannabis sativa*
- *Cannabis indica*
- *Cannabis ruderalis*

Sativa is the most common cannabis species used in the world today, is taller and narrower than indica and its leaflets are relatively thin and long. Sativa originates from the equator – Colombia, Mexico, Thailand and Southeast Asia.

The indica species is the second most common in the world, grows lower and broader than sativa and having relatively wide and short leaflets. Indica originates from the Middle East and the Afghanistan and Pakistan region.

Ruderalis is a relatively rare strain originating from Russia. It grows relatively consistently and is less affected by light-darkness ratios. It has efflorescence only at its tip and has minimal percentages of the psychoactive substance THC.



There are more than 461 different chemical compounds in the cannabis plant, most of which are in three families of plant metabolites: terpenoids, flavonoids and the best known chemical group known as cannabinoids. These groups of plant metabolites have a wide range of unique functions related inter alia to the plant's development, protection from pests, attraction of pollinizers and a broad spectrum of therapeutic effects on human health.

Terpenoids and flavonoids are compounds that exist in most plants that have a major contribution to the functioning and development of the plant and for its various properties such as scent and flavor. In addition,

these compounds are ostensibly attributed various therapeutic effects, but at this time no specific effect may be attributed to any exact compound and their mechanism of activity cannot be described.

The phyto-cannabinoids are considered as pharmacologically active compounds. They are synthesized in microscopic glandular secretions that accumulate at the tips of resinous growths that are called trichomes. The trichomes occur in every plant and are expressed in a high concentration in unfertilized female flowers. The cannabinoids accumulate primarily in an efflorescence area, but may also be found at lower concentrations in other plant parts.

These groups of plant cannabinoids contains more than 100 compounds that are unique to the cannabis plant and as botanic and medical research of the plant and its compounds expends new compounds are discovered. At this time, "Medical grade cannabis products" that are approved for medical use (see Chapter 10) are defined and classified according to the ratio and quantity of the cannabinoids THC, CBD and CBN.

However, it should be remembered that besides THC, CBD and CBN, the cannabis plant contains many dozens of different compounds, for which there is less empirical knowledge of their pharmacological effect both individually and separately.

Throughout history, many cannabis plant species and strains plants have been hybridized in order to achieve a range of desirable properties. These hybridizations have caused a wide variety of cannabis strains over time, each of which has a different genetic profile, resulting in a different profile of composition and active substance ratio. The characterization of the sativa species as having higher THC percentages and of the indica species as having higher CBD percentages relative to each other is based on the original character of those species predating the many hybridizations done for enhancing properties and does not necessarily correspond with the situation today.

The genetic, morphological and chemical difference between the original species of sativa and indica was also characterized, inter alia, by unique physiological effects that did not necessarily stem only from the concentrations of THC and CBD. It is common to attribute the expressions "sativa character source" and "indica character source" today to a broader division by genetic source, and accordingly by character of effect of the "cannabis product" on the patient.

A "sativa character source" that is more suitable for use during the day refers to a "cannabis product" that has a characterization of giving an energetic feeling, providing a "light" feeling, improving mood and increasing concentration and creativity.

An "indica character source" refers to a "cannabis product" that has a characterization of giving a soothing feeling, imparting a sensation of "general tranquility" that facilitates sleep, reduces muscle tone and that is therefore more suitable for use at nighttime.

In general, the "character sources" may be clarified according to the following features:

Sativa character sources	**Indica character source**
Increased mental effect	Increased physical effect
Stimulates	Soothes
Stimulates appetite	Reduces anxiety
Stimulates creativity	Induces sleep
Reduces depression	Relieves pain
Recommended for daytime use	Recommended for nighttime use

4. The endocannabinoid system

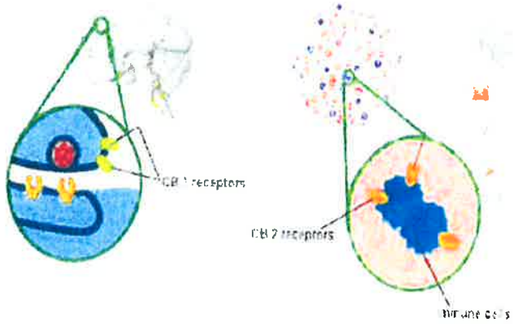
The endocannabinoid system is a signal transmission system in the bodies of animals and humans. The system consists of a group of receptors that are expressed inter alia in the nervous system (central and peripheral) and ligands that are endogenous to those receptors that serve as neuromodulators and are referred to as endo-cannabinoids (see Chapter No. 5 – cannabinoids). The endocannabinoid system has been researched extensively, inter alia through various chemicals, biological and pharmacological methods. These studies have revealed the involvement of the cannabinoids in a wide range of physiological and pathological processes, including: nerve conduction, neurogenesis, insulin metabolism control, immune system control, motor learning, appetite, sensation of pain, mood and memory. The endocannabinoid system that was first characterized and studied by Prof. Rafael Mechoulam, quickly became a new area in biochemistry and brain research, in which a number of key components were quickly identified, including:

- Lipid endogenous molecules originating from arachidonic acid referred to as Anandamide (N-arachidonoylethanolamide) and 2-AG (2-arachidonolyglycerol) are the physiological ligands of the cannabinoid receptors and are also referred to as endocannabinoids.
- Enzymes that are responsible for the synthesis and degeneration of endo-cannabinoids such as fatty acid amide hydrolase or monoacylglycerol lipase.
- The receptors CB1 and CB2 are the most relevant and their expression is significantly higher in the central and peripheral nervous system. These receptors are of G protein-coupled receptors, whose activation by the cannabinoid ligands leads to a decrease in cyclic AMP concentration and accordingly an inhibitory effect.

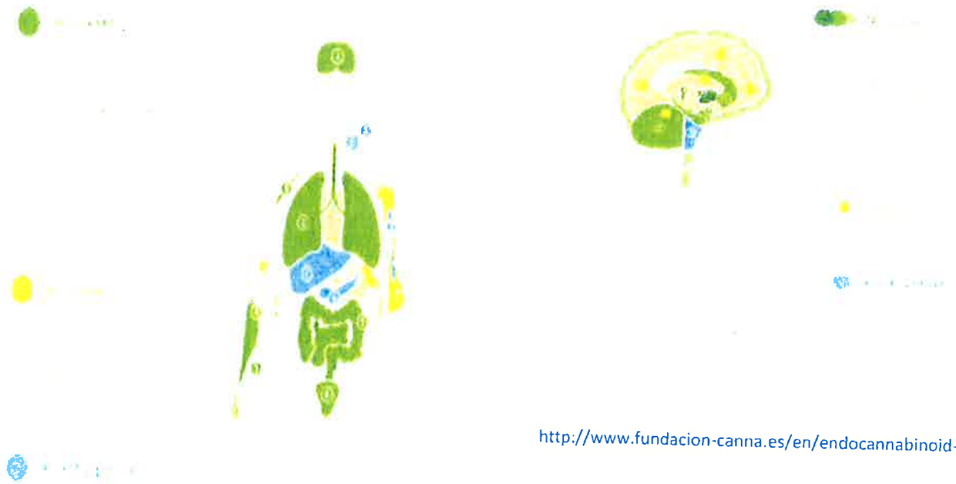
The first receptor that was discovered is called **cannabinoid receptor type 1 (CB1)**. This receptor is expressed primarily but not exclusively in the central nervous system (CNS) and probably constitutes the connecting link between the CNS and cannabinoids (whether endogenous, plant or synthetic). Peripherally, one may find expression of CB1 in immune system cells, reproductive system tissues, digestive system tissues, the superior cervical ganglion, heart, blood vessels, lungs, liver, adipose tissues, urinary bladder and adrenal gland. The CB1 receptor is also located in the termini of the central and peripheral nervous system, and when activated, probably causes suppression of release of various neurotransmitters such as acetylcholine, noradrenalin, glutamate, aspartame and more.

The second receptor that was discovered is called **cannabinoid receptor type 2 (CB2)**. This receptor is expressed exclusively in the periphery, primarily in immune system cells with very high levels in B cells and in NK cells. Despite this, it was reported previously that CB2 is probably also expressed in microglia cells of the CNS and in neuron stem cells of in the brain.

In recent years, the complexity of the endocannabinoid system has been expanding, and today the reception of cannabinoids and the expression of cannabinoids receptors (CBR) in other tissues and organs is are being studied, although the mechanism for their activity has not yet been found, and the involvement of additional receptors belonging to the endocannabinoid system that probably also constitute a pharmacological target for cannabinoid ligands is being studied too.



/https://bcachemistry.wordpress.com/tag/cannabinoid



http://www.fundacion-canna.es/en/endocannabinoid-system

5. Cannabinoids

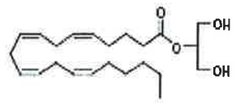
Cannabinoids are a diverse group of chemical compounds, which are used as ligands that bind to receptors of the endocannabinoid system. The cannabinoids are classified into three groups by source: endo-cannabinoids, which are produced in the human or animal body, synthetic cannabinoids, which are produced in the laboratory, and the group that will be discussed at length in this clinical guide, the phyto- cannabinoids, which are produced in the plant and constitute the active substances in medical grade cannabis.

1. Endo- cannabinoids

The endogenous cannabinoids that are produced in the human and animal body and constitute an integral part of the endocannabinoid system are lipophilic molecules whose chemical structure is based on arachidonic acid. The main endo-cannabinoids that have been discovered until today are anandamide (n-arachidonoylethanolamide) and 2-AG (2-arachidonoylglycerol).

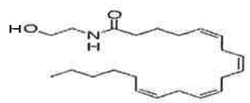
Anandamide is used as a neurotransmitter that is formed by synthesizing arachidonic acid and ethanol-amine, is present in the body in minimal quantities and has a short half-life due to the activity of the enzyme fatty acid amide hydrolase. Pharmacologically speaking the activity of the endo- cannabinoid anandamide and the phyto- cannabinoid THC is similar, despite them having different chemical structures. Anandamide easily passes the blood brain barrier (BBB) and binds at high affinity to CB1 in the CNS. In addition it also binds as a partial agonist with lower affinity to CB2 in the periphery. It is of importance in fetal development in pregnancy and is probably related to feelings of happiness and joy. It may be found primarily in the brain and its level increases after hypoxia or brain damage.

2-AG 2-arachidonoylglycerol



The endo-cannabinoid 2-AG also has similar affinity to CB1 and CB2 and is used as a full agonist for both. Its levels in the brain are significantly higher than those of anandamide and there is a dispute concerning which of them is primarily responsible for the activation of the neural signal system via CB1. One may find significant levels of 2-AG in the spleen too, which probably alludes to its function in the immune system and in blood pressure regulating processes.

Anandamide N-arachidonoylethanolamide



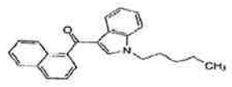
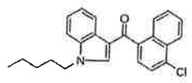
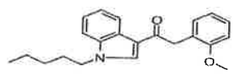
2. Synthetic cannabinoids

The synthetic cannabinoids are molecules that are synthesized in the laboratory as analog compounds to the natural cannabinoids, primarily to the psychoactive cannabinoid THC. These are chemicals that bind at high affinity to the cannabinoid receptors CB1 and CB2. The feeling of intoxication that is caused following the binding of synthetic cannabinoids to the endocannabinoid system's receptors is much more powerful than that known as a result of binding of THC.

According to evidence from experts, the phenomenon of adolescents reaching intoxication following the consumption of synthetic cannabinoids mixtures has been gaining frequency. This is a dangerous cocktail of drugs that causes severe hallucinations, vomiting and restlessness (irritability). The effect of the cocktail is dangerous to the cardiovascular system and manifests in pallor, increased blood pressure and heart rate. The effect on the central nervous system also manifests in seizures. These dangerous effects are not known from the consumption of cannabis, because the effect of the substance as reported is 10 times higher than that of THC. According to information from New Zealand, synthetic cannabinoids that have been developed as agonists to receptors in the endocannabinoid system may cause the eruption of psychosis in predisposed individuals. The consumption of these substances results in tolerance and withdrawal symptoms upon discontinuation.

Recently, patients who consumed a synthetic cannabinoid of JWH-018 type, which binds receptors in the endocannabinoid system at high affinity and that may cause very severe psychoactive effects and mental deterioration resulting in recurrence of active psychosis, restlessness and irritability, confusion and paranoid and grandiose delusions, has been reported. This synthetic compound started to be widely distributed in Europe from 2004. By 2009, additional substances from the synthetic cannabinoid group had also been identified: in the USA, the substance HU-210 and in Germany and in Great Britain JWH-398 and JWH-250 were identified.

Warning: the synthetic cannabinoids constitute a chemical group of a range of compounds that may pose a danger to health. These compounds are prohibited under the Dangerous Drugs Ordinance, have not been tested for toxicity or side effects and therefore **their use is prohibited!**

JWH-018	1-pentyl-3-(1-naphthoyl)indole	
JWH-398	1-pentyl-3-(4-chloro-1-naphthoyl)indole	
JWH-250	1-pentyl-3-(2-methoxyphenylacetyl)indole)	

3. Phyto- cannabinoids

The phyto-cannabinoids are cannabinoids of plant source that are unique to the cannabis plant. The biosynthetic pathway that occurs in the cannabis plant leads to the formation of cannabinoids that are divided into two subgroups of phyto-cannabinoids, which are based on the length of their alkyl group (3 compared to 5 hydrocarbons). The enzyme prenyl-transferase, which is involved in the biosynthesis of cannabinoids, may use as a substrate two compounds that are almost identical, which differ only in the length of their alkyl groups: three carbons in the case of divarinic acid and five carbons in olivetolic acid, and accordingly, the phyto-cannabinoids that will be formed later in the pathway will be characterized by the same length of carbon residue.

In the cannabis strains in Israel, we will find mostly the compounds that form in the biosynthetic pathway that begins with olivetolic acid, forming cannabigerolic acid (CBGA), from which, through enzymatic reactions, the phyto- cannabinoids, such as cannabidiolic acid (CBDA), tetrahydrocannabinolic acid (THCA) and cannabichromenic acid (CBCA) are formed.

In the plant in its natural form, these phyto-cannabinoids are found mainly in their acidic form (THCA, CBDA). After a decarboxylation reaction (loss of a carboxyl group as a result of exposure to heat), the known neutral form of the molecules is received, to which most of the pharmacological activity is attributed. The spontaneous reaction rate of the decarboxylation process is very slow at room temperature but is speeded up at high temperatures. In effect, the combustion process in smoking cannabis efflorescence assists in stimulating the decarboxylation reaction, thus allowing for the absorption of the phyto-cannabinoids in their active form into the bloodstream.

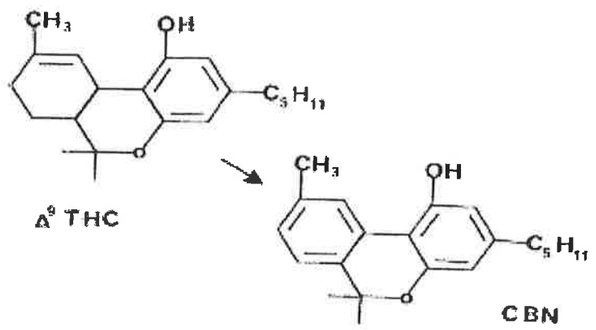
/https://oxigem2015.wordpress.com/2015/07/20/synthetic-biology-is-making-medical-marijuana-drugs-cheaper

Until now, about 100 phyto-cannabinoids have been identified in the cannabis plant, the main ones being, in order of relative concentration in the plant and pharmacological knowledge accrued about them from research, are: Δ-9-tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN). Besides these, the plant also contains a large number of cannabinoids, which probably have a pharmacological effect in the human body, such as cannabigerol (CBG) and cannabichromene (CBC), but the empirical knowledge concerning their pharmacological effect is still very meager.

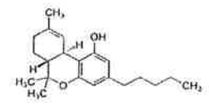
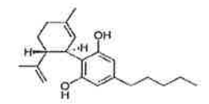
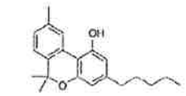
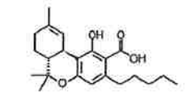
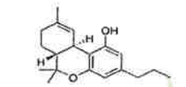
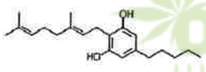
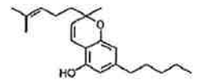
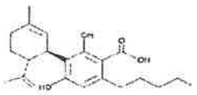
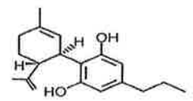
The phyto-cannabinoid THC was first isolated and characterized in its pure form in 1964 by Prof. Rafael Mechoulam, Yechiel Gaoni and their colleagues at the Hebrew University in Jerusalem. The decoding of its chemical structure opened the gateway to a range of studies on the cannabinoid molecules. At low temperature, THC is a glazy solid, and when heated becomes sticky and viscous. It has very low ability to dissolve in water, but good ability to dissolve in organic solvents, particularly oils and alcohol. THC is a phyto- cannabinoid that has dominant psychoactive effect, and besides that, its physiological effect range is broad and characterized by local anesthetic, anti-tremor, anti-nausea, appetite stimulation and anti-inflammatory effects. In addition it is attributed other effects, such as calming, causing visual, auditory and olfactory perception change.

In 1963, Prof. Rafael Mechoulam published the stereochemical structure of CBD, another key component of the cannabis plant. This substance is not water soluble, but dissolves well in organic solvents such as pentane. At room temperature, it is a colorless, crystalline solid. The phyto-cannabinoid CBD is not attributed any psychoactive effect and is considered the key component of the cannabis plant opposing the psychoactive effect of THC. The range of activity attributed to it includes anti-inflammatory, anti-tremor, antioxidant, anti-psychoactive (thus neutralizing / reducing the psychoactive effect of THC), neuroprotective and anxiolytic activity.

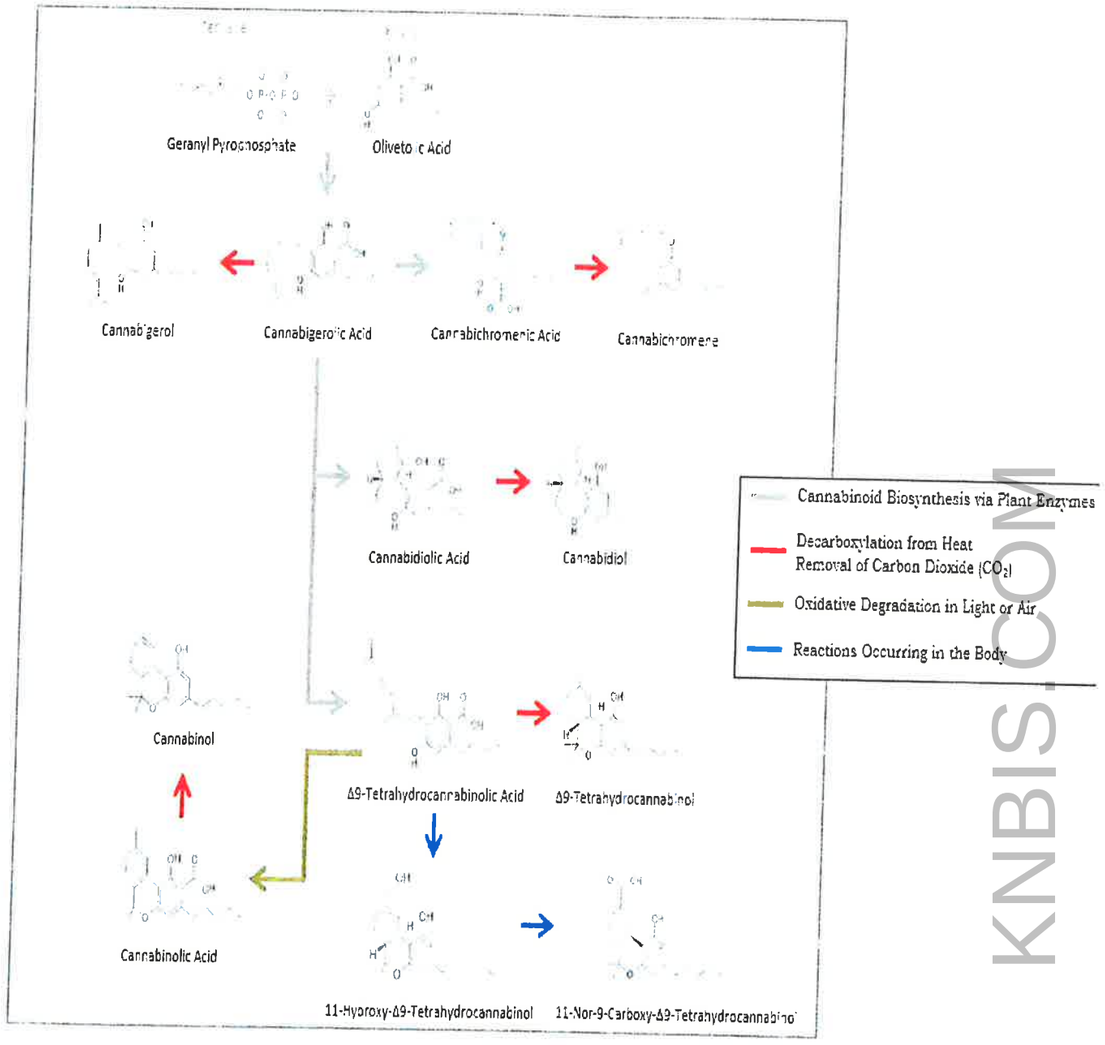
The phyto-cannabinoid CBN is a metabolite that forms from the breakdown of THC to which weak psychoactive activity is attributed. It may be found only in minimal quantities in the cannabis plant and may usually be found at a relatively high concentration in cannabis products that have aged.



Examples of phyto-cannabinoids

THC	**Δ -9-tetrahydrocannabinol**	
CBD	**Cannabidiol**	
CBN	**Cannabinol**	
THCA	Tetrahydrocannabinolic Acid	
THCV	Tetrahydrocannabivarin	
CBG	Cannabigerol	
CBC	Cannabichromene	
CBDA	Cannabidiolic Acid	
CBDV	Cannabidivarin	

The biosynthetic pathway of phyto-cannabinoids beginning from olivetolic acid:

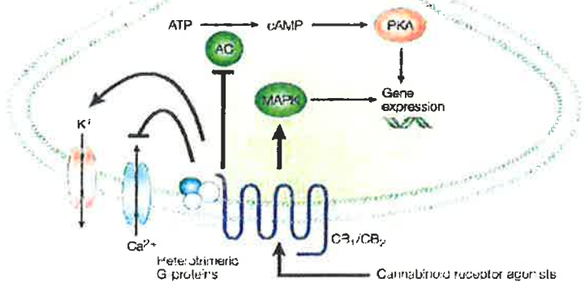


/http://www.isascientific.com/isa-rd/cannabidiol

6. The mechanism of action of the phyto-cannabinoids at the cellular level

The cannabinoid receptors (CBRs) are activated by the cannabinoids, whether endogenous, synthetic or of plant source (phyto-cannabinoids). The phyto-cannabinoids bind to receptors of the endo-cannabinoid system CB1 and CB2, which belong to the family of receptors that are coupled to GTP binding proteins (GPCR). It may be said in general that the activation of CBR mainly causes inhibition of the enzyme adenylate cyclase (resulting in inhibition of formation of the secondary messenger molecule cAMP), but today there is evidence that after binding and activation of CBR, a wider range of signal transmission pathways are activated (intracellular signal transduction) depending on the phyto-cannabinoid type, its concentration and other factors.

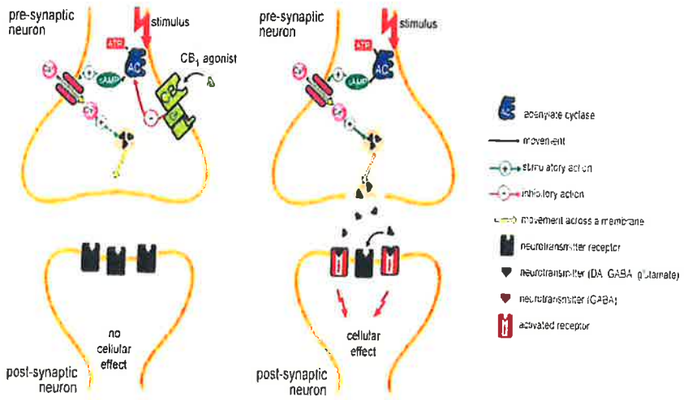
The cannabinoid receptors in the nervous systems are located on the presynaptic membrane. At the cellular level, following the binding and activation of the endocannabinoid system receptors, conventionally there is an effect of suppression of the adenylate cyclase system, which continues respectively to affect levels of cAMP, activity of voltage dependent calcium and potassium channels, levels of release of neurotransmitters, finally manifesting in systemic physiological levels such as pain relief, anti-inflammatory effect and more.



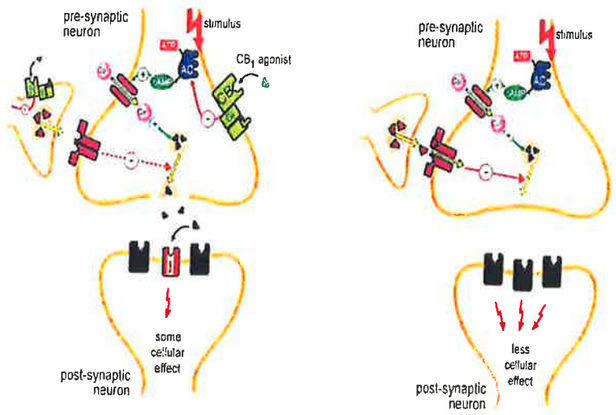
/http://www.nature.com/nrd/journal/v3/n9/images/nrd1495-f3.jpg

Studies that have dealt with the molecular mechanism through which changes in the membrane voltage related to the CB1 receptor are induced have shown that the binding of agonists to and activation of this receptor causes a decrease in the calcium flux by blocking the activity of voltage dependent calcium channels. In addition to the effect on the calcium channels, the activation of Gi/o and Gs type CBRs, which are the two main cannabinoid GPCR receptor types, also affects the activity of potassium channels. Studies have also shown that activation of CB1 specifically increases the flux of potassium ions through a family of calcium channels called GIRKs. In the central nervous system, the CB1 receptors affect neural excitability by reducing the synaptic signal. The mechanism known as presynaptic inhibition occurs when a postsynaptic nerve releases endo-cannabinoid by retrograde transmission, which binds to CBR at the presynaptic terminal. In this state, CB1 causes a decrease in the release of the neurotransmitter, so that as a result, excitation of the presynaptic nerve causes a reduced effect in the postsynaptic nerve. There are probably other intracellular signal mechanisms that act in the mediation of activating cannabinoid receptors that are still being studied.

Regulatory effects of cannabinoids Vs. Normal neurotransmission:



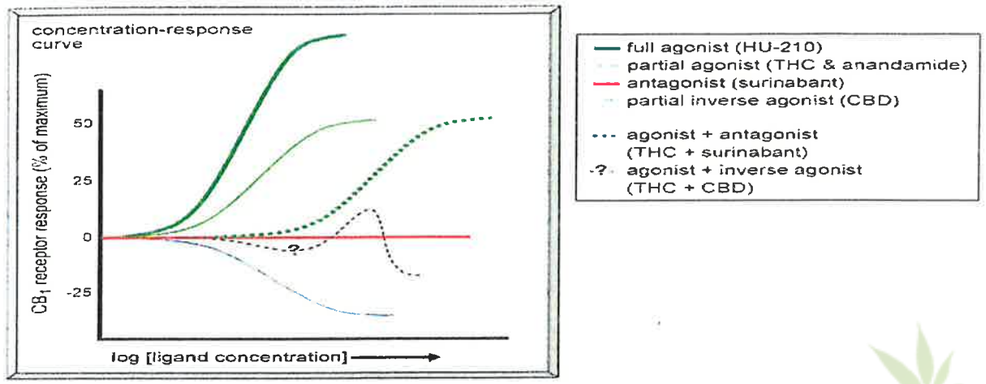
Regulatory effects of cannabinoids Vs. Normal neurotransmission in a network:



Pertwee RG, Br J Pharm, 2008

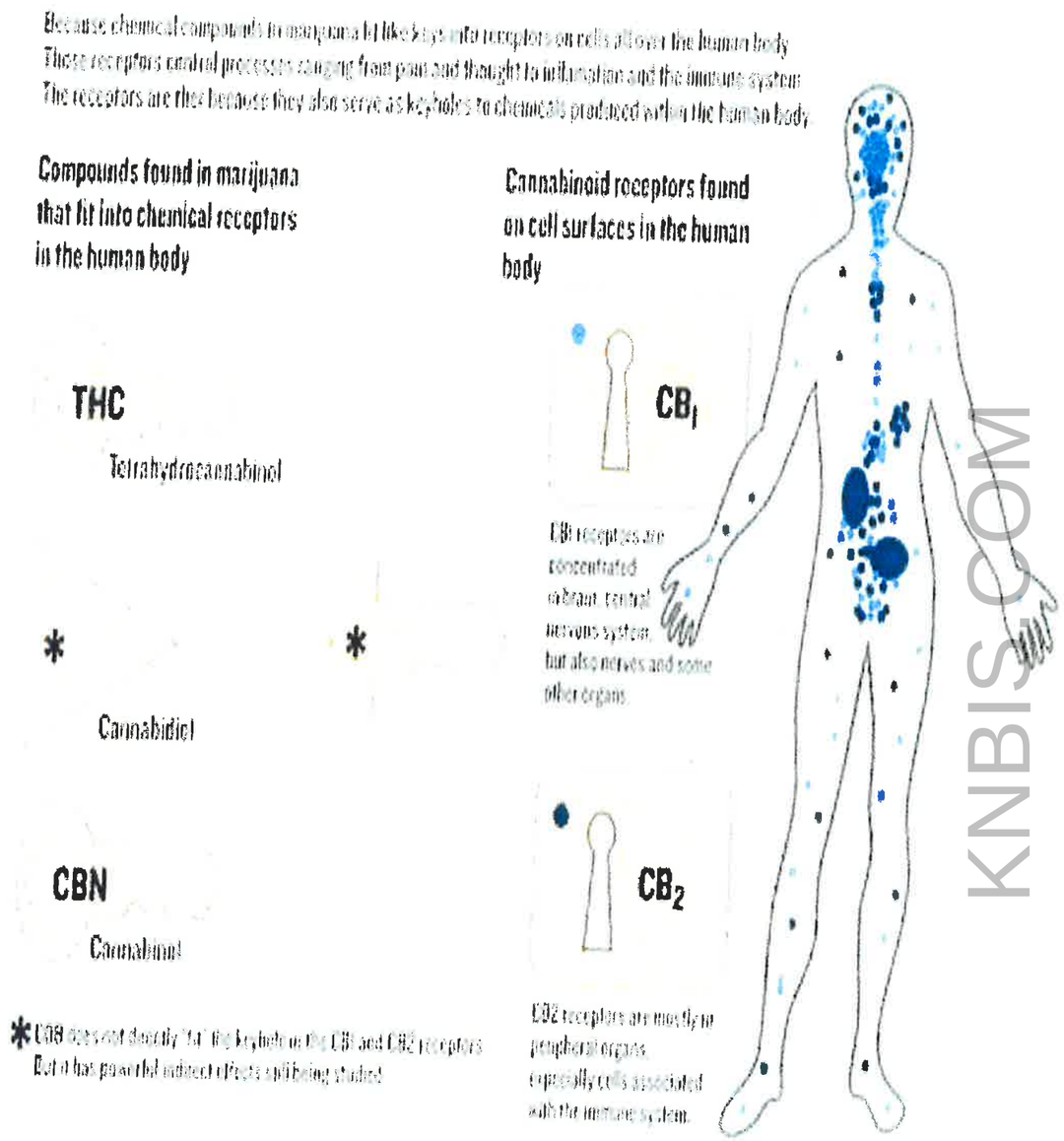
In the examination of the affinity of phyto-cannabinoid for CBR, it has been found that THC is a partial agonist of the receptors CB1 and CB2, but its affinity for CB1, which is to be found primarily in the CNS, is 10 times higher, which may account for its psychogenic effect. In contrast, CBD is an antagonist of CB1 and CB2, with higher affinity for CB2 that is to be found primarily in the periphery, inter alia on immune system cells, which may account for its anti-inflammatory activity.

In addition, the activity of CBD as an antagonist of CB1 is also probably responsible for the moderating effects of the psychoactive effects of THC. The phyto-cannabinoid CBN is a metabolite of THC, and like it, is an agonist of the two receptors, but with higher affinity for CB2 and with a total affinity that is much lower than that of THC.



(Laura M. et al. 2013)

Receptors of the endo-cannabinoid system:



/#/http://seed2cure.org/resources/introduction-to-the-endocannabinoid-system

7. Pharmacokinetics – routes of administration of medical cannabis and THC absorption, distribution, metabolism and clearance

The "cannabis products" that are approved for use in Israel as detailed in Chapter 10, are intended and adapted for different pharmacological administration. Each mode of administration has a unique pharmacokinetic profile according to the patient's needs, which differs in bloodstream absorption levels and in bioavailability of the active substances in cannabis.

1. Dried cannabis efflorescence – intended for administration by inhalation using ready to smoke rolls or using an inhaler. By inhalation, the active substances are absorbed through the lungs into the bloodstream more quickly.

2. Cannabis oil extract – intended primarily for sublingual administration, in which the active substances are absorbed from the oral mucosa directly into the bloodstream, thus skipping the metabolism in the gastrointestinal tract and liver.

3. Cannabis cookies for children only* - intended for oral administration, in which the active substances are absorbed into the bloodstream through the gastrointestinal tract.

At present, most of the empirical knowledge that has accumulated concerning the pharmacokinetic profile of phyto-cannabinoids in the human body is for THC. The second cannabinoid in terms of accrued empirical knowledge is CBD, for which, like all other phyto-cannabinoids, knowledge is minor relative to THC. The pharmacological data and values appearing in this clinical guide were taken from a number of sources in scientific literature. These data and figures should be treated as range values that may be updated at a higher level of precision, to the extent that empirical information accumulates.

The pharmacokinetic processes are dynamic and may change over time, and may also be affected by the frequency and intensity of cannabis use. In addition it is important to remember that the chemistry of the cannabis plant is much more complicated than that of THC alone. Different, additional effects may be seen, given the presence of other cannabinoids and chemicals in the plant. In cannabis, there are at least eighteen different known groups of chemicals, which probably also contribute to cannabis's pharmacological and toxicological properties.

The pharmacokinetics of phyto-cannabinoids includes a number of processes:

1. The process of absorption into the bloodstream in each of the routes of administration detailed above.
2. The process of distribution of cannabinoids that have been absorbed into the body's organs and tissues.
3. Metabolism processes that occur in the liver and other compartments of the body.
4. Processes of clearance through the stool, urine, sweat, saliva and hair follicles.

The absorption of phyto-cannabinoids into the bloodstream

Inhalation administration

The route of administration and formulation of the "cannabis product" determine to a great extent the rate and degree of absorption of the active substances into the bloodstream. Smoking is the common to effect administration by inhalation of cannabis, which provides an effective, rapid method of systemic absorption of the active substance in cannabis from the lungs into the bloodstream and brain. The almost immediate exposure to the central nervous system (CNS) and the intense sensation of pleasure that is caused may contribute to addictive potential. In a comparative study it was observed that the peak concentration of THC in the blood after smoking is only slightly lower than by intravenous administration.

In terms of absorption rate, there is no significant difference between administration by inhalation through smoking and inhalation using an inhaler, meaning that absorption in both methods occurs through the alveolar epithelial cells directly into the blood vessels.

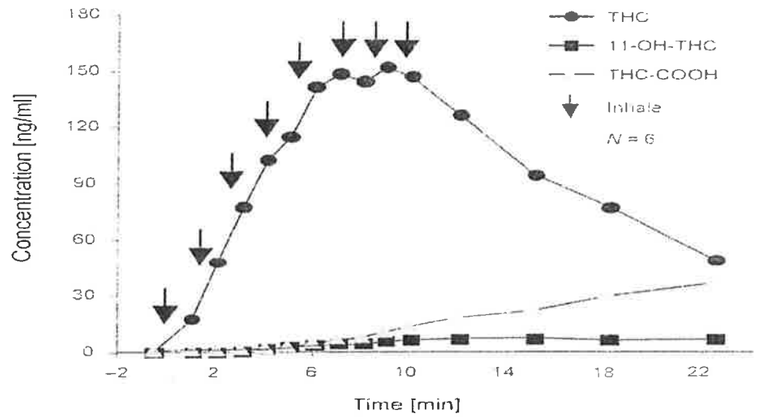
When examining the pharmacokinetic profile of THC after administration by inhalation through smoking, it would seem that the bioavailability ranges from 2% to 56%. The high variance stems from parameters between the subjects and from parameters of the subject himself, including: temperature and heating time of the cannabis, the time between inhalations, the number of inhalations, the length of the inhalation and the patient's lung endurance.

Table III. Systemic bioavailability of Δ^9-tetrahydrocannabinol (THC)

Subjects	Systemic bioavailability (%)		Formulation
	average	range	
Inhalational			
9 heavy users	23 ± 6	6–56	Marijuana cigarette
9 light users	10 ± 7	2–22	Marijuana cigarette
5 heavy users	27 ± 10	16–39	Marijuana cigarette
4 light users	14 ± 1	13–14	Marijuana cigarette
11 frequent or infrequent users	18 ± 6	8–24	THC in cigarette

Grotenhermen, 2003

The rate of the metabolites formed by THC in the liver is very slow and their peak concentrations are relatively low. The maximum concentration of THC in the plasma appears after 8-12 minutes when smoking a cannabis roll.



Marilyn, Huestis et al 2007

The graph above shows the mean concentrations of THC and its metabolites during and after smoking a single cannabis roll containing 3.55% THC. The arrows in the graph show the time of inhalation from the cannabis roll. The peak concentration is observed after 9 minutes on average, before the last inhalation is taken at time 9.8 minutes. In this study, many parameters contributing to variance have been neutralized, such as number of inhalations and length of inhalation, but many parameters such as difference in breathing depth of each patient contributed to variance.

Additional pharmacokinetic data of THC after smoking cannabis:

- Distribution half-life ($T_{1/2}$ distribution): 15-30 minutes
- **Terminal half-life ($T_{1/2}$ elimination): 25-36 hours**

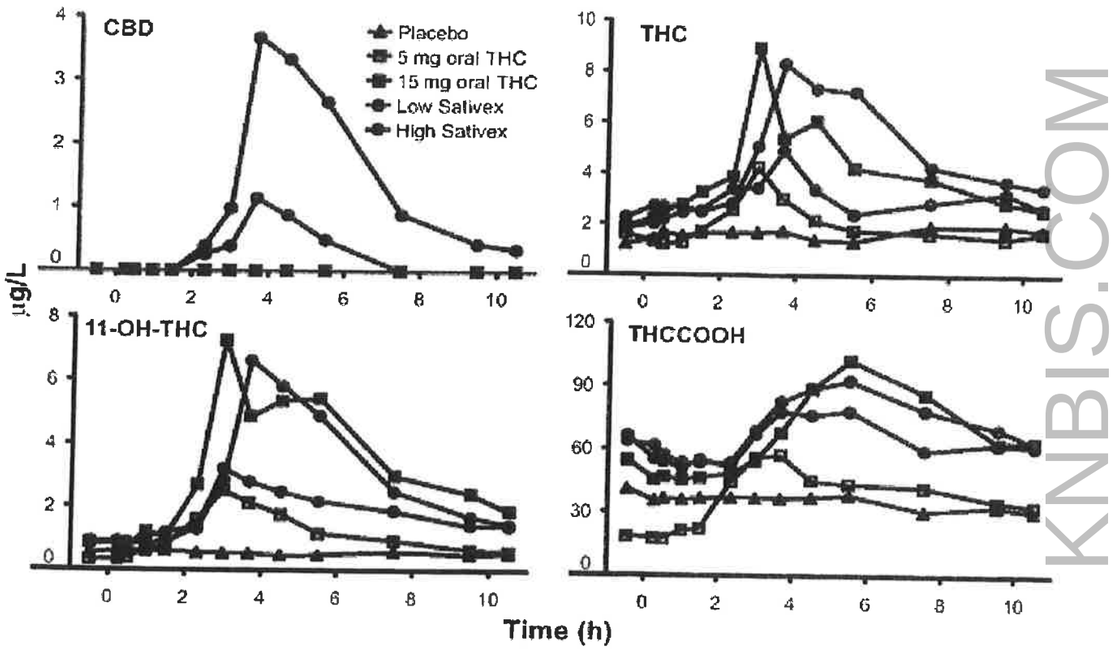
The bioavailability of cannabidiol – CBD after smoking, in the few cases studying it, ranged from 11% to 45%. The presence of CBD in the plasma may inhibit the metabolism (by CYP450) and affect the levels of THC and other cannabinoids.

Sublingual administration

The main advantage of sublingual administration is high ability to control the dosing process and self-titration relative to administration by inhalation and oral administration. Another advantage is that by sublingual administration, the active substances absorb directly into the bloodstream and to not pass through the digestive system, thus skipping the "first pass effect" in the liver.

The pharmacokinetic information for sublingual administration cannabis is not extensive. Existing knowledge is based primarily on studies that were conducted on the product Sativex™, which is approved in Canada for treating neuropathic pain associated with MS and consisting of nearly identical levels of THC and CBD.

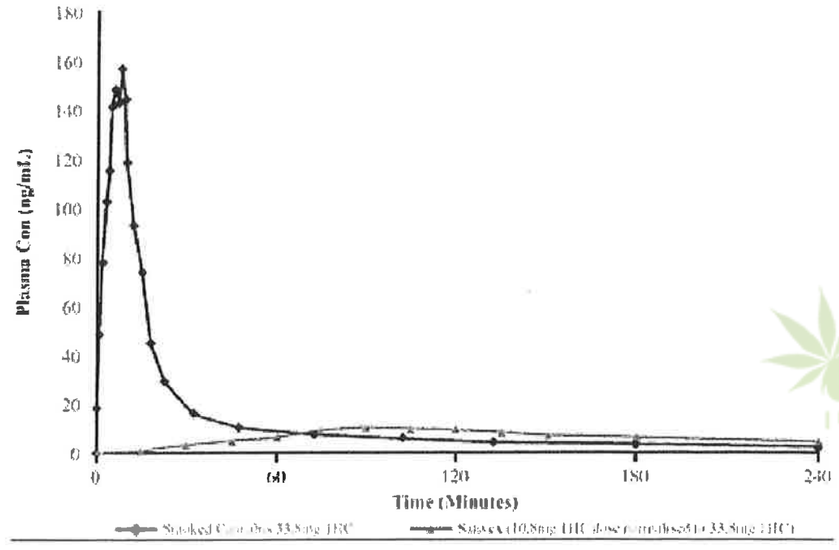
In a study by Karschner and coworkers (2011), it was found that the degree of absorption is similar and almost identical between sublingual administration and oral administration, at 10-20%.



Karschner et al. 2011

Another study that examined the pharmacokinetics of THC, 11-OH-THC and CBD after sublingual administration of THC and CBD, 10 mg from each, levels identifiable in the bloodstream of each of the three analytes were observed about 30 minutes after administration with a higher concentration of THC than that of CBD. After 45 minutes, the concentration of 11-OH-THC in the blood exceeded that of THC. The mean maximum peak concentration of THC was up to 5 ng/ml, of 11-OH-THC was up to 2 ng/ml, and of CBD was up to 7 ng/ml. In this test, high variance was demonstrated between one administration and another in the same patient and between patients.

In a comparison between Sativex™ and smoking cannabis, it may be seen that the rate of absorption and the peak concentration of THC are significantly lower by sublingual administration than by inhalation administration.



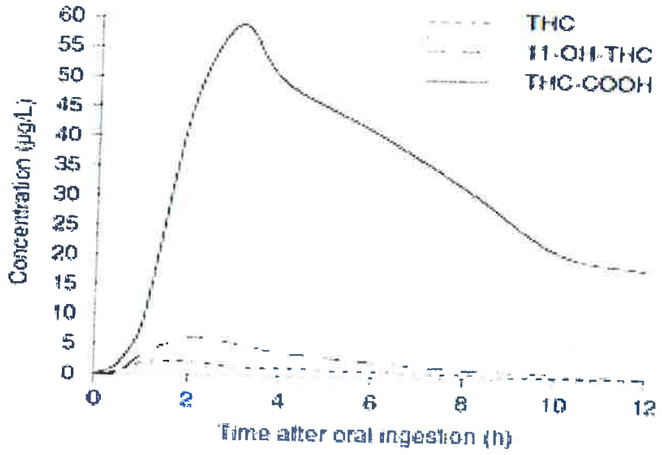
Huestis et al. 1992, Huestis et al 2009

Oral administration

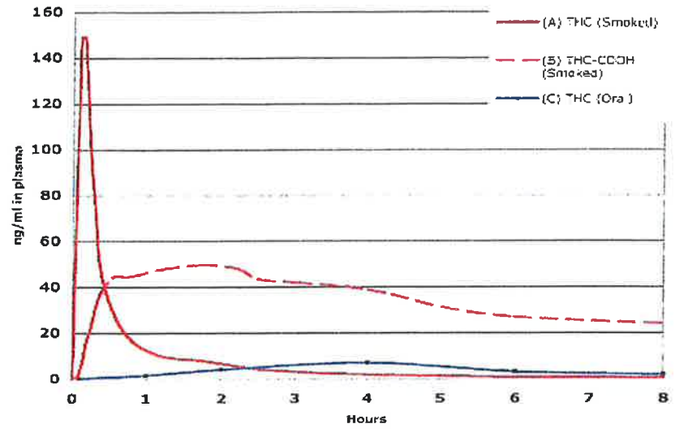
In a study that compared administration by inhalation and oral administration of THC, it was observed that the inhalation rate and bioavailability of THC by oral administration is much lower than that of inhalation administration, ranging from 2% to 20%, and with high variance between patients. It may be estimated that the bioavailability is about 1/3 of that of inhalation administration. A major part of this remarkable difference is a result of extensive metabolism that occurs in the liver. In order to assess the pharmacokinetic profile of THC by oral administration, it is important to factor the levels of the three metabolites: THC, THC-COOH and 11-OH-THC combined.

Table III. Systemic bioavailability of Δ^9-tetrahydrocannabinol (THC)

Subjects	Systemic bioavailability (%)		Formulation
	average	range	
Oral			
11 frequent or infrequent users	6 ± 3	4–12	THC in chocolate cookie
6 men, 6 women	10-20		THC in sesame oil
7 men, 10 women	7 ± 3	2–14	THC in sesame oil



Grotenhermen, 2003



Huestis et al. 1992

Law et al. 1984

The pharmacokinetic profile of THC after oral administration:

- Bioavailability: 2%-20%
- Bloodstream absorption half-life ($T_{1/2}$ absorption): 1-3 hours
- Distribution half-life ($T_{1/2}$ distribution): 3.8 hours
- **Terminal half-life ($T_{1/2}$ elimination): approximately 25 hours.**

Studies that were conducted on an orally administered product containing THC and CBD showed that the absorption and bioavailability of the two cannabinoids separately were different. Their blood concentration increase gradually up to a maximum concentration of about 45 minutes until two hours after the administration, depending on consumption with food or without and with physiological variance differences between patients.

The following table summarizes the pharmacokinetic data of the THC absorption profile by different routes of administration. Row 1 relates to sublingual administration, row 2 to oromucosal administration, rows 3, 4 to oral administration and row 5 to administration by inhalation, all figures are normalized for a dose of 10.8 THC.

Administration by smoking is characterized by rapid absorption and reaching the highest peak concentration in a relatively short time. In contrast, sublingual administration and oral administration are characterized by slower absorption, reaching a lower peak concentration in longer time frames.

The AUC (area under curve) values are for the concentration of active substance in the plasma as a function of time elapsing since administration. This value expresses the degree of plasma exposure to the active substance (AUC is not an effect).

The diagrams of combined AUC values for THC and 11-OH-THC in the various routes of administration show that the degree of plasma exposure to the active substances is lower in inhalation than for sublingual and oral administration.

	THC		11-OH-THC		THC + 11-OH-THC
	C_{max} (µg/L)[6]	$AUC^{1,6}$ (µg/L*min)	C_{max} (µg/L)[6]	$AUC^{1,6}$ (µg/L*min)	$AUC^{1,6}$ (µg/L*min)
Sativex[2] (spray under the tongue) (49)	5.13	749	5.77	1409	2158
Sativex[2] (spray inside the cheek) (49)	5.58	696	5.68	1197	1893
Marinol[3] (dronabinol, capsule) (50)	6.22	580	7.51	1545	2125
Cannabis extract in oil capsule[4] (30)	4.04	450	4.89	1003	1453
Smoked cannabis[5] (23)	26.3	748	1.39	153	901

1. AUC, represents the area under the curve of the graph of THC and 11-OH-THC concentrations in the effect by time graph.
2. Sativex, an extract of the cannabis plant administered by 4 sprayers into the mouth (10.8 mg THC, 10 mg CBD).
3. Marinol, contains dronabinol that is administered as a capsule (10 mg THC produced synthetically).
4. An extract from the cannabis plant that is administered as an oil capsule (10 mg THC, 5.4 mg CBD).
5. Smoking of cannabis, 13.8 – 22 mg THC (on average 18.2 mg).
6. All values are normalized for administration of THC 10.8 mg.

Huestis et al. 1992

Huestis et al 2009

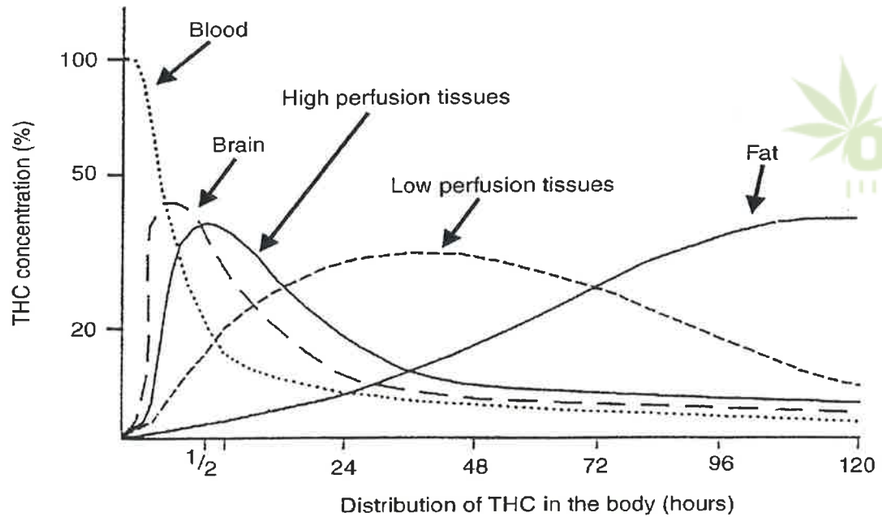
Distribution to THC into the body's tissues and organs:

The plasma concentrations of THC rapidly decrease at the end of consumption, following distribution into the tissues at a rate that depends on the blood flow and following metabolism that occurs in the liver. The distribution volume (V) of THC is approximately 3.4 liters per kg.

Because these are lipophilic molecules, they are capable of crossing the blood brain barrier and accumulating in adipose tissue. Upon their accumulation in adipose tissue for an extended period, their distribution pattern changes and they are released slowly back into the bloodstream. In a study that was conducted on animals after intravenous administration, higher THC levels were observed to reach the lungs than other tissues. Another study demonstrated peak levels of THC in the brain 2-4 hours after intramuscular administration.

A study that was conducted on swine into which THC was injected into the jugular vein at a dose of 200 mg per kg of body weight, demonstrated that at different time points after the administration there were high levels of THC in the lungs, kidneys, liver and heart.

The THC concentration in the brain was roughly twice its general concentration in the blood after 30 minutes, with higher levels in the cerebellum, occipital and frontal cortices; the lowest levels were observed in the medulla oblongata.



Ashton, C. Heather. 2001

Metabolism of THC in the liver and "first pass effect"

After absorption of THC into the bloodstream, it spreads inter alia into the liver, where it is metabolized by cytochrome CYP-450. The main metabolite of THC is 11-OH-THC, which undergoes secondary metabolism into the metabolite THC-COOH.

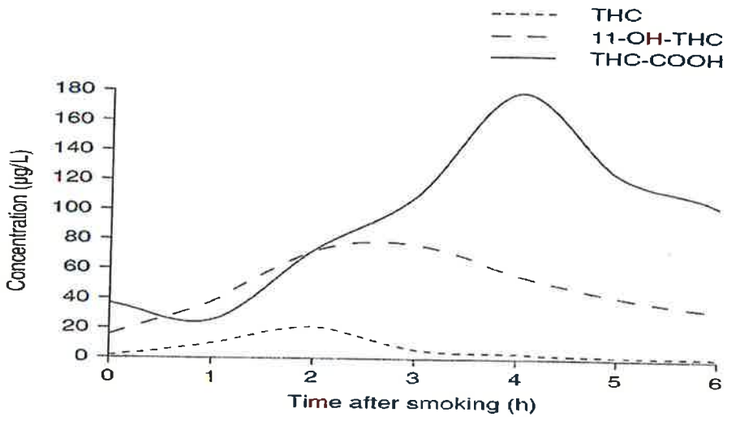
By oral administration of cannabis and absorption through the gastrointestinal tract, THC first reaches the liver directly (before absorption into the systemic bloodstream), where initial metabolism referred to as the "first pass effect" occurs. This effect causes a low absorption rate and accordingly low levels of THC in the plasma after oral administration relative to those after the other routes of administration.

The primary metabolite 11-OH-THC has a physiological activity rate that is similar but not necessarily identical to that of THC. It has higher potency and passes the blood brain barrier more easily, whereas the secondary metabolite THC-COOH is not attributed any psychoactive activity, but probably plays a function in the analgesic and anti-inflammatory effects of cannabinoids.

Clearance of THC from the body:

Within 5 days, 80-90% of the THC is cleared from the body, mostly in the form of metabolites 11-OH-THC or THC-COOH. More than 65% is excreted through the stool and about 20% through the urine. The primary metabolite that may be found in the urine is THC-COOH, which is acidic when coupled to glucuronide, whereas 11-OH-THC is the primary metabolite in the stool. The clearance of all cannabinoids and their metabolites occurs up to about 21 days after consumption.

The graph below shows the mean concentrations of THC and its metabolites in the urine as a function of time after smoking a roll that contained 27 mg of THC.

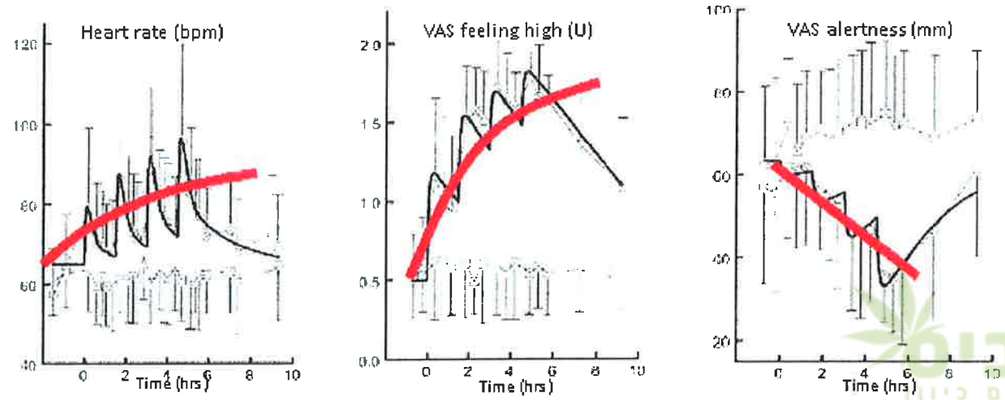


Grotenhermen, 2003

Pharmacokinetic / pharmacodynamic model of THC:

A review article in 200 that gathered information from 165 studies about the response of healthy subjects to THC examined parameters of pharmacodynamic effects in order to evaluate direct biomarkers of THC effect. The graph below, which summarizes some of the results of this review, shows the effect of administration of THC in increasing concentration and at intervals of an hour and a half between one administration and the next, over pharmacodynamic parameters such as heart rate, alertness and euphoria. In this study, a consistent response was observed between the subjects with regard to the effects studied:

- Increased heart rate (10 bpm above the average)
- Increase in euphoria of subjects
- Decrease in subjects' alertness
- Increase in motor instability



(Zuurman L. et al. 2009)

The phyto-cannabinoid THC causes an effect through a wide range of domains in the central nervous system. At low doses of THC, it would seem that a soothing effect occurs, which reduces the concentration level, accompanied by weakness of the response as observed in other CNS tests, which necessitate motivation and active participation. At higher doses of THC, it seems that the effect of the drug is more stimulatory. Subjective responses are the most reliable biomarker for learning the effect of administration of cannabinoids, along with an increase in the heart rate, which reflects the peripheral effect of cannabinoid activity. These parameters are effective biomarkers that may serve in the future for studies that are intended to examine the effect of doses of THC or other agonistic cannabinoids on the CNS.

8. Main side effects and interactions

The consumption of cannabis may cause side effects that are divided into physiological effects, such as dizziness, unstable heart rate (increased or decreased), reduced blood pressure and blood glucose, increased appetite, red eyes, headaches, abdominal pain, fatigue, poor coordination, instability and dryness of mucous membranes such as those of the eyes and mouth, and cognitive effects such as: loss of short term memory, impaired train of thought and changes in perception of time and space. These effects usually resolve shortly after adjustment to the product. When cannabis is ingested, the side effects may last up to 72 hours after taking the product. Regular use of high quantities may lead to impaired cognitive abilities.

Side effects that usually stem from an overdose, which require special attention:
Loss of consciousness, major changes in blood pressure, heart rate, blood glucose level or breathing rate. A high dose of the substance may, in certain cases, in predisposed individuals, cause a temporary outbreak of psychotic states, anxiety or hallucinations.

The drugs / treatments whose administration with cannabis is prohibited are:
Cannabis is known to have a cumulative effect with opiates, alcohol and anesthetic drugs. Such a combination must be avoided.

Drugs that inhibit the metabolism of cannabis are: primidone, phenobarbital, carbamazepine, rifampicin, rifabutin, troglitazone, as does the medicinal herb hypericum perforatum.

If the patient is taking or is starting to take any of these medications while taking cannabis, the attending physician must take this into account for adjusting the effective dose of cannabis. In addition, if the patient stops taking that medication or reduces its dose during treatment combining cannabis and one of these drugs, the attending physician must take this into account.

Detailed information may be found in Appendix C of this clinical guide – "**main side effects and interactions in using medical cannabis**", as published by the Pharmaceutical Society of Israel, January 2014, drafted by Konstantin Itin, Dr. Noya Machtiger-Azoulay, Dr. Yael Ratz, Prof. Shimona Yosselson-Superstine and Dr. Ilana Schumacher.

9. Approved medical indications for treatment with medical cannabis

A license for using cannabis will be issued after exhausting standard treatments, for a recognized indication only. The list of recognized indications and contraindications as detailed in Procedure 106 of the Ministry of Health follows. This information is partial. For full information, see Procedure 106, which is updated from time to time, appearing as a link via the website of the Ministry of Health.

The approved medical indications at this time are as follows:

In the oncology field:

- For patients during chemotherapy up to six months from its end or relieving nausea, emesis or treatment related pain (even without exhausting standard treatments for relieving nausea, etc.). In cases in which the attending physician believes that treatment with cannabis must be continued after six months – the reasons for continuing the treatment and the period that in his opinion it should be continued should be specified.
- For relief of pain of metastatic cancer source and after exhausting standard treatment options.

In the gastroenterology field:

For patients suffering from active, proven inflammatory bowel disease (Crohn's disease, ulcerative colitis) and meeting all of the following criteria:

- Standard medication using at least one immunomodulatory (such as: Imuran or Purinethol), for a period of 3 months at least, and in addition at least one TNF inhibitor (such as: Humira or Remicade) with a full loading dose, i.e. 3 treatments, has been exhausted and has failed.
- Ruling out the option for surgical treatment of removal of a short diseased intestine section.

The recommendation for treatment with cannabis is to be submitted by a gastroenterologist who has been caring for the patient for at least 3 months, with:

A. Detailed documentation of the said treatments.

B. Details on the reason for ruling out the surgical treatment option.

In the pain field:

Patients suffering from neuropathic pain of a clear organic source, who are treated at a recognized pain clinic for at least one year before submitting the application, after exhausting standard treatment options and with the recommendation of the pain clinic at which they are treated, along with:

A. A filled in Brief Pain Inventory (BPI) questionnaire, which will be used as a tool for following the patient in the context of the efficacy of treatment with cannabis.

In the infectious diseases field:
For patients diagnosed with acquired immunodeficiency system (AIDS), after exhausting standard medication and suffering from extreme weight loss (cachexia – more than 10% weight loss) for improving their appetite or relieving emesis and gastrointestinal symptoms.

In the neurology field:

- For patients diagnosed with multiple sclerosis in spastic states who have not responded to standard treatment.

- For patients diagnosed with Parkinson's disease, who have been treated for at least a year with antiparkinsonian treatment, who are suffering from pain (chronic pain or pain caused by rigidity) who have not responded to standard pain treatment.
  Contraindication to treatment – active psychosis.
  The recommendation for treatment by medical cannabis will be submitted by the caring neurologist who undertakes to conduct medical follow up every three months at least.

- For adult patients who are diagnosed with Tourette syndrome, who suffer from significant dysfunction in everyday life, who have not responded to standard treatments.
  Contraindication to treatment – active psychosis or (first degree) family heredity of psychotic diseases.
  The recommendation for treatment using medical cannabis will be submitted by the caring neurologist, along with:
  A recommendation of a psychiatrist who has examined the patient.
  In the first year of treatment, the license will be limited to three month periods each time and the renewal of the license will be on the condition of joint examination and recommendation by the caring neurologist and psychiatrist each time.
  From the second year of treatment, the license will be restricted to periods of up to one year each time, requiring a recommendation of the caring neurologist and a psychiatric recommendation.

- For adult patients with epilepsy, who fulfill all of the following criteria:
  Diagnosed as having severe epilepsy for at least two years, suffering from significant dysfunction [disabling epileptic seizures, including generalized clonic seizures, complex-partial focal dyscognitive seizures, other focal seizures if they cause a danger of falling and injury and generalized tonic or atonic seizures].
  The epilepsy is treatment resistant, after failure of at least five antiepileptic drugs prescribed as a monotherapy or as a drug combination, and is characterized by a seizure frequency of at least one seizure per month under documented medication.
  The recommendation to treat will be submitted by an expert neurologist caring for the patient at an epilepsy clinic at one of the medical centers in which the patient has been under follow up for at least the six months preceding the submission of the application, with documentation of failure of at least 2 drugs within the period of treatment at that clinic, and with an undertaking of the neurologist to conduct medical follow up and with a recommendation of a psychiatrist who has examined the patient.

- For minor patients who suffer from severe, uncontrollable epilepsy, after failure of standard treatments with at least five drugs / treatments, including resistance to or failure of one or more of the following: ketogenic diet, vagus nerve stimulator, surgery.
  The recommendation to treat will be submitted by a caring pediatric neurologist who has undertaken to conduct medical follow up every three months at least.
  At the beginning of the treatment with cannabis, the patient must be taking at least two recognized anticonvulsant drugs at full dosage and continue the treatment with them without reducing the dose for a period of six months without seizures following which reduction and keeping the patient on a single anticonvulsant drug and cannabis may be considered.

In the palliative care field:
For terminal patients (six month expected life expectancy).

In the psychiatry field:
For adult patients who are diagnosed with posttraumatic stress disorder (PTSD) and who meet all of the following criteria:

- Medium and greater severity posttraumatic stress disorder meeting the criteria of 30% disability at least under National Insurance Institute sections, persisting for more than 3 years and characterized by significant mental distress.
- At least 2 standard medicinal interventions for a minimal time of two months per intervention have been exhausted and 2 standard psychological interventions have been exhausted.
- Absolute contraindication to treatment – history of psychosis or narcotics abuse.

The recommendation for treatment with cannabis is to be submitted by an expert psychiatrist caring for the patient, on the "appendix to application for adjuvant therapy with cannabis for PTSD patients" via the link published on the website of the Ministry of Health http://www.health.gov.il along with:

A. Detailed documentation of the treatments as set forth above.

B. Recommendation of the recommending expert psychiatrist, confirming that he has explained the risks of treatment to the patient.

C. An undertaking of the recommending expert psychiatrist to continue the medical follow up throughout the license period.

In the first year of treatment: the license to use cannabis will be restricted to a period of up to six months each time and the renewal of the license will require a report of the caring psychiatrist concerning the results of the treatment through to the time of submitting the application and his recommendation to continue treatment.

From the second year of treatment: the license to use cannabis will be restricted to a period of up to one year each time and the renewal of the license will require a report of the caring psychiatrist concerning the results of the treatment through to the time of submitting the application and his recommendation to continue treatment.

10. Medical grade cannabis products

In a study of the chemical difference of cannabis from various sources in Israel that was conducted by Prof. Lumir Hanus (the Hebrew University of Jerusalem), the use of cannabis for medical purposes in Israel was also assessed. Within that study, the homogeneity of buds (female efflorescence tops with and without the surrounding small leaves) that were taken for the study from one cannabis plant, from different plants of the same strain and from plants of different strains, was studied.

The findings showed great variation in the concentrations of the active substances in the plant, even when the same cannabis "strain" was used, in the same quantity and within the same treatment. The study revealed a venerable glut of "strains", with the companies supplying medical grade cannabis using the different "strains" in accordance with availability and other considerations. Therefore, in the opinion of the researcher, a limited number of "strains" that are amenable to matching to different medical conditions should be chosen.

In an examination that was conducted (as may be found on the website, including in the "encyclopedia of strains" in Israel http://cannapedia.co.il or elsewhere in the world http://cannapedia.me), it has been found that there is a plenitude of "strains" in the State of Israel, and that on the one hand a genotypic and chemotypic match may be found between "strains" with different names, but on the other hand there is variance and genotypic and chemotypic mismatch within the "strains" themselves.

Moreover, even within the wide variety of strains grown in the various growing farms, there is diversity in the growing and production processes, and as a result, in the composition of active substances in the plant too. This variance exists not only between strains, but also between growing cycles of a given strain, and between plants of the same growing cycle of the same strain too.

In view of the extent of the uncertainty stemming from such great variance, and its consequences for a standard pharmacological denominator and reproducibility in therapeutic sequences, the need for regulatory determination for medical use of cannabis (according to a protocol) is needed now more than ever. Such a determination should rely, to the extent possible, on currently established scientific information that defines inter alia the quantity of use, daily dosage, frequency of use and most importantly the characterization of the product and its chemical composition, as commonly practiced in medicine.

An experts committee discussed the subject of concentrations of recommended active substances and their recommended combinations, as they will be available in medical grade cannabis products and dispensed to patients. The success of the members of the experts committee has been confirmed by the inter-ministerial steering committee on medical grade cannabis and subsequently by the Director General of the Ministry of Health.

"Cannabis products" (see tables on the following pages) will be available in three consumption forms: dried cannabis efflorescence, cannabis extract dissolved in oil and cannabis cookies – for children only (Appendix D – Ministry of Health Director General response letter). Only the cannabis products detailed below are approved at this time for marketing and distribution.

1. Standardization of medical cannabis products:

Medical cannabis products that will be approved of marketing in Israel will be manufactured and will be at a level of quality that is suitable for medical use, and will be marked "**IMC – Medical Grade**".

In order to reach a high level of standardization and in order to ensure a high level of reproducibility and uniformity as appropriate for a product for medicinal use, the breeding and growing processes of the cannabis plants used for forming the raw materials (cannabis efflorescence), the manufacturing and packaging processes of the cannabis products and their distribution and dispensation processes will all be done under close oversight and control in the form of good practices, in accordance with the IMCA good quality practice procedures – IMC-GAP, IMG-GMP, IMG-GDP, IMC-GSP, which engage, respectively, in growing, manufacturing, distribution and security under appropriate conditions, which define the lines of activity and criteria that the links of the chain are required to fulfill.

According to the foregoing, throughout the process, from the breeding material stage to the final medical grade cannabis product, optimal, uniform environmental conditions must be closely followed, as well as defined, uniform work processes that are based on standard operating procedures (SOPS).

Throughout the process, regular and periodical analytic checks will be done as required to ensure and document the compliance of the stem lines, reproduction batches, growing plants, growing batches and production batches of cannabis with the required analytic standards and quality level, as prescribed for each of the stages of the process.

Genetic source:
From the initial stage of the process, in order to ensure a high level of uniformity throughout the process, select cannabis plants will be used as stem lines (a genetic source for cannabis products), which are characterized by their ability to produce effloresces that contain defined concentrations of the active substances THC and CBD, according the concentrations required in the finish cannabis products.

These stem lines will contain a known, defined genetic sequence that is adapted for the synthesis of the active materials at the desired levels in the cannabis plants used for creating the raw materials, followed by production of the final cannabis products. Each stem line is a single genus ("strain"), which is maintained under appropriate, uniform conditions.

The breeding batch:
From each stem line / genetic source, "a breeding batch", which is a line of cannabis plant saplings of a single genus ("strain"), with genetic identity, originating from a single stem line, grown in a single growing complex and in the same growing season or time, will be prepared by vegetative reproduction (use of living plant tissue originating from a stem line).

Each breeding batch will be selected at various points in time, by genotype (identical, defined genetics of all saplings) and by phenotype (identical plant traits).

The selected cannabis plant saplings the constitute a "breeding batch" will be grown under uniform conditions up to the end stage mature sapling point (a young plant of up to 20 cm height).

Growing plant line:
The breeding batch that has reached the final stage in a uniform state will become the "growth plant line" at the next stage, this being a line of plants of a single genus ("strain"), grown in a single growing complex, in the same growing season or time, with genetic identity, orientating from a single breeding batch. The "growing plant line" will be grown under uniform conditions to the adult propagation stage and will be transferred in the end to the flowering stage.

Each "growth plant line" will be selected at different points in time by genotype (identical, defined genetics of all plants) and phenotype (same plant traits).

The growing batch:
From each "growing plant line", a "growing batch" constituting a defined quantity of cannabis effloresces of a single genus ("strain") with genetic identity, originating from one growing plant line, grown in a single growing complex in a single growing season or time, harvested at a single time and treated after harvesting at a single time and site, will be produced.

Each "growing batch" will be selected at various, defined points in time, by phenotype (same traits) and chemotype (defined, desired concentrations of active agents).

The production batch:
From each "growing batch", a "production batch", which is a defined quantity of cannabis product produced from one or more "growing batches" at one production and packaging time, will be produced.

2. Packaging and configuration of products:

A cannabis product will be only a product that is part of a "production batch", i.e. a product whose concentrations of the substances CBD, THC and CBN are known and verified and is one of the following only:

A. Dried "cannabis efflorescence", packed in cases in which the total (net) weight of the cannabis in each case is 10 gr.

B. "Rolled cannabis efflorescence" ("roll") – dried, cut and rolled efflorescence in roll form with a filter or holding tip – a mouthpiece for inhaling from, in cases in which the total (net) weight of the cannabis in each is 10 gr.

C. "Cannabis extract" ("cannabis oil") – a cannabis extract diluted with oil, packed in bottles in which the total (net) diluted cannabis extract weight is 10 gr.

D. "Cannabis cookies" – the total weight of the cannabis (net) in the cannabis cookies in each case is 10 gr.

Note: Other products may be distributed, whether in other forms or with another concentration of active ingredients, if they are approved by the Ministry of Health after the applicant has convinced it of the product's safety and efficacy.

3. The product types:

"Cannabis products" that will be dispensed to patients will be matched to the requirements of the active substance concentration range and accordingly will be classified by:

A. Cannabis products of THC-rich type or of CBD-rich type

"THC-rich" type

- "T10/C2 medical cannabis", "T15/C3 medical cannabis", "T20/C4 medical cannabis" (containing 10%, 15%, 20% THC concentrations, respectively).
- Balanced "T10/C10 medical cannabis" product (containing 10% CBD and 10% THC).

"CBD-rich" type products

- "T5/C10 CBD medical cannabis", "T3/C15 CBD medical cannabis", "T1/C20 CBD medical cannabis", "T0/C24 CBD medical cannabis" (continuing CBD concentrations of 10%, 15%, 20% and 24% respectively).

B. Cannabis products of sativa strain source / character and of indica strain source / character

Sativa strain source / character

Specimens with a characterization of imparting an energetic feeling, stimulation of appetite, etc. (originally of sativa strain character basis but this is not binding – following hybridizations and genetic enhancement).

Indica strain source / character

Specimens with a characterization of imparting a soothing feeling, reducing muscle tone, inducing sleep, etc. (originally of indica strain character basis but this is not binding – following hybridizations and genetic enhancement).

"IMC - Medical Grade Cannabis Efflorescence":

Type	Item	THC	CBD	CBN	Exp.	E.P
CBD rich	"T0/C24 CBD medical cannabis"	0% (0.0% - 0.5%)	24% (20% - 28%)	0% (Up to 1.5%)	Minimum six months	8
	"T1/C20 CBD medical cannabis"	1% (0.0% - 2.5%)	20% (16% - 24%)	0% (Up to 1.5%)	Minimum six months	7
	"T3/C15 CBD medical cannabis"	3% (0.5% - 5.5%)	15% (11% - 19%)	0% (Up to 1.5%)	Minimum six months	5.5
	"T5/C10 CBD medical cannabis"	5% (2.5% - 7.5%)	10% (6% - 14%)	0% (Up to 1.5%)	Minimum six months	5
	"T10/C10 medical cannabis"	10% (6% - 14%)	10% (6% - 14%)	0% (Up to 1.5%)	Minimum six months	6.5
THC rich	"T10/C2 sativa medical cannabis" – sativa strain source / character	10% (6% - 14%)	2% (0.2% - 3.8%)	0% (Up to 1.5%)	Minimum six months	4
	"T10/C2 indica medical cannabis" – indica strain source / character	10% (6% - 14%)	2% (0.2% - 3.8%)	0% (Up to 1.5%)	Minimum six months	4
	"T15/C3 sativa medical cannabis" – sativa strain source / character	15% (11% - 19%)	3% (0.5% - 5.5%)	0% (Up to 1.5%)	Minimum six months	6
	"T15/C3 indica medical cannabis" – indica strain source / character	15% (11% - 19%)	3% (0.5% - 5.5%)	0% (Up to 1.5%)	Minimum six months	6
	"T20/C4 sativa medical cannabis" – sativa strain source / character	20% (16% - 24%)	4% (1% - 7%)	0% (Up to 1.5%)	Minimum six months	8
	"T20/C4 indica medical cannabis" – indica strain source / character	20% (16% - 24%)	4% (1% - 7%)	0% (Up to 1.5%)	Minimum six months	8

(Zuurman L. et al. 2009)

"IMC - Medical Grade Cannabis Oil"

Type	Item	THC	CBD	CBN	Exp.	E.P
CBD rich	"T0 C24 CBD medical cannabis oil"	0% (0.0% - 0.5%)	24% (20% - 28%)	0% (Up to 1.5%)	Minimum six months	8
	"T1/C20 CBD medical cannabis oil"	1% (0.0% - 2.5%)	20% (16% - 24%)	0% (Up to 1.5%)	Minimum six months	7
	"T3/C15 CBD medical cannabis oil"	3% (0.5% - 5.5%)	15% (11% - 19%)	0% (Up to 1.5%)	Minimum six months	5.5
	"T5/C10 CBD medical cannabis oil"	5% (2.5% - 7.5%)	10% (6% - 14%)	0% (Up to 1.5%)	Minimum six months	5
	"T10/C10 medical cannabis oil"	10% (6% - 14%)	10% (6% - 14%)	0% (Up to 1.5%)	Minimum six months	6.5
THC rich	"T10/C2 medical cannabis oil"	10% (6% - 14%)	2% (0.2% - 3.8%)	0% (Up to 1.5%)	Minimum six months	4
	"T15/C3 medical cannabis oil"	15% (11% - 19%)	3% (0.5% - 5.5%)	0% (Up to 1.5%)	Minimum six months	6
	"T20/C4 medical cannabis oil"	20% (16% - 24%)	4% (1% - 7%)	0% (Up to 1.5%)	Minimum six months	8

"IMC - Medical Grade Cannabis Cookies" (for children only):

Type	Item	THC	CBD	CBN	Exp.	E.P
CBD Rich	"T0 C24 CBD medical cannabis cookies"	0% (0.0% - 0.5%)	24% (20% - 28%)	0% (Up to 1.5%)	Minimum six months	8
	"T1/C20 CBD medical cannabis cookies"	1% (0.0% - 2.5%)	20% (16% - 24%)	0% (Up to 1.5%)	Minimum six months	7
	"T3/C15 CBD medical cannabis cookies"	3% (0.5% - 5.5%)	15% (11% - 19%)	0% (Up to 1.5%)	Minimum six months	5.5
	"T5/C10 CBD medical cannabis cookies"	5% (2.5% - 7.5%)	10% (6% - 14%)	0% (Up to 1.5%)	Minimum six months	5
	"T10/C10 medical cannabis cookies"	10% (6% - 14%)	10% (6% - 14%)	0% (Up to 1.5%)	Minimum six months	6.5
THC Rich	"T10/C2 medical cannabis cookies"	10% (6% - 14%)	2% (0.2% - 3.8%)	0% (Up to 1.5%)	Minimum six months	4

Note: for use by children only. Manufacturing cookies requires compliance with any law pertaining to manufacturing and marking of food including packaging with clear marking of all product ingredients (including marking of allergens)*

*** Extract from a decision of the Director General of the Ministry of Health concerning "cannabis products" (see Appendix D)**

"…In an attempt to form appropriate criteria for all relevant fields, including the field of medicine, one issue that has started to receive specific attention is the issue of the types of products that are to be approved for patients. Thus, for example, criteria have been established concerning the maximum and minimum permitted concentrations of the key active substances in the plant (THC and CBD) and their combinations.

On February 14, 2013, the subject was discussed by the inter-ministerial steering committee and the categorical recommendation of the persons present was not to approve continued manufacturing of cookies, primarily after no therapeutic or pharmacological advantage was found to having products besides dried efflorescence and oil, and these were only to be approved if their composition was clear and known. Moreover, in the opinion of the steering committee, it would seem that in additional products, including cookies, there are disadvantages that in and of themselves justify terminating the ability to market them, including concerns stemming from the manufacturing procedure and its effects on the active substances and fear of unintentional misuse (primarily in the context of cookies, given the concern that third parties including children would consume them by mistake, as it does not look like a medicinal product) and more.

After having carefully examined the various documents and reconsidered all factors, I have reached the conclusion that in effect there is no room for justifying the continued manufacture of cookies, after they were manufactured without the considerations for approving the manufacture having been clear from the outset. Even in the case of existing reality, I still do not believe that at the time of the change I must persuade others that any particular product is unneeded. Because a reality has formed without any actual scrutiny of the products, particularly scientific scrutiny, to show for their need, I believe that the Ministry of Health is responsible today, even in retrospect, for doing so, and should it find that any product is not justified on medical ground or owing to medical and pharmacological considerations, there is no room to approve its continued production only for the reason that it exists today and has caused no harm heretofore.

After having contemplated the factors repeatedly, I do not consider there to be any room to continue to approve the manufacturing of the cookies, and subject to the exception that I stated above, this must be announced to the relevant parties so that they prepare for it accordingly.

"Cannabis cookie" products that will remain for manufacturing and marketing for children with licenses to use medical cannabis will be at concentrations corresponding with the efflorescence and oil concentrations only, while also fulfilling the following conditions:

A. The products will be packed in childproof / child resistant packaging.

B. Compliance with the provisions of any law pertaining to manufacturing and marketing food, including packaging that includes clear marking of all cannabis product ingredients and any other ingredient (including marking of allergens)."

11. Matching the appropriate treatment type to the patient

Determining the cannabis product type for starting treatment by indication

The active ingredients in cannabis products (phyto-cannabinoids) have distinct pharmacological uses, it is being learned, such as pain relief, anti-nausea, antioxidant, neuromodulation and anti-inflammatory use, but scientific literature shows a small number of clinical studies that have been performed properly.

Because cannabis products have been classified in this manner according to the cardinal active substances THC and CBD, both with regard to concentration and pharmacological effect, they are what determine the product's potency (estimate potency).

The greater the total cannabinoid concentration in the product, the more potent the product may be said to be. According to the concentration of the active substances in it, cannabis products may be divided into two groups, THC-rich type cannabis products and CBD-rich type cannabis products.

THC is the phyto-cannabinoid with a dominant psychoactive effect, and besides this its physiological effect range is broad and characterized by anesthetic, anti-tremor, anti-nausea, appetite stimulant and anti-inflammatory effects. In addition, it is attributed other effects such as soothing, visual and auditory alternation and altered of the sense of smell.

CBD is a phyto-cannabinoid that is not attributed any psychoactive effect, its attributed range of activity including anti-inflammatory, anti-tremor, antioxidant, anti-psychoactive activity (thus neutralizing / reducing the psychoactive effect of THC), neuroprotective activity and anxiolytic activity.

Many of the publications in scientific literature dealing with THC and the scope of knowledge concerning CBD are limited. However, these studies provide a reasonable factual basis to support its therapeutic potential for a number of medical, physiological and psychological conditions, the main ones being anti-inflammatory states, spasticity, a range of anxiety disorders including PTSD and extension of sleep time.

As published in many studies, combining CBD in "cannabis products" helps neutralize and reduce the undesirable side effects stemming from THC. In addition, studies offer support that even acute administration of CBD does not result in significant toxicity for humans, irrespective of the route of administration, whether oral, by inhalation or even intravenous. In other words, the sensitivity of a patient to THC constitutes a key factor for deciding to adapt the dosing regimen with regard to CBD : THC ratio

for adjusting the treatment with "cannabis products" of CBD-rich type, because a greater ratio of CBD to THC means a lower chance for undesirable side effects.

The only and ostensibly significant risk that using CBD poses is its potential to cause immunosuppression (Cannabinoids Inhibit Nucleoside Transporter to Mediate Immunosuppression, Science's STKE 23 May 2006). As reported in articles, CBD may induce a biphasic response in the immune system; potentially high doses correlate with an inhibitory response whereas low doses result in stimulation of immune system processes. Therefore, the recommending physician must take extra care before recommending a high CBD dose to immunosuppressed patients until more comprehensive research is conducted.

A treatment plan that is based on "cannabis products" of CBD-rich type is desirable in many cases, particularly in the case of one or more of the following conditions:

1. When suspicion of patient sensitivity to THC exists, is reported or arises, whether before or after treatment with cannabis.
2. For treating approved indications that include inflammatory conditions, spasticity, PTSD and sleep disorders.
3. In the case of chronic patients who are children under the age of 18, whose nervous system is still developing and for whom there is no significant scientific information on how THC affects this development. For them, treatment with the cannabis product T0/C24 should be started and only if necessary for specific, short treatments may products containing a low THC concentration such as T1/C20 or T3/C15 be combined, with special approval for T10/C10.
4. For patients suffering from liver cancer (hepatocellular carcinoma) it is advisable not to use a product containing THC.

According to the approved indications for treating cannabis (Procedure 106), an experts committee has established recommended lines for building a treatment plan according to the concentrations of active substances in cannabis products, according to current knowledge from scientific literature and knowledge accrued in recent years in Israel and elsewhere in the world concerning the effect of cannabis treatment.

The table below details recommendations of the experts committee concerning each approved condition, the cannabis product recommended for starting the treatment and the recommended later line of treatment.

The table was prepared in conjunction with physicians, under the guidance of Prof. Mechoulam and with the assistance of an empirical and therapeutic summary of a group of researchers from Harvard University in the USA (Ref. 132).

Section of indication in procedure	Details of indication per Procedure 106	Recommended product for starting treatment	Gradual E.P route for continuing the recommended treatment
3.2.1.1	Patients on chemotherapy and up to six months afterward for relieving treatment related nausea, emesis or pain	T10/C2	"THC-rich" products To T10/C10 To T15/C3 To T20/C4
3.2.1.2	For relief of pain of cancerous source at the metastatic stage	T10/C2	"THC-rich" products To T10/C10 To T15/C3 To T20/C4
	*** In hepatocellular carcinoma patients it is advisable not to use products containing THC	T0/C24	If necessary T1/C20
3.2.2	Patients suffering from active, proven inflammatory bowel disease (Crohn's disease or ulcerative colitis)	T5/C10	"CBD-rich" products To T3/C15 To T1/C20 To T0/C24
3.2.3	Patient suffering from neuropathic pain of clear organic source	T10/C10	"THC-rich" products for immediate relief combined with "CBD-rich" products for long term treatment.
3.2.4	Patients diagnosed with acquired immunodeficiency syndrome (AIDS), after exhausting standard medication and suffering from extreme weight loss (cachexia – more than 10% weight loss) for improving their appetite or relieving emesis and gastrointestinal symptoms	T10/C10	"THC –rich" products To T10/C2 or to T15/C3 To T20/C4
3.2.5.1	Patients diagnosed with multiple sclerosis in spastic states who have not responded to standard treatment.	T10/C10	"THC –rich" products To T10/C2 or to T15/C3 To T20/C4 If necessary a combination of "CBD-rich" products for relieving spasmodic states
3.2.5.2	Patients diagnosed with Parkinson's disease, who have been treated for at least a year with antiparkinsonian treatment, who are suffering from pain (chronic pain or pain caused by rigidity) who have not responded to standard pain treatment.	T10/C2	"THC –rich" products To T10/C2 or to T15/C3 To T20/C4

3.2.5.3	Adult patients who are diagnosed with Tourette syndrome, who suffer from significant dysfunction in everyday life, who have not responded to standard treatments.	T10/C2	"THC –rich" products To T10/C10 To T15/C3 To T20/C4
3.2.5.4	Adult epileptic patients	T1/C20	To T0/C24 If necessary, treatment may be combined or adjusted to products containing a slightly higher THC concentration such as: T3/C15 or T5/C10
3.2.5.5	Minor patients suffering from severe uncontrolled epilepsy	T0/C24	T1/C20 product If necessary, treatment with a product containing a slightly higher THC concentration can be combined, such as: T3/C15
3.2.6	Terminal patients (six months expected life expectancy)	T01/C10	"THC-rich" products To T10/C2 or to T15/C3 To T20/C4
3.2.7	Adult patients diagnosed with posttraumatic stress disorder (PTSD)	T10/C10 or T10/C2	"CBD-rich" products To T5/C10 To T3/C15 To T1/C20 To T0/C24 If necessary combining "THC-rich" products for immediate relief of symptoms at the most T15/C3

Adjusting the potency of the cannabis product, later building the therapeutic plan

As detailed above, the cardinal active substances in cannabis products, both in terms of concentration and pharmacological effect, are THC and CBD. Cannabis products have been classified by THC and CBD concentrations, and these are the ones that determine the potency of the product (estimate potency).

During the treatment follow up, one may see whether there is positive therapeutic effect for the symptoms from which the patient is suffering. If it seems that there is positive but insufficient effect, one may consider an increase in the level of potency of the cannabis product according to the recommended treatment line, for example, from "T10/C2 cannabis", one may increase the potency level of "THC-rich" products to "cannabis T15/C3" or continuing to "T20/C4 cannabis".

If strong side effects are observed after starting a recommended treatment plan and treatment with a "cannabis product", usually from "THC-rich" products, one may combine or switch to treatment with a CBD-rich type "cannabis product.

An increase in the monthly quantity of cannabis, and accordingly over the day as detailed in the following chapter, is derived from the need for even distribution that is appropriate for the purposes of the patient during the day, with the effect from the potency of a cannabis product being sufficient.

Establishing the route of administration of cannabis for a patient

As detailed expansively in the pharmacokinetics chapter, the "cannabis products" that are approved for use are intended for and matched to a different pharmacological administration. Each route of administration has a unique pharmacokinetic profile according to the patient's needs, which differs in the levels of absorption into the bloodstream and bioavailability of the active substances in cannabis.

1. Dried cannabis efflorescence – intended for administration by inhalation using ready to smoke rolls or an inhaler. In administration by inhalation, the active substances are absorbed through the lungs into the bloodstream in the quickest way.

2. Cannabis oil extract – intended for sublingual administration, in which the active substances are absorbed via the oral mucosa directly into the bloodstream, thus skipping the breakdown in the gastrointestinal tract and liver.

3. Cannabis cookies for children only* - intended for oral administration, in which the active substances are absorbed into the bloodstream through the gastrointestinal tract.

As detailed in the pharmacokinetics chapter, administration by smoking is characterized by rapid absorption and reaching the highest peak concentration in a relatively short time. In contrast, sublingual administration and oral administration are characterized by slower absorption and reaching a lower peak concentration than by inhalation, and takes longer to achieve. The degree of exposure in the body to the active substances is lower in inhalation than in sublingual administration and oral administration.

In the decision of the attending physician as to which mode of administration to recommend, he should consider the patient's needs and symptoms.

If ad hoc treatment for acute, transient symptoms is required, such as for acute pain, inhalation is the best form of administration, characterized by rapid absorption, high peak concentration and short exposure time of the active substances in the bloodstream.

In the case of treatment of chronic, persistent symptoms, sublingual administration is the best form of administration, characterized by relatively slow absorption, a low peak concentration and long exposure time of the active substances in the bloodstream. In addition, when deciding on the form of administration, the following factors must also be considered:

- Does the patient smoke on a regular basis? A person not accustomed to smoking will find it difficult to smoke cannabis. If administration by inhalation is necessary, it is advisable to use an inhaler.
- Is the patient suffering from dyspnea or from a medical condition that makes it difficult for him to consume cannabis by inhalation and pulmonary absorption? In these conditions, sublingual administration is better.
- Does the patient observe the Sabbath? In these cases, it is better to combine sublingual administration using oil extracts.
- Patient age? It is advisable to give elder patients and children sublingual / oral administration using a product that is not intended for smoking.
- Is the product type that the patient is taking "THC rich"? When these products are inhaled, the effect of inhalation may lead to a strong, immediate feeling of intoxication and form a sense of anxiety. In these cases it is better to use oil extract products for sublingual administration.

Establishing the source / character of the cannabis product

"THC-rich" type cannabis products will be available in two source / character types:

1. "Sativa character source", which is more suitable for use during the day, relates to a "cannabis product" that has the characterization of giving an energetic feeling, provides a "light" sensation, improves mood and increases one's concentration ability and creativity.

2. "Indica character source" refers to a "cannabis product" that has a characterization of giving a soothing feeling, imparting a sensation of "general tranquility" that relieves drowsiness, reduces muscle tone and that is therefore more suitable for use at nighttime.

In general, the "character sources" may be clarified according to the following features. It is desirable to adjust or combine source / character types in treatment according to the patient's needs and the effect of a source / character. It is advisable to treat using a combination of "cannabis products" of sativa / indica source / character types in order to achieve a suitable effect for all hours of the day.

Sativa character sources	Indica character source
Increased mental effect	Increased physical effect
Stimulates	Soothes
Stimulates appetite	Reduces anxiety
Stimulates creativity	Induces sleep
Reduces depression	Relieves pain
Recommended for daytime use	Recommended for nighttime use

Combination of different cannabis products in the treatment plan

Each patient has his own unique needs. It is likely that in order to fulfill patient needs, it will be necessary to combine more than one cannabis product for patients to get the most suitable treatment.

Combining another "cannabis product" at a different active substance concentration or in a different form of administration or of different source / character may allow for significant relief of symptoms from which the patient is suffering, thus leading to a desirable and more effective therapeutic effect at a price of reduced side effects.

12. Adjusting the monthly quantity of cannabis to the patient

Establishing the initial quantity of the cannabis product

The active ingredients in cannabis products (phyto-cannabinoids) have distinct pharmacological uses, it is being learned, such as pain relief, anti-nausea, antioxidant, neuromodulation and anti-inflammatory use. However, it is important to know that there is a major shortage of properly established information in scientific literature and therefore difficulty in basing decisions concerning exact dosing from which a purposeful dosing regimen and recommended monthly quantity may be derived.

At the same time as the expansion of the understanding and knowledge of the physiological and pharmacological mechanism of cannabis, it is becoming necessary to lay down guidelines for dosing. The IMCA is aiming to form a structured treatment plan for adjusting doses during the cannabis treatment period.

Recommendations concerning the formation of a dosing regimen that is based on CBD or combining it with THC are very lacking in scientific literature. In addition, extrapolation of an animal weight based dosing models to humans is problematic due to the high variance in bioavailability between different animal models. Published preclinical and clinical studies indicate the use of a very high dose range, but there is still a great distance between knowing what the ideal doses/ combinations are considering the critical pharmacogenomic variance between patients. Therefore the dosing process for CBD at this stage is not sufficiently based, but unlike THC, the risks in administration of CBD are very low and as of this time no case report has been reported in scientific literature of a CBD overdose. In view of this, the decision concerning the permitted monthly quantities is for all cannabis products irrespective of the cannabinoid type and concentration.

The rules below, which have been established as a pharmaco-regulatory decision at this time, rely on professional knowledge that has accumulated in recent years from information at the IMCA concerning patients and daily and monthly consumption quantities accordingly (mean monthly quantity of cannabis per patient at this time is 33.6 grams), as well as the professional knowledge that has been accumulated by various parties in Israel and overseas and in scientific literature dealing with the subject, including based on the article "Medical Cannabis: Rational guidelines for dosing", which offers guidelines for adjusting the dose of cannabis efflorescence for smoking according to a combined study of the Medical Rehabilitation Department, the Neurology Department and Medical Laboratory Department of the Seattle School of Medicine at the University of Washington, the Computational Anthropology Institute in Seattle, and of the Hematology / Oncology Unit of San Francisco General Hospital, the Department of Medicine at the University of California San Francisco.

Parameters that have been taken into account when determining the monthly quantities for consuming cannabis in its natural form:

1. THC and CBD are not the only clinically and pharmacologically active cannabinoids in the cannabis plant; there are other ingredients with psychoactive effects.

2. The effects of THC and CBD are clearly mediated with other cannabinoids, which also have unique effects of their own.

3. Patient tolerance.

4. The various routes of administration that may affect absorption rates and bioavailability.

5. The metabolites of the cannabinoids that also have clinical and pharmacological activity and some of which also have a psychoactive effect.

The accrued data taken into account when determining the monthly quantities for consumption of cannabis in its natural form:

- According to the dosing model for dronabinol (mg) approved by the FDA, for a per day quantity of THC.
- According to the article "Medical Cannabis: Rational guidelines for dosing", the calculated quantity of cannabis for adjustment of equivalent quantities of THC for a dronabinol product (2.5 to 60 mg).
- According to the pharmacokinetic profile of THC in administration by smoking.
- According to the "cannabis products" approved for marketing and dispensation.
- According to reported data: the low dose of dronabinol is 5 mg per day and the average is 12.5 mg per day.

The initial recommended quantity of cannabis determined for treatment is approximately <u>0.6 grams per day</u>.

<u>Therefore</u>:

- **The recommended monthly quantity of cannabis per patient at the beginning of treatment with the product "cannabis oil" is 20 grams.**
- **The recommended monthly quantity of cannabis per patient at the beginning of treatment with the product "cannabis efflorescence" is 20 grams.**

<u>Adjustment of the quantity of the cannabis product later in developing the therapeutic plan</u>

1. Adjustment of the daily and monthly dose is individual for each individual patient and it is therefore recommended to use a titration model using which the recommended monthly quantity may be adjusted for continuing the treatment. The attending physician has the responsibility for adjusting the treatment appropriately with regard to product type, monthly quantity, potency and daily cannabis dose per patient. After a period from the beginning of the treatment in which the dose and daily consumption times will be adjusted by personal titration of distribution of inhalations / drips during the day and examining the quality and efficacy of the treatment, a recommendation to change the monthly quantity may be considered as necessary.

2. Whenever a cannabis treatment plan is developed, it is advisable to use a titration model for setting the daily dose and its distribution over the day. The triturative model is acceptable given the high variance between patients, between routes of administration and given and considering cannabis' low toxicity level. This model is not unique to cannabis and there are many treatments with relatively low toxicity levels and high dosing limits (such as gabapentin) that have a triturative model.

3. If the therapeutic effect is beneficial but deficient, it is advisable first to increase the monthly dose, change the type to a product whose active substance concentration is higher and more potent (such as from "T10/C2" to "T15/C3"). In any case the attending physician must take into account the potency of the products that the patient is taking before considering increasing the monthly dose.

4. Upon reaching the desired titration point, it is preferable to make sure to take the recommended dose 4 to 6 times a day at fixed, defined intervals on a regular daily basis, sometimes, with a number of inhalations / drops each time.

5. The increments of the monthly dosing quantity of cannabis to be recommended and/or per the decision of the "director" are increments of 10 grams over not less than two months.

6. <u>Quantity above 40 grams per month</u>: is a higher dose increment, as the increment (according to the article and dosing model adjustment of dronabinol, i.e. THC) at this quantity is equivalent to the following quantities:

   - To 20 mg per day of THC (when using the "cannabis product": "T10/C2 or T10/C10 cannabis").
   - To 30 mg per day of THC (when using the "cannabis product": "T15/C3 cannabis").
   - To 40 mg per day of THC (when using the "cannabis product": "T20/C4 cannabis").

   Therefore, compared to data reported that the low dose of Dronabinol is 5 mg per day and the average is 12.5 mg per day, it is shown that these doses constitute a dose of <u>2-3 times</u> more than compared to the dosing model for the daily quantity of THC.

7. <u>A quantity of 50-60 grams per month and more</u>: constitutes a test increment, at which the decision concerning whether the patient has reached the cannabis treatment exhaustion point or a decision to give additional approval for increasing dose or changing product potency as detailed above will be carefully considered.

   In addition, at the quantity above, and of course according to all of the patient's medical data, the concern that he is unfit to drive must be examined. If the attending physician fears that the patient is unfit to drive, the attending physician must issue a "caregiver notice" to the National Road Safety Medical Institute, or must detail in the patient's medical record why in the opinion of the attending physician the patient is fit to drive notwithstanding his existing medical circumstances.

8. More than a quantity of 100 grams per month: additional answers, documentation and clinical and administrative recommendations are required as set forth in Procedure 106, concerning the manner and character of the use of cannabis.

Titrative balancing between potency and quantity of cannabis products during the treatment

Today it is still not possible with certainty to determine rules between a medical condition, the complexity of the disease, intensity of pain, quantity of background analgesics, body weight, height, age, etc., and required ideal dose. In addition there is no unequivocal consistent evidence of the preference of a cannabis product of a certain type (or "strain", as it is known) and a specific disease and there is still room for comprehensive research concerning the character of use of the various cannabis products, their efficacy and exact doses.

Alongside the expansion of the understanding and knowledge of the physiological and pharmacological mechanism of cannabis, a need arises to substantiate guidelines for dosing. The IMCA is aiming to lead to a state of creating a structured treatment plan for adjusting the dose in the cannabis treatment period.

The researchers in a study based on the article "Medical Cannabis: Rational guidelines for dosing" used cannabis containing a mean concentration of THC 19%, which was found to correspond with administration of 44-88 mg per day of THC. In addition the researchers used data from two other studies. In the first study, administration of 87.5 mg per day of THC was examined for a person of average height (Chang and coworkers) and in the other administration of 35 mg per day of THC for an average sized person (Vinciguerra and coworkers), the underlying assumption of this study being that "an average sized person" would be 1.70 meters high, would weigh 63.6 kg and have a 1.75 m^2 surface area.

Most of the study related to the cannabinoid THC; the other cannabinoids were examined at a lower level. The study was based on the guidelines published by the manufacturer and approved by the FDA with the prescription instructions of the product dronabinol, which is intended for oral administration, contains THC only and has a known pharmacokinetic model. By comparing the administration of dronabinol in the conservative dosing model of 2.5-60 mg per day, and administration by inhalation (by smoking) at a body weight equivalent dose of cannabis in its natural form containing a fixed concentration of the cannabinoid THC, researchers recommended a dosing model for consumption of cannabis in its natural form by smoking.

The researches recommend that a titration model must be continued for continuing to determine the effective dose, like dosing titration of dronabinol, which constitutes a product that is defined in a coherent manner, with an approved, available dosing paradigm from the FDA.

However, the following parameters that are relevant to the consumption of cannabis in its natural form are needed:

1. THC is not the only cannabinoid that is clinically and pharmacologically active.
2. The effects of THC are clearly mediated by other cannabinoids, which have their own unique effects.
3. Patient tolerability.
4. The various routes of administration that can have an effect on the absorption rate and bioavailability.
5. The table below describes the rationale for building a treatment plan using a triturative model for quantity change depending on product potency, as detailed below.

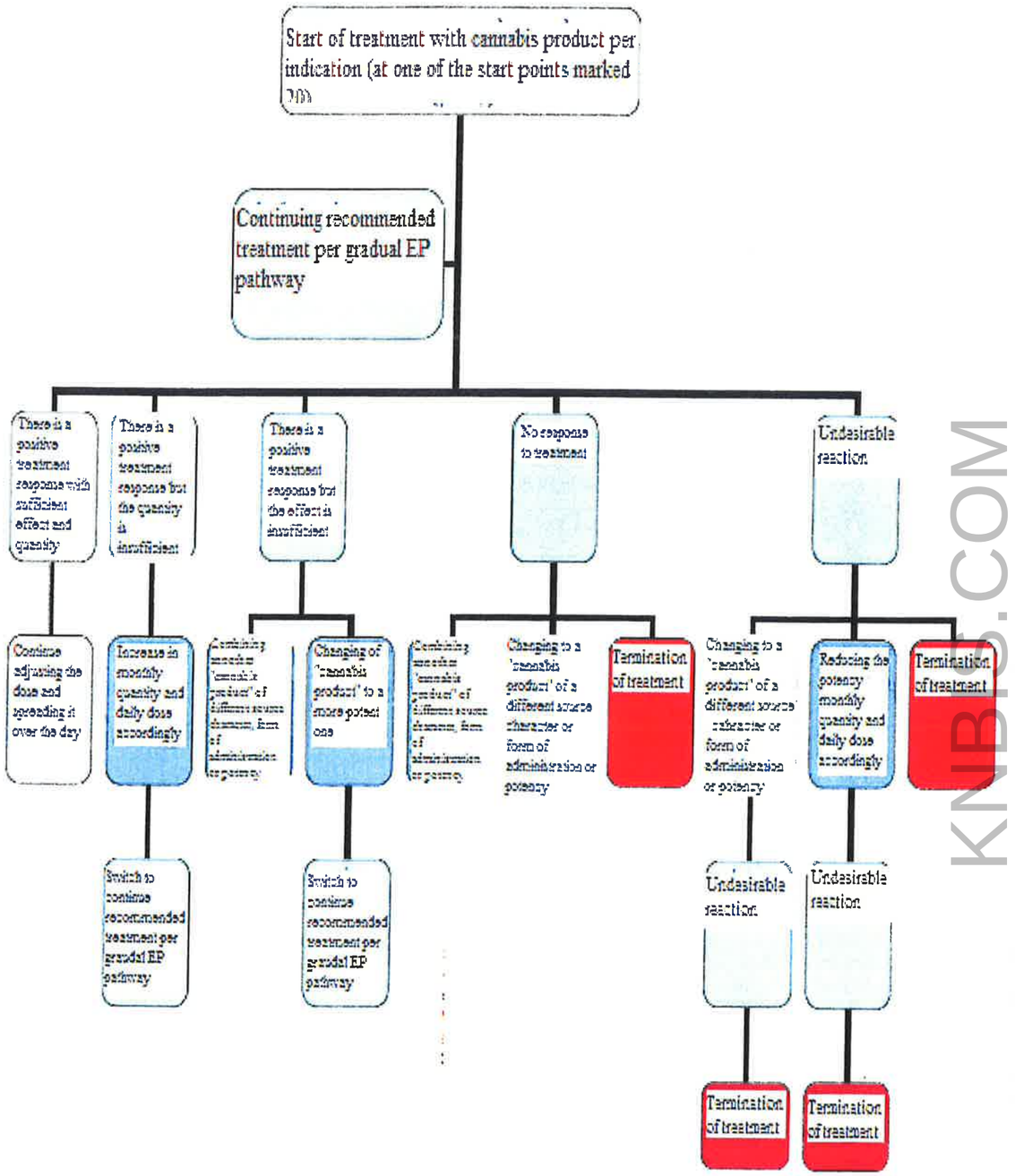
Quantity of THC per day according to the dosing model of dronibanol (mg)	**Daily cannabis quantity** (grams) according to equivalent quantities of THC [per article and in coordination with the dronabinol dosing model]			**Monthly cannabis quantity** (grams) according to equivalent quantities of THC [per article and in coordination with the dronabinol dosing model]		
	"T10/C2 cannabis" (10% THC)	**"T15/C3 cannabis"** (15% THC)	**"T20/C4 cannabis"** (20% THC)	**"T10/C2 cannabis"** (10% THC)	**"T15/C3 cannabis"** (15% THC)	**"T20/C4 cannabis"** (20% THC)
2.5	0.30	0.16	0.10	9.1	4.9	3.0
10	0.62	0.41	0.31	18.9	12.5	9.5
30	1.85	1.23	0.93	56.3	37.4	28.3
60	3.70	2.46	1.86	112.5	74.9	56.6

Steps of the Titrative protocol for change quantity (potency dependent) of cannabis products

	THC Rich								**CBD Rich**						
E.P	**8**		**6**		**6.5**		**4**		**5**		**5.5**		**7**		**8**
The cannabis product	**T20/C4**		**T15/C3**		**T10/C10**		**T10/C2**		**T5/C10**		**T3/C15**		**T1/C20**		**T0 C24**
Monthly quantity of the cannabis product (grams)	**20**	←	**20**	←	**20**	↔	**20**	↔	**20**	↔	**20**	↔	**20**	↔	**20**
	↓	↖	↓	↖	↓	↖	↓		↓	↖	↓	↖	↓	↖	↓
	30		**30**		**30**	←	**30**	↔	**30**	→	**30**	→	**30**	→	**30**
	↓	↖	↓	↖	↓	↖	↓		↓		↓		↓		↓
	40		**40**		**40**	←	**40**		**40**	→	**40**	→	**40**	→	**40**
	↓	↖	↓	↖	↓	↖	↓		↓		↓		↓		↓
	50		**50**		**50**	←	**50**		**50**	→	**50**	→	**50**	→	**50**
				↖	↓	↖	↓		↓		↓		↓		
	*		*		**60**	←	**60**		**60**	→	**60**	→	**60**		*
	*		*		*		*		*		*		*		*

1. One may start treatment/s as set forth in Chapter 11 "matching the suitable treatment type to the patient" only at one of the start points marked with 20 (underlined).
2. One may advance only between treatment steps with an arrow (→) marked, in the direction of the arrow.
3. If a treatment step leads to an undesired effect, it is advisable to return to the previous treatment step. Returning to another initial treatment point that in the opinion of the attending physician is appropriate for treatment with regard to product type and potency may also be considered.
4. The quantity of cannabis per month is the maximum quantity in grams of cannabis to be recommended / for licensing per calendar month (considering wastage and residues of an average month) for consumption.
5. A square containing * indicates a monthly quantity that is not recommended, except with a detailed, compelling explanation from the physician as to why this special quantity is required.
6. The cannabis products are packed by weight of cannabis (net) of 10 grams per pack.

Cannabis treatment management protocol



13. Recommendation for dosage and consumption times adjustment during the day using a titration model

There are two methods of dividing the monthly quantity of cannabis over the weekdays and during the day by "cannabis product/s" type approved and their combination. Both methods are good. The more convenient method may be chosen with the patient.

It is important to note that adjusting the dose over the weekdays, as indicated in the examples below, relates to maximum consumption according to the given monthly dose, the guiding rule during the titration being that the lowest dose achieving the aim of the use must be taken.

	Method 1	**Method 2**
Dose	Use of a single "cannabis product"	Use of more than one "cannabis product"
Advantages	A simple method that reduces the risk of mixing up "cannabis products" and allows gradual adjustment to treatment	The method allows for more even distribution of the dose as necessary
Disadvantages	One "cannabis product" type will not always be suitable for a patient for all hours of day	Distribution of "cannabis products" over the day is not even. Use of multiple products, each of a different ingredient concentration, may cause a mix-up between them.

The daily dosing is very personal and requires adjusting using a dose titration process during the hours of the day. Each patient needs a different number of inhalations / drops in order to provide the most effective relief with the least number and intensity of undesirable effects.

It is advisable to start the treatment with the "cannabis product/s" at an initial daily dose of 1 to 2 inhalations / drops once a day or divided into multiple instances. Each time, a quantity of 1 to 2 inhalations / drops twice a day must not be exceeded at the beginning of the treatment.

Afterward, one may slowly and gradually increase the dose until adjustment. This gradual process is intended to examine the effect of the treatment and the onset of undesirable side effects.

During the month, one may gradually increase the number of inhalations / drops and taking times during the day, preferably with an instructor / the attending physician in attendance, until reaching a daily dose that achieves the desired symptomatic relief. The effective dose required for improvement is usually lower than the dose that causes psychoactive phenomena.

After the number of inhalations / drops during the day that achieve symptomatic relief for the patient is found, one may adjust the interval between them according to the patient's feeling.

In a 1 gram roll there is an average of about 18 inhalations, and on average in 1 ml there are about 18 to 20 drops.

With correct instructing and use of cannabis, assuming a daily division into 4 to 6 taking times, the patient will reach a recommended monthly cannabis quantity about 20 grams. Reaching an optimal effect may take weeks to months.

In the initial treatment period until the patient stabilizes on the most effective daily and monthly dose for him, it is advisable to follow up on the patient on a daily basis alongside the titration period.

Filling in a table such as the following will help the patient and attending physician follow the effect and efficacy of his treatment and will help in the titration process achieve an optimal treatment effect.

Example of a balancing table to be filled in by the patient

Treatment day	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Dose / Symptoms	1 inhalation morning	1 inhalation morning 1 inhalation evening	1 inhalation morning 1 inhalation noon 1 inhalation evening	1 inhalation morning 1 inhalation noon 1 inhalation evening	..	...	....
Pain (0-10) 0 – pain free 10 – intolerable pain	6	5	4	4	3	1	1
Sleep (did not help, partly helped, helped) Detail the number of pain free sleep hours	Did not help (2 hours)	Partly helped (3 hours)	Partly helped (3 hours)	Partly helped (4 hours)	Partly helped (5 hours)	Helped (7 hours)	Helped (7 hours)
Nausea (did not help, partly helped, helped) Please elaborate	Partly helped Relief in the morning	Partly helped Relief in the morning	Partly helped Nausea at night	Helped	Helped	Helped	Helped
Appetite (did not help, partly helped, helped) Please elaborate	Partly helped, mainly in the morning	Partly helped, mainly in the morning	Helped	Helped	Helped	Helped	Helped
Adverse effects Such as: dizziness, vomiting, diarrhea Please elaborate	None	Dizziness	Slight dizziness	None	None	None	None

In conclusion, the success of the treatment with medical grade cannabis using the titration model for achieving an exact dose is a complex process that is related to a range of issues, including balancing the cannabis treatment, which may take a long time. One of the problems in finding the appropriate exact dose is the degree of patient perseverance in the long titration process.

There are patients who believe that they know what effect cannabis has after five days, although in many cases a balance and match may only be achieved after several months.

It is important to emphasize that like many medicinal products, one may also develop a certain degree of tolerance to cannabis over time, meaning that changing the manner of treatment may become necessary. The change may be done in one of the following common ways: a decision on a treatment remission period, a change in the "cannabis product" for a certain time or frequency, or a change in dose.

No correlation has yet been reported to be found between dose and weight. At this time a dose for a patient cannot be predicted and the response to cannabis cannot be predicted either. Therefore, the treatment must be started at a low dose, with follow up and titration – gradually increasing the dose until finding the optimal one, balancing efficacy of treatment with side effects.

The success of treatment with medical grade cannabis depends on adequate medical follow up, seeing the patient for frequent meetings and checkups. While there are objective obstacles and practical considerations, only by close follow up may the effect of the treatment be truly understood and properly followed.

One must be aware that there are patients who think that treatment with cannabis is a kind of magic drug, which within days will solve their problem, but that is not the case. Medical follow up and processes required for finding the patient's optimal dose must be attended to carefully.

The attending physician assumes the responsibility for matching the treatment that is appropriate in terms of substance type, monthly quantity, potency and daily cannabis dose to the patient.

14. Guidelines and recommendations for effective use of medical grade cannabis

It is the desire of every patient to reach a significant therapeutic effect and relief of symptoms characteristic of the indication for which he is receiving cannabis. For example, when the indication is pain, a number of studies show that pain relief is perceived to the patient as being significant when the pain reduction is 3 points at least (a scale of 0 to 10, in which "0" is pain free and "10" unimaginably intense pain). Therefore one must aim to reach that degree of pain relief, and it is common to attempt to reach a pain intensity of less than 4 on that scale.

However, the physician is not duty bound to recommend treatment with cannabis, but should he decide to recommend it, the recommendation must meet the professional criteria and correspond with his discretion. Thus, there is no difference between recommending the use of cannabis and any other recommendation made by a physician to his patients. The treatment with medical grade cannabis must be planned out with the patient and he must be involved in the existing therapeutic options, with emphasis on the advantages and disadvantages of each option. It is important for the patient to know that the therapeutic plan is dynamic and modifiable, according to the clinical response and side effects.

There is great variance between patients with regard to tolerance and response to cannabis. For some patients, a beneficial response may be identified within weeks. Many patients will respond to a low dose of cannabis and others will only react when reaching a relatively high dose. Side effects may develop at any dose level. In view of this, it is very difficult to determine a binding minimum period for a therapeutic trial or a binding threshold dose for any "cannabis product". Therefore, according to the knowledge that has accumulated, it has been determined that after starting the treatment and determining the monthly quantity and daily dose, treatment must last for about two months before the change in quantity / product.

For some patients, one may consider a change in monthly quantity within a short time (2-3 months), whereas in others, the adjustment of the daily treatment to the required monthly quantity will take longer. Sometimes the effect that is achieved by the cannabis treatment is suboptimal, i.e. the patient reports that the pain persists (albeit of lower intensity sometimes), but there seems to be a positive effect on the patient's quality of life, i.e. the pain has stopped interfering with having a normal, productive lifestyle. If after the period of examining the therapeutic effect of the "cannabis product/s" for a patient at increasing doses no significant therapeutic effect is achieved, there is room for defining the therapeutic attempt as a failure.

In addition, using cannabis may cause side effects, so any necessary increase in dose must be gradual. The inability to reach an effective dose due to the development of undesirable side effects before achieving significant pain relief will also be defined as a therapeutic failure. Therapeutic failure with

one "cannabis product", primarily due to the onset of side effects, does not rule out switching / combining with another "cannabis product" at a different concentration of active substances or with a different mode of administration. Another / additional "cannabis product" will allow for significant relief and a desired, effective therapeutic effect at the price of reduced side effects. In the absence of additional evidence, treatment using a combination of "cannabis products" from a sativa / indica character source is recommended in order to achieve an effect that is suitable for all hours of day.

It is the responsibility of the attending physician to make the consequences of each treatment clear to the patient – in the case of cannabis and when the physician is of the opinion that a patient is not medically fit to

drive, whether due to treatment with cannabis or for any other reason, he must issue a caregiver notice concerning him pursuant to the Road Transport Ordinance, just as he is duty bound to issue a caregiver notice under the Firearms Law if he believes that the patient may endanger himself or others, whether due to treatment with cannabis or any other treatment.

Pharmaceutical and clinical instructing that is directed at gradual progress at a uniform rate in the course of treatment using cannabis, will help in the medical treatment. In the encounter between the attending physician and/or the caring pharmacist, the attending physician and pharmacist must explain what cannabis is, what the side effects that may occur are and of course details on the recommended manner of taking the product. The attending physician must make sure that the treatment process is kept gradual by titration monitoring, until an optimal dose is reached.

Although taking cannabis by inhalation has an almost instantaneous effect, medical cannabis is not an emergency treatment, but a gradual, long-term one that involves regular, orderly intake of the product.

Starting the use of medical cannabis

1. It is advisable to start using medical cannabis while at home.
2. It is advisable to start using cannabis for the first time in a relaxed atmosphere, in the presence of another responsible adult.
3. Consuming cannabis may cause a decrease in blood glucose levels and may cause a sensation of fatigue and dizziness. It is advisable to have a snack or sweet food or a cold, sweetened drink nearby.
4. The minimal dose should be started with and the effect followed, preferably using a table to follow it up.
5. Treatment should start with 1-2 inhalations / drops per day, and using a titration process the appropriate daily dose of inhalations/ drops and fixed intervals may be reached to achieve relief of and improvement in symptoms that the product is intended to treat.
6. It is advisable to use the self-balancing table shown in the previous chapter.
7. To facilitate the self-balancing process, it is advisable during the first few weeks to follow the symptoms carefully during and after use.
8. Keeping a self-balancing table will help the attending physician adjust the individual monthly dose necessary for continuing the treatment.
9. The process of learning the individual effect will last for about two weeks to a few months, until the optimal dose is reached.

Recommendations for effective use of a cannabis product consumed by inhalation

One should consider the advantages of administration by inhalation (rapid effect) against the disadvantages, including potential smoking damage, passive smoking in the patient's vicinity and damage from smoking and smoking byproducts.

Cannabis products contain no combustion boosting agents or flavoring, so treatment by inhalation may involve soreness and productive cough.

In order for the treatment to be effective, no substance of any kind should be added to the cannabis product (including tobacco). The cannabis inhalation product is designed to be used as is. Any modification or addition may impair the medical benefit of the product and treatment. To relief the possible sensation of soreness, it is advisable to consume cold water or a sweetened, cold soft drink during and after treatment.

1. **Correct holding** – the patient should hold the cannabis product in its usage form (whether a roll or by inhaler) using his or her dominant hand, and for rolls, in the area of the mouthpiece (filter) using two fingers – the thumb and index finger, while the second hand is used for holding a lighter / burner. The product should be first lit while held in the hand and not in the mouth (as opposed to smoking an ordinary commercial cigarette).

   The right way to light the product is use a lighter or burner with a hot, concentrated flame.

2. **Lighting** – at the first stage, the roll is held in the hand and the surface of its distal tip (not the one with the mouthpiece or filter) is burned with the flame until it glows orange, in order to ensure uniform combustion.

3. **Inhalation** – inhaling the cannabis product is not necessarily the same as inhaling an ordinary (commercial) cigarette.

   The recommended inhalation action: the filter should be held gently between the lips and the smoke gently inhaled into the oral cavity at a constant rate, for one to three seconds.

   After that, the mouthpiece must be taken out of and away from the lips and the patient continues to inhale the smoke into the trachea and lungs. It is advisable to try to inhale for a fixed time and gentle, constant rate lasting about two to three seconds.

   Inhale gently, not strongly or quickly. Inhalations that are too strong, powerful, long or frequent will result in the flame heating up, which may result in soreness of the airways and a productive cough.

   If there is no combustion or it is not even, one can use a lighter to burn the roll very gently, holding the roll between one's lips and burning its end while gently inhaling.

   A good rule of thumb: an interval of about 30 to 60 seconds between puffs (according to the inhalation dose given by the attending physician).

4. **Exhalation** – after inhaling, exhale the cannabis product through the lips, blowing it out at a controlled rate. Exhaling too quickly may also result in a feeling of soreness and productive cough.

5. If the cannabis product is to be used again, put it on a clean ashtray until it stops burning. It must not be put out using any other agent, including water.

Recommendations for using cannabis oil extract for sublingual administration

The sublingual region contains blood vessels that are used to absorb the extract diluted in oil directly into the bloodstream, unlike ingestion, in which the extract components may undergo initial breakdown in the gastrointestinal tract (first pass effect).

In other words, sublingual administration is likely to result in higher availability of the active agents in the bloodstream.

1. Manufactured medical cannabis oils contain the cannabis plant extract diluted in oil (such as sesame oil or olive oil).
2. It must be made sure that the patient is not allergic to the type of oil being used for diluting the cannabis extract.
3. To begin with, one drop under the lounge should be used, then wait 3-4 hours, while following the effect.
4. For ensuring effective absorption, wait for 15 minutes before eating or drinking.
5. After a few days, if there is just partial effect or none at all, one may add another drop at intervals of at least 4 hours between taking times.
6. The process of learning the effect will take about two weeks until reaching the optimal dosage.
7. In any case, the daily dose prescribed by the physician should not be exceeded.
8. It is advisable to keep the cannabis oil refrigerated.

15. Cannabis abuse and addiction (dependence)

In an article that was published in the journal JAMA Psychiatry, the researchers reported the findings of a new study indicating that adults using cannabis had an increased risk of alcohol and drug use disorders, including nicotine dependence. The findings in the study clearly show the risks posed by the use of cannabis, including at relatively low doses.

The researchers examined the use of cannabis and the risk of psychiatric disorders and alcohol, drug and nicotine use disorders. In a representative sample consisting of more than 34,000 adults in the United States, who took part in the National Epidemiologic Survey on Alcohol and Related Conditions, they were asked in 2001-2002 (wave 1) and again after three years (2004-2005 (wave 2).

The analysis of the data reveals that the use of cannabis in wave 1, which 1,279 adults reported, was significantly associated with alcohol, drug and nicotine use disorders in wave 2, but no connection with anxiety or mood disorders was identified.

The researchers report that upon using cannabis, the odds ratio for alcohol use disorder was 2.7 times higher, the odds ratio for drug use disorder was 2.6 times higher, with an odds ratio of 1.7 for nicotine use disorder.

The researchers admitted that they were slightly surprised by the lack of increased risk for development of anxiety and mood disorders among those who used cannabis and expected cannabis to have an effect on all disorders, but the figures showed that the connection was more specific for drug and alcohol use disorders.

Although the study cannot establish causality between the use of cannabis and the onset of substance use disorders, one must take these psychiatric disorders into account in the clinical evaluation and planning of the therapeutic protocol.

Frequent, extended use of cannabis poses potential for development of physical and mental dependence (addiction). In many places in the world, such as the USA, Canada and Australia, cannabis addiction is one of the most common, immediately after tobacco and alcohol. Studies show that one in every nine users will develop cannabis dependence (primarily among those who started to use it in their teens).

Addiction is defined as a "chronic brain disease" that appears due to neuro-plastic changes at the neural level and at the molecular level in the brain, some of which are reversible and some irreversible, which occur as a result of the use of drugs. Addiction is a disease that has recurrent eruption characteristics along with bio-psycho-social aspects, characterized by obsessive-compulsive behavior in searching for drugs, alcohol or other psychoactive substances and consuming them despite the derived adverse consequences. Addiction is characterized by the existence of physical dependence, which includes withdrawal symptoms in the absence of the drug and craving for the drug on the other hand.

Abuse is defined as a pattern of using a psychoactive substance that causes damage to health, whether physical or mental, despite awareness of the damage that the continued use causes.

Tolerance – for any material that is consumed in large quantities and violates the balance in the body, the brain tends to develop tolerance towards it and block its effect. This compensatory mechanism of the body also exists in addictive behaviors such as computer games and when using various addictive substances, including prescription drugs.

Most addictions stem from a combination of psychological and psycho-social factors, genetic awareness, with differences between addictions to substances and addictions to various behavior patterns; sometimes there is a combination of addictions.

Addictions to psychoactive substances such as drugs and alcohol stem from a combination of biochemical and genetic factors that increase the vulnerability to addiction and psychosocial and behavioral factors: a lack of coping skills and/or emotional regulation are associated with emotional distress and/or stressful life events, leading to the use of a substances as an alternative means of coping. The positive reinforcement (reduced distress) caused by the use of a substance results in its prolonged use and an addiction process.

Addictions to behaviors (gambling, television viewing, sex, Internet, eating and more) have different primary causes but in most cases the addiction constitutes an ineffective way of coping with various difficulties.

Like addiction to substances, addiction to behavior also leads to relief in the short term and over time dependence on it develops.

In many cases, addiction stems from a phenomenon called "self-medication", which describes the use of a drug in order to relieve emotional conditions such as a sense of not belonging, boredom, anxiety and depression. The drug becomes a means for coping with everyday difficulties at work, in the social or relationships field. Smoking cannabis for "self-medication" purposes characterizes cannabis abuse and may lead to addiction.

In recent years, "self-medication" with cannabis has become common for coping with attention and concentration disorders. It appears that sufferers of this disorder feel that the drug slows down the thinking rate and hyperactivity inherent to this disorder. Medical opinions and studies show that ostensibly, extended use of cannabis may impair memory and concentration ability and is likely to worsen the disorder.

Addiction diagnosis:

According to the World Health Organization, addiction can be diagnosed when three of the following six criteria are fulfilled:

- There is an intense desire or compulsive urge to use a substance or perform the activity to which the person is addicted.
- It is difficult to control the quantity and time of use of the substance, or difficult to restrict the time of engaging in the addictive activity.
- The onset of 'withdrawal symptoms' (physical reactions) without using the substance of engaging in the addictive activity.
- The existence of tolerance – an increasing quantity of the substance is required to maintain its effectiveness or a need to increase the engagement in the addictive activity.
- The use of the addictive substance or engagement in the addictive activity is at the expense of significant life aspects (social life, studies, work, family).
- The use of the addictive substance or engagement in the addictive activity continues despite the awareness of the damage that it causes.

Besides the use of medical grade cannabis, use that is not for medical purposes is common among elderly and young people, men and women, in all classes of the population, and regrettably among children and adolescents too, despite its illegality. The use of cannabis is perceived today by many as non-dangerous, non-addictive and also as being less harmful than alcohol, and there are calls for legalizing its use. However, this

drug can also result in addiction, and of course there is a danger of switching from it to harder drugs. When using cannabis, it is not always clear or obvious to the consumer when he is still considered to be in control and when he starts to lose that control and slide towards addiction.

The adverse consequences of using cannabis manifest in a different manner in each user according to the scope of use, degree of damage and severity of dependence. Sometimes, family members and close friends are the ones who identify cannabis addiction. The addict may downplay the allegations and argue that cannabis is not addictive and is much less dangerous than alcohol or tobacco, and that it is legal in some countries. Just as alcohol is a legal drug whose consumption at high doses is not recommended, the consumption of cannabis also has a price that it is important for people to be aware of. Sometimes the addict understands that its uses causes damage but has difficulty in quitting alone. Addiction is an obsessive behavior that is very difficult to quit unassisted. Suddenly stopping using the substance may result in withdrawal symptoms, and in the case of cannabis these are usually emotional and psychological, but sometimes physical too.

Self-diagnosis by the patient:

A number of questions may direct the patient or user to examine himself to see whether he suffers from cannabis addiction. Try to answer the questions as honestly as possible and check with yourself whether you have lost your control of using cannabis and whether it is worth seeking professional health:

A. Check of frequency, quantity and control:

- On the days on which you decide to take a break, do you still find yourself smoking cannabis?
- Have you made a decision to use less but still find yourself smoking cannabis to the same amount or more?
- Compared to the day on which you started smoking cannabis, do you consume more of it?
- Do you try to avoid experiencing stress, irritability or restlessness by always keeping some "spare" cannabis?

In almost all cases, an increase in use, increase in quantities and inability to quit even for a single day indicate a very likely possibility of substance addiction.

B. Examination of the effect of smoking cannabis on the various life cycles:

Think about activities that you used to engage in irrespective of cannabis:

- Do you have to engage in them while smoking cannabis (sex, sleeping, learning, hanging out with friends, etc.)?
- Look at your friends – do most or all of them use cannabis too?
- Do you spend more money on cannabis than you would want to or more that you are capable of spending?

Friends, money, work, studies and so on are fields that are relinquished to the point of total disengagement in the case of addiction. Some people argue that they are able to combine the too, but a careful check shows that usually the drug beats everything else.

C. The effect of cannabis on the body and mind:

- When you run out of substance, do you experience irritability, anger or restlessness?

- Have attempts to quit use caused you to feel that life has become boring, sad or uninteresting?
- Are there matters that you must attend to but due to fatigue or lack of motivation you defer or neglect and continue to smoke cannabis instead?
- Do you continue to smoke cannabis despite signs of dry throat, phlegm, red eyes, memory loss, wrinkles, skin discoloration or even paranoia?

Cannabis addiction will usually be accompanied by anxiety, depression, loneliness and other difficult feelings while not taking the drug. Usually, to make up for these feelings, addicts will increase the use in quantity of substance and the time spent using it.

If the answer is affirmative more than once, this is probably a state of cannabis addiction or the characterization of the beginning of addiction, and it is advisable to seek professional help.

Diagnosis by the attending physician:

Throughout the treatment with medical cannabis, it is the responsibility of the physician to be familiar with and pay attention to the warning signs indicating addiction or a danger of addiction. In these cases, the physician must question and follow the patient more closely than usual and if necessary also refer the patient for continuing the addiction treatment.

At the first stage, in which the attending physician considers recommending the start of treatment with cannabis, he must ask the patient to fill in a CAGE-AID questionnaire, in order to check whether there is a risk or chance of abuse or whether the patient is prone to become addicted (dependent).

Adult patients must be asked the following questions routinely and repetitively.

This way is effective for finding and early identification of substance abuse and finding health disorders at early stages. Experience shows that questions that are directed at identifying the use of alcohol or drugs, which are asked during a general interview about lifestyle, are proven to be less threatening for patients.

1. Have you ever thought that you need to drink less alcohol or use substances / drugs less?
2. Have people criticized your drinking and use of substances that made you feel uncomfortable or annoyed you?
3. Have you ever felt bad or guilty about drinking alcohol or using substances/ drugs?
4. Have you ever used alcohol or drugs first thing in the morning in order to wake up or calm down?

When a patient answers yes to at least one question, consider a brief intervention.

The full questionnaire is the CAGE-AID questionnaire that appears at the link:

http://www.integration.samhsa.gov/images/res/CAGEAID.pdf

The intervention stage constitutes the beginning of the recovery stage.

The stage combines the principles of motivational interviews and/or short interventions, with the aim of assisting the patient in becoming aware of his disease and take steps to reduce the difficulties in the future. In motivation interviews, the physicians examine consumption habits and base themselves on the FRAMES (Feedback, Responsibility, Advice, Menu of Options, Empathy, Self-Efficacy) model. They explain the

dangers (Feedback), encourage patients to take responsibility for change, advise them (Advice) and offer a range of options (Menu of Options), maintain an empathic attitude towards the patient (Empathy), and support the patient's self-efficacy.

Short interventions are broader and are based on a range of tools for instructing the patient on normal consumption characteristics, emphasizing the dangers involved in excessive consumption, offering ways of reducing or quitting consumption, and assisting in identification of and abstention from conditions in which there is a strong likelihood of excessive consumption.

The two approaches are intended to increase patient motivation to make changes and alter their perception concerning their condition and the importance of the change.

Check for objections to change in examinations of patients and take the required steps that the patients are prepared to go ahead with.

In addition, at the history taking stage, in order to check for risk or opportunity for abuse, or whether the patient is prone to addiction (dependence), the attending physician must pay attention to the following points:

1. Has he/she ever been addicted and received treatment for that addiction? Something it means that the treatment is contraindicated.
2. Does he regularly take prescription drugs with addictive potential such as: benzodiazepines for calming or sleep, ritalin or other drugs for treating ADHD and opioid analgesics, and if so, the patient is to be followed with greater attention and action must be taken to taper down these drugs and examine the efficiency of the product in reduction or relief of pain.
3. History of alcohol use or cigarette smoking.
4. Family history of substance abuse and/or mental disorders, a condition requiring close following again.
5. At all times, discretion must be used and the efficacy of administration of cannabis must be examined against the potential for developing mental and physical dependence and/or various side effects. For example: a patient suffering from severe, metastatic cancer will be treated differently to a patient suffering from low back pain.

Dual morbidity:

Mental comorbidity: The presence of a significant mental disorder combined with abuse of or addiction to psychoactive substances, drugs and alcohol.

Physical comorbidity: The presence of a significant physical disease combined with abuse of or addiction to psychoactive substances, drugs and alcohol.

Multiple morbidity: A simultaneous combination of a range of morbidities

The attending physician must take into account that a patient who has developed cannabis addiction is defined as a patient suffering from comorbidity or multiple morbidity.

If you have identified a risk for developing addiction or abuse, how should you act?

Firstly, it is recommended that the attending physician ask questions using the SOAPP questionnaire, in order to deepen the examination of the risk of abuse or addiction (dependence) and evaluate the severity in the patient's case.

		Never (0)	Seldom (1)	Sometimes (2)	Often (3)	Very often (4)
1	**How often do you have mood swings?**					
2	**How often do you smoke a cigarette within an hour after you wake up?**					
3	**How often have any of your family members, including parents and grandparents, had a problem with alcohol or drugs?**					
4	**How often have any of your close friends had a problem with alcohol or drugs?**					
5	**How often have others suggested that you have a drug or alcohol problem?**					
6	**How often have you attended an AA or NA meeting?**					
7	**How often have you taken medication other than the way that it was prescribed?**					
8	**How often have you been treated for an alcohol or drug problem?**					
9	**How often have your medications been lost or stolen?**					
10	**How often have others expressed concern over your use of medication?**					
11	**How often have you felt a craving for medication?**					
12	**How often have you been asked to give a urine screen for substance abuse?**					
13	**How often have you used illegal drugs (for example, marijuana, cocaine, etc.) in the past five years?**					
14	**How often, in your lifetime, have you had legal problems or been arrested?**					

- A score above 7 indicates a high risk
- A lower score is not a high risk

If the risk is high or if during the treatment there is an impression that the patient does not adhere to the medical instructions or it seems that there is high treatment tolerance (usually manifesting in repeat requests to increase the dose), specialists in the field of addiction medicine / narcology should be consulted through the Addiction Treatment Department.

Dr. Paola Roshka: paola.Roshka@MOH.GOV.IL

Fax number of the department: 02-5655906

Discontinuing treatment with cannabis

Withdrawal symptoms are distress signals of the body when discontinuing use, manifesting in irritability and adjustment difficulties. Withdrawal symptoms in individuals attempting to stop using cannabis include: restlessness, irritability, headaches, anxiety, depression, low irritation threshold, concentration difficulties, insomnia, appetite disorders and drug craving. Therefore, to prevent withdrawal symptoms and distress, in a decision to discontinue treatment with cannabis, the attending physician must plan with the patient the process of stopping using cannabis based on tapering down until termination.

16. General warnings and directions in treatment using medical grade cannabis

Cannabis must not be used if:

1. The patient fulfills one or more of the contraindications.
2. Medical cannabis is not to be used for an extended period without consulting a physician. Continuous medical follow up is mandatory.
3. The patient is planning to become pregnant, is pregnant or breastfeeding.
4. Allergy to cannabis exists or develops.

Before recommending treatment with cannabis, you must evaluate and carefully examine the following conditions:

1. The patient is pregnant or is planning to become pregnant. Women and men must use effective birth control measures during treatment with cannabis and for at least three months after the treatment is ended.
2. The patient is under the age of 18.
3. The patient suffers from liver or kidney disease.
4. The patient suffers from severe cardiovascular disease such as: angina pectoris, previous heart attack, uncontrolled hypertension or cardiac arrhythmia, or if changes in heart rate or blood pressure have been observed after starting treatment. Treatment with cannabis is not recommended in patients suffering from severe cardiovascular diseases.
5. The patient has a history of addiction to any drug or substance.
6. The patient is elderly, particularly if he has difficulty in performing everyday activity such as making food and hot drinks.
7. If the patient is taking various drugs, including over the counter drugs and nutritional supplements such as:
   A. Sleep inducing drugs, tranquilizing drugs and drugs with a tranquilizing effect, because they may increase the tranquilizing and muscle relaxation activity and lead to an increased risk for falls and other accidents.
   B. Muscle relaxant drugs such as baclofen or benzodiazepines, such as: diazepam, because they may cause a decrease in muscle strength, leading to an increased risk for falls.

Storage and keeping:

Cannabis ingredients may break down, oxidize and lose activity upon exposure to heat, moisture and light. According to the recommended packing / storage conditions, "cannabis products" keep for only a limited period, so attention must be paid and the following storage and keeping conditions should be observed:

1. Please pay attention to the product's expiry date.
2. Keep the product in its original case and store in a dark, dry place at under 25°C.
3. It is important to keep the container tightly closed to prevent penetration of light and moisture and keep away from fire.
4. Do not discard a cannabis product into a bin or drain. Ask the cannabis dispenser how to dispose of this product that is not in use, using means that will help protect the environment.
5. Do not store with other drugs / medicinal products in the same container.

Do not mix or add any other substance to the content of the cannabis product. The medical cannabis product content is fir tor use as is and any addition to it may impair the medical efficacy for the patient.

Alcohol consumption:
Avoid drinking alcoholic beverages during the cannabis treatment period, particularly when starting the treatment or when the product / dose is changed. Drinking alcohol during treatment with cannabis may increase various effects such as loss of balance or extended reaction times, thus impairing the ability to drive and operate machinery and increasing the risk for falls and other accidents.

General warnings and restrictions at the time of use:

1. The "cannabis product" is defined as a "narcotic drug", its use for medical purposes is at the patient's address indicated on the usage license only.
2. When using a narcotic drug, performing actions that require concentration such as driving and/or operating heavy machinery is prohibited.
3. Use of a narcotic drug/s in the presence of minors or in public is strictly prohibited.
4. A narcotic drug and its products are not to be taken out of Israel.
5. Do not exceed the recommended dose. In the absence of an instruction to the contrary from a physician, the lowest dose that achieves the purpose of use is to be taken.
6. Avoid poisoning. "Cannabis products" are to be kept in a closed place out of reach of children and/or infants, thus preventing poisoning. If an overdose has been taken or a child has inadvertently swallowed the drug, present immediately to the hospital emergency room and bring the product container.
7. Do not take "cannabis products" in the dark.
8. Check the product and lot before any use of a "cannabis product".
9. Do not transfer this product from its case to another person; it may harm them even if it seems that their condition is similar. In addition, such an act would constitute drug trafficking and may lead to loss of the license and a criminal record.
10. When using a "cannabis product" of efflorescence type in smoking roll form, take all necessary fire precautions.
11. Each "cannabis product" is intended for appropriate pharmacological administration. Do not exceed the recommendation of the manner of administration that has been defined for the product, for example: do not swallow efflorescence. Swallowing cannabis efflorescence may cause adverse side effects
12. Read and observe the restrictions and terms of the license shown in the patient's usage and keeping license.
13. This clinical guide does not constitute an alternative to talking with the physician.
14. For diabetics: the consumption of cannabis may cause a decrease in blood glucose levels and may cause a sensation of fatigue and dizziness. It is advisable to keep a snack or sweet food or sweetened, cold soft drink nearby.

Additional attention:
During a conference of the American Academy of Pain Medicine, experts discussed the issues pertaining to cannabis and road accidents, and legal issues for protecting employers interested in a workplace without drug exposure.
It was shown that during driving, cannabinoids may affect reaction times, vision and attention.
Simulation studies and studies on roads have proved that cannabis has an effect on special perception, maintaining speed, response to stimuli and assessment of times and distances. The experts explained that these factors might explain the increase in the rate of road accidents due to the use of marijuana and presented data from 2014 whereby driving was involved in about 28% of deaths and that the combination of alcohol and marijuana increased the chances of death by 24%.

Functional MRI studies have also demonstrated a decrease in psychomotor functioning and significant impairment of driving, including in patients with a relatively low THC concentration (1.5 nanograms / ml).
The deficiencies due to exposure to marijuana may also affect the workplace. Statistics shown by the experts show that persons using marijuana experience an increase of 85% or more in injuries at the workplace, and an increase of 78% in loss of workdays, with a 55% increase in chances of accidents at the workplace compared to those who have not used medical marijuana.
In view of the fact that cannabis is a psychoactive drug, with the implications presented, against the expected benefit from consuming medical grade cannabis, one should not be deterred from maximizing the possible therapeutic potential with care and monitoring, meaning that the attending physician must ensure frequent medical follow up.

If an overdose (too high a dose) has been inadvertently taken:
The patient may experience severe toxicity effects that include dizziness, drowsiness, confusion, hallucinations (seeing or hearing nonexistent things) and believing incorrect things (delusions), anxiety or paranoia (an increase in anxiety or fear), changes in heart rate combined with low blood pressure (a feeling of dizziness when getting up).
If an overdose has been taken or a child has inadvertently swallowed a "cannabis product", present immediately to the attending physician or hospital emergency room and bring the product container. After taking an overdose, one must meet the physician for follow up purposes.
Do not induce vomiting without an explicit instruction from a physician.

Discontinuing cannabis use:
Consult a physician before deciding to stop using cannabis after regular use.
Suddenly stopping use may affect sleep, appetite or feeling.

17. Appendices

1 Appendix 1: procedure 106 – cannabis usage licenses

2. Appendix B: procedure 105 – work of the cannabis use indications committee

3. Appendix C: main side effects and interactions of using medical cannabis

4. Appendix D: consumption of medical grade cannabis in cookie form

5. Appendix E: the Dangerous Drugs Ordinance [New Version] 1973 – linked: http://www.health.gov.il/LegislationLibrary/Samim_01.pdf

Appendix A – Procedure 106 – cannabis usage licenses:

Ministry of Health
For a healthier life

The Medical Technologies
and Infrastructures Administration
The Pharmaceutical Division

www.health.gov.il

	Name of the procedure: cannabis usage license		
Date: March 2013	Procedure No.: 106	Update No.: 2 July 2014 Update 3: July 2015	Page 1 of 10

78776815

1. Background:

Cannabis is not a medicine, is not registered as one and its efficacy and safety in use for medical purposes have not been proved. However, there is evidence that cannabis may help patients suffering from certain medical conditions and relieve their suffering.

According to the provisions of the Dangerous Drugs Ordinance [New Version] 1973, (hereinafter the Ordinance), cannabis is a substance that is defined as a "narcotic drug" whose use is prohibited except as duly licensed.

The Director General of the Ministry of Health or a person authorized thereby (hereinafter – "the Director") has the power to permit the use of cannabis in accordance with the Ordinance.

The Director has the power to permit the use of cannabis for medical and research purposes in accordance with the provisions of the Ordinance and the regulations thereunder.

In addition to the provisions of the Ordinance and the regulations, the Single Convention on Narcotic Drugs 1961 establishes a unique regimen of control and monitoring of this drug, including the existence of a governmental agency responsible for regulating the issue.

According to Government Resolution No. 3609, it was determined that the Ministry of Health is to serve as a "governmental agency" in accordance with the provisions of the said convention, to which end the Ministry of Health formed the Israel Medical Cannabis Agency (IMCA).

Pursuant to Government Resolution No. 1050, the outline for regulating the field of medical grade cannabis and for producing a controlled supply source according to fixed criteria was approved.

In Update No. 1 of July 2013, two indications were added in the neurology field (Parkinson's disease, Tourette syndrome), with the relevant reservations as prescribed in the procedure, to the list of approved indications for use of cannabis (Section 3.2.5) and an update was made to the of manners of contact for sending the recommendations to the cannabis unit (Section 3.7).

In Update No. 2 of July 2014, an indication in the psychiatry field was added (posttraumatic stress disorder, PTSD), with the relevant reservations as prescribed in the procedure, to the list of approved indications for use of cannabis (Section 3.2.7), contraindications were added (Section 3.1), indications in the field of gastroenterology and infectious diseases was update (Section 3.2.2, 3.2.4) and means of referring the request and recommendations for treatment with cannabis, renewal and appeal were updated (Sections 3.6, 3.7, 3.8).

In update No. 3 of July 2015, an indication was added in the neurology field (epilepsy), with relevant reservations as stated in the procedure, to the list of approved indications for using cannabis (Section 3.2.5.4), an update was made to indications for treatment in the field of oncology and in the field of infectious diseases (Sections 3.2.1.1, 3.2.4), a direction was added for dosing at the beginning of the treatment and in the manner of follow up and reporting (Section 3.3).

Purpose of the procedure:

Establishing procedures concerning licenses for using medical grade cannabis.

2. **Definitions:** (in this circular) –

"Director" – the Director General of the Ministry of Health or a person authorized thereby in writing to issue licenses for using medical grade cannabis/

"IMCA" – the Israeli Medical Cannabis Agency.

"Cannabis" – as defined in the Dangerous Drugs Ordinance, subject to the directions as prescribed by the IMCA.

"License" – a written permit issued by the Director pursuant to the Dangerous Drugs Ordinance for using medical grade cannabis.

3. **Conditions required for receiving a license for using medical grade cannabis:**

3.1 General

3.1.1 Submission of an application for receiving a license to use medical grade cannabis, as set forth in this procedure.

3.1.2 As a rule, a license for using cannabis will not be issued until after exhausting the standard treatments under a recognized indication only. The list of recognized indications is provided in Subsection 3.2. The list will be updated from time to time to the extent that additional information justifying such an update is accumulated.

3.1.3 Contraindications – before submitting a recommendation and request for approval of use of medical grade cannabis, the recommending physician must rule out full or partial contraindications.

Relative contraindications to administering cannabis are: heart failure, psychosis, past psychotic state, anxiety disorder and significant psychiatric heredity in a first degree relative, particularly in the case of young patients from the age of 30 and a history of drug addiction or abuse.

3.1.4 The following reflects the main contraindications known today, but does not constitute a final list and additional contraindications derived from the specific state of the patient may occur, including concurrent use of drugs or products and concern of adverse interaction of undesirable side effects due to the combination.

Ministry of Health
For a healthier life

The Medical Technologies
and Infrastructures Administration
The Pharmaceutical Division

www.health.gov.il

3.2 **The medical indications currently recognized are as follows:**

3.2.1 **In the oncology field:**

3.2.1.1 For patients during treatment with chemotherapy, and up to six months after it is over for relieving nausea, emesis or pain related to the treatment (even without exhausting standard treatments for nausea relief, etc.).

In cases in which the attending physician believes that cannabis treatment should be continued after the six months are over, he is to detail the reasons for continuing the treatment and for what period he intends to continue it.

3.2.1.2 For relief of pain of cancer source at the metastatic stage after exhausting standard treatment options.

3.2.2 **In the gastroenterology field:**

For patients suffering from active, proven inflammatory bowel disease (Crohn's disease, ulcerative colitis) and meeting all of the following criteria:

3.2.2.1 Standard medication using at least one immunomodulatory (such as: Imuran or Purinethol), for a period of 3 months at least, and in addition at least one TNF inhibitor (such as: Humira or Remicade) with a full loading dose, i.e. 3 treatments, has been exhausted and has failed.

3.2.2.2 Ruling out the option for surgical treatment of removal of a short diseased intestine section.

The recommendation for treatment with cannabis is to be submitted by a gastroenterologist who has been caring for the patient for at least 3 months, with:

A. Detailed documentation of the said treatments.

B. Details on the reason for ruling out the surgical treatment option.

3.2.3 **In the pain field:**

Patients suffering from neuropathic pain of a clear organic source, who are treated at a recognized pain clinic for at least one year before submitting the application, after exhausting standard treatment options and with the recommendation of the pain clinic at which they are treated, along with:

A. A filled in brief pain inventory (BPI) questionnaire, which will be used as a tool for following the patient in the context of the efficacy of treatment with cannabis.

3.2.4 **In the infectious diseases field:**

For patients diagnosed with acquired immunodeficiency system (AIDS), after exhausting standard medication and suffering from extreme weight loss (cachexia – more than 10% weight loss) for improving their appetite or relieving emesis and gastrointestinal symptoms.

3.2.5 **In the neurology field:**

3.2.5.1 For patients diagnosed with multiple sclerosis in spastic states who have not responded to standard treatment.

3.2.5.2 For patients diagnosed with Parkinson's disease, who have been treated for at least a year with antiparkinsonian treatment, who are suffering from pain (chronic pain or pain caused by rigidity) who have not responded to standard pain treatment.
Contraindication to treatment – active psychosis.

The recommendation for treatment by medical cannabis will be submitted by the caring neurologist who undertakes to conduct medical follow up every three months at least.

3.2.5.3 For adult patients who are diagnosed with Tourette syndrome, who suffer from significant dysfunction in everyday life, who have not responded to standard treatments.
Contraindication to treatment – active psychosis or (first degree) family heredity of psychotic diseases.

The recommendation for treatment using medical cannabis will be submitted by the caring neurologist, along with A recommendation of a psychiatrist who has examined the patient.

In the first year of treatment, the license will be limited to three month periods each time and the renewal of the license will be on the condition of joint examination and recommendation by the caring neurologist and psychiatrist each time.
From the second year of treatment, the license will be restricted to periods of up to one year each time, requiring a recommendation of the caring neurologist and a psychiatric recommendation.

3.2.5.4 For adult patients with epilepsy, who fulfill all of the following criteria:

Diagnosed as having severe epilepsy for at least two years, suffering from significant dysfunction [disabling epileptic seizures, including generalized clonic seizures, complex-partial focal dyscognitive seizures, other focal seizures if they cause a danger of falling and injury and generalized tonic or atonic seizures].

The epilepsy is recalcitrant, after failure of at least five antiepileptic drugs prescribed as a monotherapy or as a drug combination, and is characterized by a seizure frequency of at least one seizure per month with documented medication.

The recommendation to treat will be submitted by an expert neurologist caring for the patient at an epilepsy clinic at one of the medical centers in which the patient has been under follow up for at least the six months preceding the submission of the application, with documentation of failure of at least 2 drugs within the period of treatment at that clinic, and with an undertaking of the neurologist to conduct medical follow up and with a recommendation of a psychiatrist who has examined the patient.

3.2.5.5 For minor patients who suffer from severe, uncontrollable epilepsy, after failure of standard treatments with at least five drugs / treatments, including resistance to or failure of one or more of the following: ketogenic diet, vagus nerve stimulator, surgery.

The recommendation to treat will be submitted by a caring pediatric neurologist who has undertaken to conduct medical follow up every three months at least.
At the beginning of the treatment with cannabis, the patient must be taking at least two recognized anticonvulsant drugs at full dosage and continue the treatment with them without reducing the dose for a period of six months without seizures following which reduction and keeping the patient on a single anticonvulsant drug and cannabis may be considered.

3.2.6 **In the palliative care field:**

3.2.6.1 For terminal patients (six month expected life expectancy).

3.2.7 **In the psychiatry field:**

For adult patients who are diagnosed with posttraumatic stress disorder (PTSD) and who meet all of the following criteria:

3.2.7.1 Medium and greater severity posttraumatic stress disorder meeting the criteria of 30% disability at least under National Insurance Institute sections, persisting for more than 3 years and characterized by great mental stress.

3.2.7.2 At least 2 standard medicinal interventions for minimal times of two months per intervention have been exhausted and 2 standard psychological interventions have been exhausted.

3.2.7.3 Absolute contraindication to treatment – history of psychosis or drug abuse.

The recommendation for treatment with cannabis is to be submitted by an expert psychiatrist caring for the patient, on the "appendix to application for adjuvant therapy with cannabis for PTSD patients" via the link published on the website of the Ministry of Health http://www.health.gov.il along with:

A. Detailed documentation of the treatments as set forth above.
B. Recommendation of the recommending expert psychiatrist, confirming that he has explained the risks of treatment to the patient.
C. An undertaking of the recommending expert psychiatrist to continue the medical follow up throughout the license period.

In the first year of treatment: the license to use cannabis will be restricted to a period of up to six months each time and the renewal of the license will require a report of the caring psychiatrist concerning the results of the treatment through to the time of submitting the application and his recommendation to continue treatment.
From the second year of treatment: the license to use cannabis will be restricted to a period of up to one year each time and the renewal of the license will require a report of the caring psychiatrist concerning the results of the treatment through to the time of submitting the application and his recommendation to continue treatment.

3.3 Follow up and reporting

The issuance of a license will be contingent to conducting medical follow up every three months at least in the first year of treatment, by an attending physician whose details will appear in the license and from the second year of treatment at least every six months.

3.3.1 The initial dose of the treatment with cannabis will be to a quantity of 20 grams per months (about 0.6 gr per day) of the cannabis product type whose active substance concentration is the lowest.
If in the opinion of the attending physician the dose must be increased, a detailed, explained request is to be submitted. The increase in dose will be gradual in increments of 10 gr.

3.3.2 In the case of approval of a request to use cannabis for the indication of pain as set forth in Section 3.2.3 – continued follow up at the pain clinic that has made the application or another pain clinic.

3.3.3 In the case of changing the attending physician, the new physician must announce this to the Director and to the IMCA, with a copy to the previous attending physician, for updating the license details.

3.3.4 In the case of scheduled conclusion of treatment or a coordinated change of an attending physician, the physician whose details are stated in the license is responsible for reporting to and updating the Director and the IMCA.

3.3.5 In the case of the contact with the patient being lost for a period in excess of three months, or the attending physician learning of the patient's death, a report is to be made to the Director and to the IMCA at the responsibility of and by the physician.

3.3.6 In the case of the attending physician believing that the patient is unfit to drive due to his medical condition or treatment with cannabis, he must give a "caregiver notice" and report this to the road safety medical institute.

3.3.7 In certain cases (such as very high doses or inappropriate use), the Director is allowed to ask the attending physician who recommended to the unit to issue a usage license for additional clarifications as a condition to renewal of the usage license or as a condition to continuing the dosing.

3.4 Extraordinary cases:

3.4.1 A request to the Director for a permit for using cannabis for patients whose condition or disease is not one of the indications set forth in Section 3.2 above will be discussed after the recommending physician explains in detail and with acceptable medical documentation the basis for believing that using cannabis may assist the patient.

In addition the applying physician must elaborate in the application parameters and follow up tools for assessing the efficacy of the treatment once approved and undertake to perform the actual follow up if the application is approved.

3.4.2 In the case of a request for approval of use under an indication that has not been previously discussed by the Director, at his discretion, the Director may, prior to making a decision, to apply to an indications committee appointed by the Director General or Assistant Director General of the Ministry of Health for their general or specific recommendation.

3.4.3 As a rule, no application will be approved for a patient who first contacts any pain clinic only for submitting an application for approving use of cannabis, or who has not been treated for a period of a year at least at a pain clinic.

3.4.4 Notwithstanding the foregoing, an application for approval of use may be submitted for a patient who has not been treated at a pain clinic for a one year period at least may be discussed, but it will only be discussed if the application is supported by the director of the clinic, with detailed explanations of the clinic director for the need for the extraordinary approval.

Ministry of Health
For a healthier life

The Medical Technologies
and Infrastructures Administration
The Pharmaceutical Division

www.health.gov.il

3.5 Application to a Director for a permit for using cannabis at doses of 100 grams per month and more will be discussed under the following conditions:

3.5.1 The recommending physician has a "specialist" degree in the field of the disease for which the treatment with cannabis is being recommended and is being employed at a public institution ("public institution" refers to a general hospital, including an outpatients clinic of such a hospital or a central professional clinic of a healthcare organization and excepting private clinics of independent physicians).

3.5.2 The recommendation will be given for a patient who is receiving treatment or who is under follow up at the public institution at which the physician is being employed.

3.5.3 The hospital director, relevant division director at the hospital, or district physician at the healthcare organization, as the case may be, has approved the recommendation of the specialist as set forth in Subsection 3.5.1.

3.6 Means of referring the application for a license for using cannabis to the Director or dosing change requests:

An application for approval of use of cannabis for medical reasons or a request to change the dose or form of consumption for a patient is to be submitted as set forth in this section.

3.6.1 The application is to be submitted by a physician specializing in the disease for which the treatment with cannabis is being recommended, who is recommending approval of use of cannabis for the medical purposes detailed in the application.

3.6.2 The application is to contain all of the details required according to the Dangerous Drugs Ordinance and a mailing address, to the extent that this address differs from the applicant's home address.

3.6.3 The application is to include a summary of full, current medical information from the family physician.

3.6.4 In the case of an application for approval of use under an indication of pain (of any type), attach a full brief pain inventory (BPI) questionnaire, which will be used as a tool for following the patient concerning the efficacy of the treatment with cannabis.

The questionnaires are to be matched to the disease from which the patient is suffering for which the application for cannabis is being submitted and is to include the relevant details required for assessing his condition.

3.6.5 If a request is made to add a carrier for the cannabis (from the dispensing point to the site of use indicated in the application), a photocopy of the carrier's identity card must be attached.

3.6.6 An application that arrives without all the details required in this procedure will not be decided on until the required details are completed.

3.6.7 The application to the Director will be made by the recommending specialist physician only through the structured form whose link is published on the website of the Ministry of Health http://www.health.gov.il. Other documents may be attached to the structured form in accordance with the circumstances.

3.6.8 The application or request will be forwarded to the Director in one of the following ways:

By ordinary mail to the address:

The Ministry of Health, the Pharmaceutical Division – the Medical Cannabis Department, 39 Yirmiyahu Street, Jerusalem 9446724.

or by email:

IMCA@Moh.Health.gov.il

or by fax:

02-6474810.

3.6.9 A decision on the application, interim decisions and correspondences will be forwarded to the attending physician with a copy to the patient, in accordance with the details made in the application.

3.6.10 A request that will be approved, the original license and its applications, if there are any, will be sent to the patient and a notice will be delivered to the attending physician and the party responsible for dispensing the drug whose details appear in the license.

3.7 Renewal of an existing license or requests for updating details of an existing license:

3.7.1 An application for renewal of a license will be forwarded to the Director by the physician in the field of the disease for which the cannabis treatment is being recommended, who was responsible for medical follow up according to the original license. The provisions of Section 3.6 will apply to the application for renewal of the license, mutatis mutandis.

3.7.2 The application is to be submitted within 45 workdays at least, before the expiration of the license, with a treatment follow up report detailing the need to continue the treatment, along with the findings for assessing the effect of the treatment with cannabis in the treatment that has passed since the giving of the license whose renewal is being applied for.

3.7.3 Requests for updating license details without significant changes, such as due to a change in home address, carrier or attending physician, may also be submitted in writing by ordinary mail (as set forth in Section 3.7.1 above), along with the original license and documentation of the object of the request.

3.8 Appeals against a "Director" decision:

3.8.1 For questions that are of medicine only, except for decisions relating to doses, after exhausting the discussion before the director, a patient or caring physical may submit a written appeal against the decision to an appellate committee.

The appeal statement is to be submitted with an "appeal" form whose link is published on the Ministry of Health website, http://www.health.gov.il, with details from the attending physician on the explanations as to why in his opinion the Director erred in his decision, along with medical / professional documentation substantiating his arguments.

3.8.2 The appellate committee will be appointed by the Director General of the Ministry of Health and will include at least 2 specialist physicians and a chairman. A representative of the Director General of the Ministry of Health will serve as the chairman of the committee – the Associate Director General, the Head of the Medical Administration or his deputy or another representative who will be appointed ad hoc for discussing a given appeal.

3.8.3 The Israeli Medical Cannabis Agency is administratively responsible for convening and the work of the appellate committee. The appeal will be submitted in writing to the secretariat of the IMCA, by ordinary mail (to the address set forth in Section 3.6.7 above).

Ministry of Health
For a healthier life

The Medical Technologies
and Infrastructures Administration
The Pharmaceutical Division

www.health.gov.il

3.8.4 The appeal documents will be submitted by the secretariat of the Medical Cannabis Department to the committee members prior to the discussion.

3.8.5 The appellate committee is allowed to dismiss an appeal in limine in the following cases:

3.8.5.1 The appeal does not contain detailed medical information on the current condition of the appellant and exhaustion of standard treatments.

3.8.5.2 The appeal does not include an undertaking of the specialist physician to conduct the medical follow up, to the extent that the appeal is sustained.

3.8.5.3 In the case of a request for approval of use under an indication that is not set forth in Section 3.2, the appeal does not contain medical information supported by evidence indicating that there is a basis for the belief that the use may assist the patient.

3.8.5.4 In the case of the decision of the Director being made after consulting an indication committee as set forth in Section 3.4.2 above and the appeal not containing new information.

3.8.5.5 To the extent that the appeal is not dismissed in limine, the appellate committee will hold a discussion and a decision will be made with a majority vote.
The decision of the committee will be sent to the applying physician with a copy to the Director and the IMCA, for implementation of the decision of the committee.

4. Responsibility for implementation:

Caring / recommending physicians
"Directors"
The Israeli Medical Cannabis Agency (IMCA)

5. Applicable documents:

The Dangerous Drugs Ordinance [New Version] 1973.
The Dangerous Drugs Regulations 1979.
The Single Convention on Narcotic Drugs, 1961.

6. Appendices:

6.1 Application form for a license for use as shown on the websites at the addresses:

www.health.gov.il

http://www.health.gov.il/Services/Citizen_Services/Pages/kanabis.aspx

http://forms.gov.il/globaldata/getsequence/ getsequence.aspx?formType=CannabisReq%40moh.gov.il

6.2 Appeal form and appendix to application for adjuvant therapy with cannabis for PTSD patients as appearing on the websites at the address:

http://www.health.gov.il/Services/Citizen_Services/Pages/kanabis.aspx

7. **Applicability:**

These procedures **are effective immediately** and any modification thereto will be binding only if done in writing and published.

8. **Dissemination:**

Director General of the Ministry of Health
Associate Director General of the Ministry of Health
Head of the Medical Administration
Head of the Medical Technologies Administration
VP Public Information and International Relations
Spokesperson of the Ministry of Health
VP Control of Healthcare Organizations and Additional Medical Services
VP Planning, Budgeting and Pricing
District physicians – Jerusalem, Tel Aviv, Haifa, Central, Northern, Southern
District pharmacists – Jerusalem, Tel Aviv, Haifa, Central, Northern, Southern
The chief medical advisor to the IMCA
"Directors"
Pharmaceutical Division pharmacists
Office of the legal advisor
Israel Medical Association (IMA)
Association of pharmacists in the Labor Federation
Pharmaceutical Society of Israel
Pharmaceutical Association of Israel, Pharmacies Branch
Directors of the pharmaceutical services of the healthcare organizations: Clalit, Maccabi, Meuhedet, Leumit
Pharma Israel – P.O. Box 2391, Kfar Saba 44641

Writer of the procedure:	**Title:**	**Signature and date:**
Mgr. Yuval Landschaft	**Director of the Israeli Medical Cannabis Agency (IMCA)**	[Signature]
Approver of the procedure:	**Title:**	[signature]
Dr. Boaz Lev	**Associate Director General of the Ministry of Health**	

Appendix B: Procedure 105 – work of the cannabis usage indications committee

Ministry of Health
For a healthier life

The Medical Technologies
and Infrastructures Administration
The Pharmaceutical Division

www.health.gov.il

3.1.2 According to the discretion of the chairman, experts in other fields of science may be enrolled.

3.1.3 The committee members will be appointed, usually or ad hoc, for examining a certain issue by the Associate Director General.

3.1.4 The members of the committee will sign a nondisclosure agreement and an undertaking of absence of conflict of interests, according to the procedure of the Ministry of Health for preventing conflicts of interests.

3.2 **Functions of the cannabis use indications committee:**

3.2.1 The indications committee will serve as an advisory committee to the Director General of the Ministry of Health and will present to him its recommendations concerning the medical indications for approving the use of medical grade cannabis.

3.2.2 The indications committee will discuss and advise on any other medical issue that will be brought forth before it by the chairman of the committee including the manners of use, doses, dosing regimen and other such medical questions pertaining to the use of medical grade cannabis.

3.2.3 According to the decision of the chairman, the indications committee will also discuss inquiries from a "director" pursuant to the Dangerous Drugs Ordinance, for examining individual requests for use of medical grade cannabis that have been submitted to him, which are not in accordance with the indications that have already been approved and recognized or in other extraordinary cases.

3.2.4 If the indications committee has made a decision pursuant to this subsection, it will bind the "director" applying to it unless the composition of the indications committee discussing and deciding on the request is not a member who by himself has authorization as a "director" pursuant to the Dangerous Drugs Ordinance.

3.3 **Bringing a subject up for discussion before the committee:**

3.3.1 The discussion before the committee will be done on issues that have been brought up before it by the chairman of the committee.

3.3.2 The chairman of the committee will determine the agenda of the committee.

3.3.3 Requests to raise issues for discussion before the indications committee will be submitted to the director of the Medical Cannabis Department, who will forward them to the chairman with his opinion on the subject.

3.3.4 The chairman of the committee will decide on whether to forward the application for discussion before the committee, under conditions or unconditionally, or to reject the application.

3.4 The work of the committee:

3.4.1 Administrative responsibility for the work of the indications committee – the Medical Cannabis Department.

3.4.2 The frequency of the meetings will be determined according to the number of issues that are to be discussed, and at least three times a year.

3.4.3 The discussions of the committee will be held based on written material and data only, which will be forwarded in advance to the committee members.

3.4.4 The committee will conduct discussions in a composition that includes at least the chairman or his representative, one specialist physician and one pharmacist.

3.4.5 At the committee, an open discussion will be held, at the end of which the recommendations of the committee will be explained and documented in writing. The documentation of the decisions will also include the explanations of the dissenting opinion, if there is one.

3.5 Dealing with recommendations:

3.5.1 The recommendations of the indications committee for adding or changing recognized indications, recommendations on other general medical subjects, will be submitted to the Director General of the Ministry of Health.

3.5.2 If the recommendation has been accepted, the Director General will announce this to the director of the Medical Cannabis Department, who will have it published and will act accordingly.

3.5.3 The decisions of the committee in individual cases will be forwarded to the Director pursuant to the Dangerous Drugs Ordinance who submitted the query to the committee.

4. Responsibility for implementation:

Office of the Associate Director General
Pharmaceutical Division
The Medical Cannabis Department
Physicians with "director" certification
Members of the indications committee

5. Applicable documents:

The Dangerous Drugs Ordinance [New Version] 5733-1973.
The Dangerous Drugs Regulations 1979.
The Single Convention on Narcotic Drugs, 1961.

Ministry of Health
For a healthier life

The Medical Technologies
and Infrastructures Administration
The Pharmaceutical Division

www.health.gov.il

Name of the procedure: work of the cannabis usage indications committee		
Date of the procedure: March 2013	Procedure No.: 105	Page 4 of 4

16435713

6. Appendices: None

7. Applicability:

These procedures are effective immediately and any modification to them will be binding only if done in writing and published.

8. Dissemination:

Director General of the Ministry of Health
Associate Director General of the Ministry of Health
Head of the Medical Administration
Head of the Medical Technologies Administration
VP Public Information and International Relations
Spokesperson of the Ministry of Health
VP Control of Healthcare Organizations and Additional Medical Services
VP Planning, Budgeting and Pricing
District physicians
District pharmacists
Pharmaceutical Division pharmacists
Office of the legal advisor
Israel Medical Association (IMA)
Association of pharmacists in the Labor Federation
Pharmaceutical Society of Israel
Pharmaceutical Association of Israel, Pharmacies Branch
Directors of the pharmaceutical services of the healthcare organizations: Clalit, Maccabi, Meuhedet, Leumit
Pharma Israel – P.O. Box 2391, Kfar Saba 44641

Writer of the procedure:	**Title:**	**Signature and date:**
Mgr. Yuval Landschaft	**Director of the Israeli Medical Cannabis Agency (IMCA)**	
Approver of the procedure:	**Title:**	**Signature and date:**
Dr. Boaz Lev	**Associate Director General of the Ministry of Health**	

The acute side effects of using medical cannabis are[2,3,7,8,11]:

1. Dizziness, which may be considered an insignificant side effect, but which may become very significant in elderly patients in whom dizziness may result in falls.
2. Emesis.
3. Exacerbation of multiple sclerosis.
4. Urinary tract infections.
5. Anxiety in new users, psychotic effects (at a high dose).
6. Neurological symptoms such as: reduced coordination diminished muscular strength, sedation and sleep, concentration difficulties, changes in psychomotor activity, unclear speech and slowed reaction time.
7. Decrease in cognitive activity.
8. Impaired alertness and increased risk for accidents, if the patient is required or is required to perform complex tasks under the influence of the product.
9. Use during pregnancy may lead to low birth weight.
10. General effects: dry mouth, headaches, cough and sore throat.
11. Tachycardia.

The side effects in chronic use of medical cannabis are [2,3,7,8,10,11]:

1. Dependence
2. High risk of chronic bronchitis and impaired lung function.
3. Psychotic symptoms and disorders are more frequent in patients with a personal or family history of psychotic disorders.
4. Decrease in levels of the hormones LH, FSH, prolactin and growth hormone.
5. Disorders of the gastrointestinal tract and disorders in the electrolyte balance, which **requires special attention in patients suffering from renal failure**.
6. Use for 10 years or longer may permanently impair cognitive ability.

Additional side effects that are described in case histories in literature [2,3,7,8,10]:

1. Cannabis arthritis.
2. Cardiac arrhythmias.
3. Heart failure.
4. Decreased body temperature and motility and in rare cases paralysis.
5. Acute decrease in sugar levels in diabetic patients.
6. Hypomania (loss of judgment and reckless behavior).
7. Smoking-related damage.

This overview is not an alternative to carefully studying the patient's medical conditions and medication before and during the use of medical cannabis, which will allow for maximum benefit while minimizing the possible damage to the patient's health.

Main interactions of medical cannabis

Results of the interaction[14,15]	Pharmacological group / active substance	Trade name in Israel[13]	Comments [1, 4-9, 11, 14, 15]
Increase in activity / toxicity of products combined with cannabis	Analgesic opioids	Tramadex, Tramal, Zaldiar;	Increased risk for respiratory depression caused by cannabis
	Barbiturates	Phenobarbital	Increased risk for sedation, probably due to inhibited barbiturate clearance
	Products containing cannabinoids		A combination of cannabinoids (by oral administration or inhalation) is not recommended, due to the increased risk for psychotic effects
	CNS inhibitors; MAO inhibitors, anxiolytics, sedatives, general anesthetics, hypnotics, phenothiazines, skeletal muscle relaxants, sedating H1 blockers, tricyclic antidepressants	Elatrol, Elatrolet; Abilify, Ariply; Sorbon; Suboxone, Subutex; Butrans, SBT, Anafranil, Marinol; Leponex, Lozapine; Deprexan; Gilex; Halidol, Haloper, Pericate; Tofranil; Licarbium; Melodil; Miro, Mirtazapin, Remeron; Nortyline Olanzapin Dexcel, Olanzapine Teva, Zappa, Zypadhera; Orap Forte; Pramipexol Teva®, Sifrol ER, Trimexol; Queti, Queiapine Teva®, Seroquel; Azilect; Rispefar, Risperdral, Risperidex, Rispond; Requip Modutab, Ropinirol Teva®; Trazodil; Surmontil; Geodon	Increased risk for respiratory suppression caused by cannabis in tricyclic antidepressants, increased risk for hallucinations or tachycardia may also occur
	Sedating H1 blockers, anticholinergic products (including antimuscarine)		In this combination, in addition to an increase in risk for respiratory suppression, there is a risk of tachycardia and dizziness
	SSRIs		Increased risk for mania
	Sympathomimetic products, amphetamines, cocaine, etc.		The combination may cause an increase in blood pressure, tachycardia and cardiotoxicity
	Alcohol (ethyl alcohol)		Ethanol may cause increased absorption of cannabinoids, increased central nervous system depression. It is advisable to monitor the effects in simultaneous administration and warn patients concerning the expected effect.

Results of the interaction[14,15]	Pharmacological group / active substance	Trade name in Israel[13]	Comments [1, 4-9, 11, 14, 15]
Increase in activity / toxicity of products combined with cannabis	Azelastine	Rhinolast	It is advisable to avoid simultaneous use
	Cocaine		Increase in the toxic effects of cocaine
	Disulfiram	Not registered in Israel	Increased risk for hypomania
	Metyrosine	Not registered in Israel	
	Paraldehyde	Not registered in Israel	It is advisable to avoid concurrent use
	Pramipexole	Pramipexole Teva®, Sifrol ER, Trimexol	
	Sildenafil	Viagra, Revatio, Sil-On, Sildenafil Teva®, Slider, Tarim, Via-Avenir	Increased risk of myocardial infarction
	Warfarin	Coumadin	Increased INR
	Zolpidem	Amien CR, Stilnox, Zodorm	

Results of the interaction[14,15]	Pharmacological group / active substance	Trade name in Israel[13]	Comments [1, 4-9, 11, 14, 15]
Increased levels / effect of cannabis when used simultaneously with products	Tobacco products / cigarettes		Use of cannabis while smoking increases the heart rate and carbon monoxide levels and may cause complications in patients treated with other products[11].
	CYP2C9 inhibitors (strong and moderate), Sorafenib, Ritonavir, Fenofibric acid	Nexavar®, Kaletra, Norvir is not registered in Israel	Due to competitive inhibition of the metabolism, it may cause an increase in THC concentrations and an increase in the side effects of THC (the active substance in cannabis), it is advisable to consider reducing the cannabis dose.
	CYP3A4 inhibitors (strong & moderate)		
	Brimonidine (topical)	Alphagan P, Brimonidine Teva®, Combigan	
	Cocaine		Increase in toxicity effects of cocaine
	Conivaptan	Not registered in Israel	
	Dasatinib	Sprycel	
	Doxylamine	Sleep Aid, Tonight	
	Droperidol	Not registered in Israel	
	Fusidic acid (systemic)	Fucidin (systemic administration)	It is advisable to avoid simultaneous use [1]
	Ivacaftor	Not registered in Israel	
	Luliconazole	Not registered in Israel	
	Magnesium sulfate		
	Methotrimeprazine	Ronexine	
	Mifepristone	Not registered in Israel	
	Perampanel	Not registered in Israel	
	Simeprevir	Fycompa	
	Sodium Oxybate	Not registered in Israel	

Bibliography

1. Lexicomp database, version 2.5.3, 2013 (THC & Cannabidiol).
2. Grant I, Medical Marijuana: Clearing away the smoke, The Open Neurol. J. 6:18-25, 2012.
3. Leung L: Cannabis and its derivatives: Review of medical use. Ja Am Board Fam Med, 24: 452-462, 2011
4. Thomas G et al: Adverse cardiovascular, cerebrovascular and peripheral vascular effects of marijuana inhalations: What Cardiologists need to know. Am J Cardiol. 113:187-190, 2014.
5. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systematic review. CMAJ 1178:1669-78, 2008
6. Hall W, Degenhardt L: Adverse health effects of non-medical cannabis use, the Lancet, 374(9698): 1383-1391, 2009
7. Itin, K. HIV, weight and cannabis, part c: Cannabis. Pharmalin, 2008; 33: 34-40.
8. Pertwee RG: Cannabis and Cannabinoids: Pharmacology and rationale for clinical use. Forsch Komplementarmed; 6 (suppl 3): 12-15, 1999
9. Ashton CH, Moore PB, Gallagher P Yong AH: Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential. J Psychopharmacol, 19(3): 293-300, 2005
10. Gur Ruth, shedding light on the dark side of medical marijuana. Medicine by Medical Group, 11-13, July 2021.
11. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy; 33:195-209. 2013.
12. Hartman RL, Huestis MA. Cannabis effects on driving skills. Clin Chem; 59(3): 478-92. 2013.
13. Drugs database of the Pharmaceutical Division

    http://www.old.health.gov.il/pages/default.asp?maincat=11&catid=38&Pageid=165
14. AltMedDex database (Micromedax)
15. MD Consult database (Dronabinol, THC)
16. Hellum BH, Hu Z, Nilsen OG: The Induction of CYP1A2, CYP2D6 and CYP3A4 by Six Trade Herbal Products in Cultured Primary Human Hepatocytes. Basic Clin Pharmacol Toxicol, 100(3):23-30, 2007.

Appendix D: consumption of medical grade cannabis in cookies

Ministry of Health
For a healthier life

The Director General

www.health.gov.il

4th of Kislev 5774
November 7, 2013
Reference: 63196413
(in reply to: state reference)

To: Mr. Yuval Landschaft, Director of the Israeli Medical Cannabis Agency (IMCA)

Re: Consumption of medical grade cannabis in cookies
(Reference – meeting of October 27, 2013)

In the referenced meeting, and after all of the arguments and considerations have been presented before me, I have decided that the use of cookies containing cannabis will only be permitted for children. at this time I have asked for a written summary to be prepared on the whole process of examination of the issue, all of the pleas and considerations raised, so that I can reconsider everything and make sure that my decision is correct.

After this summary was prepared and forwarded to me, and after reexamining it, it is my conclusion that there is no room to continue approving the consumption of medical grade cannabis in cookies, subject to an exemption of use by children according to the recommendation of the caregiver, and this decision, which will take effect from January 1, 2014, must be announced.

A breakdown follows -

Factual background:
The subject of using medical grade cannabis is a relatively young subject in Israel and elsewhere in the world. in Israel, the issue rose to the agenda of the Ministry of Health in the late 1990s, early 2000s, while applications for approving the use of medical grade cannabis slowly reached the Ministry of Health.

In the first years, the response to applications was on a per case basis irrespective of the procedural or general plane, in view of the limited scale of the phenomenon. In the first years, at any given time there were no more than a few dozen applications and valid licenses. At some stage there was a rapid increase in the scale of demand and the approvals that were given for using medical grade cannabis, which led to some cases being "learned on the fly", as the state also admitted in the hearing that was held at the High Court of Justice as part of a petition of one of the growers.

It was learned in retrospect that some of the decisions were made based on the assumption that it was a simple issue that did not require deep governmental involvement or regulation, while today it is clear in the sharpest possible manner that the situation is much more complex than initially thought.

2/..
Director General
Ministry of Health
P.O.B 1178 Jerusalem 91010
mankal@moh.health.gov.il
Tel: 02-5081209 Fax: 02 5655988

המנהל הכללי
משרד הבריאות
ת.ד 1178 ירושלים 91010
mankal@moh.health.gov.il
טל: 02-5081209 פקס: 02-5655988

Like many other contexts, as is the case concerning cannabis products that have bene approved for production and manners of use, here too it would seem that the development was from the outset without any deep contemplation of the issue. It should be noted that an attempt to reconstruct this action factually revealed deficiencies in the relevant factual underpinnings.

If it was initially obvious that the licenses that were issued were licenses for patients for growing for their own use only (or a number of patients growing cannabis together), and there was no contemplation of the form of use of the drug grown by those patients themselves, it is less clear when exactly the issue was first considered in the licenses issued to growers (as opposed to licenses issued individually to patients).

With the transition from licenses for growing for personal use (initially all licenses for patients were lionesses like these) to licenses for growing and production that were given to growers and suppliers, at some stage, approvals were given not only to grow and process the cannabis plant for a desiccated efflorescence form for smoking or evaporation, but these and other licenses were also given for producing two other products, despite the products first not having been named, but instead the licenses contained a text approving the production of products "from sampling parts that are processed for smoking or ingestion".

As of the date of this decision, there are licenses for manufacturing cookies but there are no clear figures concerning the degree of actual consumption of these cookies, as opposed to consumption in another way, but there is no dispute that cannabis is consumed in this form.

Concerning the manners of consumption of the drug by patients, it may be said that at least in recent years, the standard consumption methods are not only by smoking but also by evaporation or brewing of the dried efflorescence, ingestion of the plant extract diluted with oil or alcohol and eating cookies containing the drug. It cannot be shown when each form was first used, and this did not prevent the patients themselves, who received the drug in one form or another, from processing it by themselves into a personalized consumption form, including baking of cookies.

It should be noted that there is evidence that at some stage the issue of products, their form and composition started to be examined properly, from a letter sent on April 30, 2012 by Dr. Baruch, the Director under the Dangerous Drugs Ordinance, to all growers and producers, in which he clarified that "the distribution of cannabis products (oil cookies) that has not been approved by the undersigned constitutes a violation of the conditions of the license".

At this time, the staff work advanced, including inter-ministerial staff work and work before the inter-ministerial steering committee, in an attempt to form appropriate professional criteria for all relevant fields, including the fields of medicine, when one issue that started to receive a specific response was the issue of the product types that should be approved for patients. Thus, for example, criteria were set concerning the maximum and minimum permitted concentrations of the key active substances in the plant (THC and CBD) and the combinations between them.

Later, a discussion was also held concerning the product types that had to be approved. In a discussion that was held before the starring committee on May 12, 2012, it was decided that –

Decision: the situation will remain the same concerning the products. Cookies and oil will be used as approved products as smoking alternatives, no additional products will be approved. The Ministry of Health is to form directions for manufacturing in cooperation with the relevant parties.

3/

Director General
Ministry of Health
P.O.B 1170 Jerusalem 91010
mankal@moh.health.gov.il
Tel 02-5081309 Fax 02-5665903

המנהל הכללי
משרד הבריאות
ת"ד 1170 ירושלים 91010
mankal@moh.health.gov.il
פקס 02-5665903 טל' 02-5081309

The discussions on the issue continued and in September 2012 the Pharmaceutical Division at the Ministry of Health was requested by Dr. Baruch to give its opinion on the subject of continuing the manufacture of cookies and such an opinion was prepared and given at the beginning of 2013 and was later presented and discussed before the steering committee.

The opinion, which was prepared by Mgr. Marom of the Pharmaceutical Division, with Dr. Shlomo Almog, a leading expert by himself, and which was submitted as set forth to the committee, was that there was no justification for continuing to manufacture the cookies, in pharmacological respects, for the following main reasons:

1) There are alternatives to cookies – **dried efflorescence for smoking or evaporation and cannabis oil**. A patient who chooses not to smoke will be able to make himself cookies (out of the efflorescence or oil) if that is his preference or to consume the oil easily by dripping a number of the drops on any food type of the patient's choice.
2) The cookie manufacturing process poses difficulties and concern for the nature of the final product, in view of the fact that the cookies are baked at an oven temperature of **160-200 degrees**, and in this temperature range, the cannabinoids, including TCH, pass from a solid to a liquid phase.
3) With regard to appropriate medical and pharmacological policy, the number of product types containing cannabis should be reduced.
4) Fear of misuse of the product by the patient or by another party who mistakenly identifies the product as a medicinal product containing a narcotic drug.

On February 14, 2013, the subject was discussed by the inter-ministerial steering committee and the categorical recommendation of everyone present was not to approve the continued manufacturing of cookies mainly after no therapeutic or pharmacological solution was found for the existence of additional products besides dried efflorescence and oil, of known, clear composition only. Moreover, in the opinion of the steering committee, it would seem that additional products, including cookies, have disadvantages that in and of themselves justify ending the possibility of marketing them, including concerns regarding the manufacturing process and its effects on the active substances and fear of inadvertent misuse (primarily in the context of cookies, with the concern that third parties including children would mistakenly consume something that does not appear to be a medicinal product) and more.

A notice of this decision was given to these manufacturing license holders who asked for the decision to be reconsidered after hearing their arguments. It was decided to defer the execution and allow for written arguments to be submitted (later frontally before the steering committee too) and reconsider the decision carefully once the procedure was over.

Later, the written and oral arguments of Tikun Olam Company and Cannabliss were heard before the steering committee, and I personally met with Prof. Reuven Or, the Director of the Bone Marrow Transplantation Department at Hadassah Hospital (and the person who at that time was also the scientific advisor of Cannabliss Company despite him not stating so in the meeting with me). In that meeting, Prof. Or emphasized patients' satisfaction with these cookies (which are not approved for us in his own department but only for ambulatory patients), but he also stated that his opinion of the cookies was effectively based on observations and the result, of patients responding well and being satisfied. Hardware stated that he had not scientifically examined the issue. He added that if dripping oil on a cookie would yield the same effect for patients, he would not consider it problematic. Later he also submitted a written opinion that repeated this.

4/..

Director General
Ministry of Health
P.O.B 1170 Jerusalem 91010
mankal@moh.health.gov.il
Tel: 02-5081309 Fax: 02-5665903

המנהל הכללי
משרד הבריאות
ת"ד 1170 ירושלים 91010
mankal@moh.health.gov.il
פקס: 02-5665903 טל' 02-5081309

The arguments of Tikun Olam Company (in writing and orally in the hearing) for supporting the continued production of cookies from the perspective of the needs of patients were as follows:

Firstly, a product that is consumed by eating and absorbed in the gastrointestinal tract has an advantage insofar as it takes effect after 30-90 minutes and will be effective for about eight hours on average. They explained that the manufacturing process of the cookies was controlled and regulated, so that the final composition could be ensured.

The company and patients using its products emphasized the satisfaction of patients and that the patient group consuming the cookies was primarily children who had been approved for receiving the treatment, Sabbath observers who cannot smoke on the Sabbath, patients who are hospitalized in the treatment period and patients who prefer not to consume the treatment in the form of smoking or oil.

The opinion of Dr. Natalya Kagan, who explained the importance of the possibility of taking medical cannabis orally, was presented. In this opinion she stated that the consumption of cookies was a standard, accepted form of consumption and that "in pharmacokinetic terms, this form of administration is quite similar to other oral administration forms, such as tablets or capsules. Some studies even show that absorption from cookies is better than gelatin tablets, possibly because of the activation of bile juices and lymphatic absorption mechanisms, as in this case of cookies, the active substance is given with food" (which does not answer the question of why dripping the oil extract on any food of the patient's choice does not represent a sufficient solution). The writer emphasized that in children "cookies are the only form of administration that gains full compliance of small patients".

Dr. Geitzin Moshe, a geriatrist specializing in gerontology and acting as the medical director of the Hadarim retirement home, also appeared before the committee and discussed the difficulty for elderly patients to consume cannabis by smoking or by drops, due to physical limitations of old age, and he stated his experience that for that population, the correct solution was capsules (not cookies), and that was his actual experience with his patients at that institution.

The arguments of Cannabliss Company (in writing and orally during the hearing) for supporting the continued manufacturing of the cookies from the perspective of patient needs were as follows:

The company emphasized that it was prepared for all the manufacturing processes to be revealed to the Ministry of Health and that it would abide by any demand pertaining to manufacturing and ensuring that the content of the cookies was measured and known and that therefore a decision to cancel the approvals for manufacturing that project based on the assumption that the products were not measured and known was unreasonable. This applied all the more so in view of the company's argument that the products had been tested and found to be at controllable doses.

Documents relating to a study conducted at Tel Hashomer, at the department of Pediatric Hematology and Oncology at Tel Hashomer and the letter of Prof. Toren, the director of the department and Dr. Huri of that department, of a study and their statements, were presented – "the decision to use cookies containing THC stemmed from two main reasons: one was that it was found that passing though the gastrointestinal tract caused a longer time of effect, and also it stemmed from the wish to avoid encouraging the smoking of cannabis" (without an explanation as to why the possibility of dripping oil on any food product was not considered).

Director General
Ministry of Health
P.O.B 1176 Jerusalem 91010
mankal@moh.health.gov.il
Tel. 02-5081309 Fax: 02-5655930

המנהל הכללי
משרד הבריאות
ת.ד 1176 ירושלים 91010
mankal@moh.health.gov.il
טל: 02-5081309 פקס: 02-5655930

The company emphasized that it would fulfill not only any demand pertaining to the manufacturing procedures and laboratory tests, but also any demand concerning marking or packing the product to prevent erroneous consumption.

The company argued that it was manufacturing a drug and that form of consumption of cannabis in cookies was not its own patent, but something extant and needed, and that it benefited patients. The cookies help people overcome the psychological aspect and revulsion from smoking. According to it, the manufacturing process was accompanied by a chemist who accompanied the process and that regular laboratory tests were conducted.

The company also cited statements of patients regarding their satisfaction and the success of the treatment using cookies and failure off any other method, including the use of oil, and Prof. Or appeared for the steering committee meeting, in which he emphasized that he through the test was the response test and if the patient responded well to the cookie, he should be allowed that option.
In addition, I also considered the arguments of the two companies of rights and financial interests on the matter in the aggregate of the considerations.

Discussion:

After carefully inspecting the various documents and reconsidering everything, my consideration is that in effect there is no room or justification for continuing to manufacture the cookies, and that it is not clear based on what considerations that manufacturing was approved from the outset. Even if it is an existing reality, I still do not think that at the time of the change I have to convince anyone that any particular product is unnecessary. Because reality was formed without any actual examination of anything, certainly not a scientific one, that any particular product is needed, I think that the Ministry of Health has the responsibility today, even in retrospect, to do so, and to the extent that it finds that any product is not medical justified, and based on medical and pharmacological considerations there is no room to approve its continued manufacturing only for the reason that it exists today and has not caused any harm heretofore.

In the end, the main argument of all the parties objecting to discontinuing the manufacture of the cookies was the outcome of use. According to those supporting continued manufacturing, the product does actually help patients and therefore allowing its continued existence is justified. Even after it was said that the efficacy of the treatment using cookies is a consideration for approving proper manufacturing, a more precise statement should be made. This efficacy is subjective and has not been clearly examined, and certainly not in a conventional scientific form, and the statements of Prof. Or before me were clear on the mater. The other documentation that was presented by professional parties made no separation of use of oil from the consumption of cakes and did not attend to the question of whether there was any difference between the two and whether cannabis oil could be consumed on many food products as an appropriate, equivalent alternative to cookies.

First hand statements from patients, although I respect them, are not a scientific basis for proving efficacy, before the placebo effect is factored into the equation.

Based on everything that has been brought before me, I have not found compelling evidence justifying the continued existence of a medicinal product in the form of cookies, and in my mind the opposite is true. One exception to this is children who cannot consume cannabis in any other form, although at this point I have many doubts as to whether consumption by cookie is the correct solution for these conditions, and I pronounced this exception, albeit with reservations.

Director General
Ministry of Health
P.O.B 1176 Jerusalem 91010
mankal@moh.health.gov.il
Tel. 02-5081309 Fax: 02-5655930

המנהל הכללי
משרד הבריאות
ת.ד 1176 ירושלים 91010
mankal@moh.health.gov.il
טל: 02-5081309 פקס: 02-5655930

If we examine things in a prism of rational, medical and scientific methodology, there is no justification or need for an additional product, which ostensibly does not contribute anything more to the current products, a product that by nature and form is a stranger to medicine (and I am well aware that there are products for children in the form of sweets, but these, as noted, are exceptions). It is actually based on the wish to regard cannabis using medical criteria, rather than as a kind of popular medicine, that I see no room for distributing it in a manner that distances and differentiates it from other medicinal products, implying that "the rules of play" for it differ from those pertaining to any other medical treatment. It is clear to me that this also applies to smoking and this form of consumption should also be scrutinized and is scrutinized, and there may be room for change there too.

Summary:

After considering and reconsidering everything, I consider there to be no room to continue to approve the manufacturing of the cookies, subject to the exception that I have stated above, and this must be announced to the relevant parties so that they make preparations accordingly.

The "cannabis cookie" products whose manufacturing and marketing to children holding licenses for using medical cannabis will be permitted will be at concentrations corresponding with the concentrations of the efflorescence and oil approved by the steering committee only and with the following conditions:

A. The products will be packed in child proof / child resistant packaging.
B. Fulfillment of the provisions of any law pertaining to manufacturing and marking of food, including a packaging containing clear marking of all ingredients of the cannabis product and any additional ingredient (including marking of allergens).

Best regards,
[signature]
Prof. Roni Gamzu

Cc: Yael German, Minister of Health
Dr. Boaz Lev, Associate Director General of the Ministry of Health
Dr. Eyal Schwartzberg, Director of the Pharmaceutical Division, Ministry of Health
Adv. Sharona Ever-Hadani, the Legal Office the Ministry of Health

Director General
Ministry of Health
P.O.B 1176 Jerusalem 91010
marka@moh.health.gov.il
Tel: 02-5091209 Fax: 02-5655968

המנהל הכללי
משרד הבריאות
ת.ד.1176 ירושלים 91010
marka@moh.health.gov.il
טל: 02-5091209 פקס: 02-5655968

18. Bibliography and recommended reading

1. R. Mechoulam and Y. Shvo. The structure of cannabidiol. Tetrahedron, 19, 2073-2078 (1963).
2. Y. Gaoni and R. Mechoulam. Isolation, structure and partial synthesis of an active constituent of hashish. J. Amer. Chem. Soc., 86, 1646-1647 (1964).
3. R. Mechoulam, P. Braun and Y. Gaoni. A stereospecific synthesis of-(-) A 1and-(-) A-6 tetrahydrocannabinols. J. Amer. Chem. Soc., 89, 4552-4554 (1967).
4. R. Mechoulam. Marihuana chemistry. Review. Science, 168, 1159- 1166 (1970).
5. Z. Ben-Zvi, R. Mechoulam and S. Burstein. Identification through synthesis of an active A6-tetrahydrocannabinol metabolite. J. Am. Chem. Soc., 92, 3468-3469 (1970).
6. J.L.G. Nilsson, I.M. Nilsson, S. Agurell, Z. Ben-Zvi and R. Mechoulam. Synthesis of a potential urinary THC metabolite. Acta Pharm. Suec., 9, 215-220 (1972).
7. R. Mechoulam, H. Varconi, Z. Ben-Zvi, H. Edery and Y. Grunfeld. Synthesis and biological activity of five tetrahydrocannabinol metabolites. J. Am. Chem. Soc., 94, 7930-7931 (1972).
8. R. Mechoulam, P. Braun and Y. Gaoni. Syntheses of Δ-1THC and related cannabinoids. J. Am. Dro kjusa gs kvekv nhych,/Chem. Soc., 94, 6159-6165 (1972).
9. R. Mechoulam, Z. Ben-Zvi, S. Agurell, I.M. Nilsson, J.L.G. Nilsson, H. Edery and Y. Grunfeld . Δ-6 Tetrahydrocannabinol-7-oic acid, a urinary Δ-6THC metabolite: isolation and synthesis. Experientia, 29, 1193-1195 (1973).
10. Greenberg I et al. effects of marijuana use on body weight and energy intake in humans. Psychopharmacology. 49, 79-84 (1976).
11. R. Mechoulam, N.K. McCallum and S. Burstein. Recent advances in the chemistry and biochemistry of cannabis. Chem. Reviews 76, 75-112 (1976).
12. I. Tamir, R. Mechoulam and A.Y. Meyer. Cannabidiol and Phenytoin: A structural comparison. J. Med. Chem., 23, 220-223 (1980).
13. J.M. Cunha, E.A. Carlini, A.E. Pereira, O.L. Ramos, G. Pimentel, R. Gagliardi, E.L. Sanvito, N. Lander and R. Mechoulam. Chronic administration of CBD to healthy volunteers and epileptic patients. Pharmacologia, 21, 175-185(1980).
14. R. Mechoulam, N. Lander, T.H. Varkony, I. Kimmel, O. Becker, Z. Ben-Zvi, H. Edery and G. Porath. Stereochemical requirements for cannabinoid activity. J. Med. Chem., 23, 1068-1072 (1980).
15. J.R. Leite, E.A. Carlini, N. Lander and R. Mechoulam. Anticonvulsant effect of (-) and (+) isomers of CBD and their dimethyl heptyl homologs. Pharmacol., 124, 141-146 (1982).
16. P. Consroe, M.A.C. Benedito, J.R. Leite, E.A. Carlini and R. Mechoulam. Effect of CBD on behavior seizures caused by convulsant drugs or current in mice. Eur. J. Pharmacol., 83, 293-298 (1982).
17. B. Law et al, "Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin," J. Pharm. Pharmacol. 36: 289-94 (1984).

18. Jerom A Yesavage etal. Carry Over Effects of Marijuana Intoxication and Pilot Performance. Am J Psychiatry. 142, 1325-1329 (1985).
19. R. Mechoulam, J.J. Feigenbaum, N. Lander, M. Segal, T.U.C. Jarbe, A.J. Hiltunen and P. Consroe. Enantiomeric cannabinoids: stereospecificity of psychotropic activity. Experientia 44, 762-764 (1988).
20. Tzu-Chin WU, M.D. et al. Pulmonary Hazards of Smoking Marijuana as Compared with Tobacco. N Engl J Med. 318, 347-51 (1988).
21. Miller NS etal. A 12 step treatment approach for marijuana (cannabis) dependence. J substance abuse treatment. 6, 241-50 (1989).
22. P.J. Little, D.R. Compton, R. Mechoulam and B. Martin. Stereo- chemical effects of 11-OH-delta-8-THC-dimethylheptyl in mice and dogs. Pharmacol. Biochem. Behavior 32, 661-666 (1989).
23. T.U.C. Jarbe, A.J. Hiltunen and R. Mechoulam. Stereospecificity of the discriminative stimulus functions of the dimethylheptyl homologs of 11-OH-delta-8-tetrahydrocannabinol in rats and pigeons. J. Pharmacol. Exper. Ther. 250, 1000-1005 (1989).
24. Johnson BA. Psychopharmacological effects of cannabis. British journal of hospital medicine. 43 (2), 114- 6,118-20,122 (1990).
25. M. Huestis , J. Henningfield and E. Cone,"Blood Cannabinoids. I. Absorption of THC and Formation of 11-OH- THC and THCCOOH During and After Smoking Marijuana",Journal of Analytic Toxicology, Vol. 16: 276-282 (1992).
26. W.A. Devane, L. Hanus, A. Breuer, R.G. Pertwee, L.A. Stevenson, G. Griffin, D. Gibson, A. Mandelbaum, A. Etinger and R. Mechoulam. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 258, 1946-1949 (1992).
27. E. Fride and R. Mechoulam. Pharmacological activity of the cannabinoid agonist anandamide, a brain constituent. Eur. J. Pharmacol. 231, 313-314 (1993).
28. Z. Vogel, J. Barg, R. Levy, D. Saya, E. Heldman and R. Mechoulam. Anandamide, a brain endogenous compound, interacts specifically with cannabinoid receptors and inhibits adenylate cyclase. J. Neurochem. 61, 352-355 (1993).
29. F. S. Guimaraes, J.C. de Aquiar, R. Mechoulam and A. Breuer. Anxiolytic effect of cannabidiol derivatives in the elevated plus-maze. General Pharmacology 25, 161-164 (1994).
30. I. Wirguin, R. Mechoulam, A. Breuer, E. Schezen, J. Weidenfeld and T. Brenner. Suppression of experimental autoimmune encephalomyelitis by cannabinoids. Immunopharm. 28, 209-214 (1994).
31. J. Weidenfeld, S. Feldman and R. Mechoulam. The effect of the brain constituent anandamide, a cannabinoid receptor agonist, on the hypothalamo-pituitary-adrenal axis in the rat. Neuroendoc- rinology 59, 110-112 (1994).
32. P.B. Smith, D.R. Compton, S.P. Welch, R.K. Razdan, R. Mechoulam and B.R. Martin. The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice. J. Pharmacol. Exp. Ther. 270, 219-227 (1994).

33. A. Abrahamov, A. Abrahamov and R. Mechoulam. An efficient new cannabinoid antiemetic in pediatric oncology. Life Sciences 56, 2097-2102 (1995).
34. Brown RL, Rounds LA. Conjoint screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. Wis Med J. 94(3):135-40 (1995).
35. F. Taura, S. Morimoto, Y. Shoyama and R. Mechoulam. First direct evidence for the mechanism of Δ-1 tetrahydrocannabinolic acid biosynthesis. J. Amer. Chem. Soc. 117, 9766-9767 (1995).
36. Galiegue S, Mary S, Marchand J, Dussossoy D, Carriere D, Carayon P, Bouaboula M, Shire D, Le Fur G, Casellas P. Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. Eur J Biochem. 232(1), 54-61 (1995).
37. R. Mechoulam, S. Ben-Shabat, L. Hanus, M. Ligumsky, N.E. Kaminski, A.R. Schatz, A. Gopher, S. Almog, B.R. Martin, D.R. Compton, R.G. Pertwee, G. Griffin, M. Bayewitch, J. Barg and Z. Vogel. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem. Pharmacol. 50, 83-90 (1995).
38. Harrison et al. Cannabis, Cognition, and Residual Confounding. JAM A. 275, 521 (1996).
39. R. Mechoulam, E.Fride, L.Hanus, T. Sheskin, T.Bisogno, V.Di Marzo, M. Bayewitch and Z. Vogel. Anandamide may mediate sleep induction. Nature, 389, 25-26 (1997).
40. Twitchell W, Brown S, Mackie K ; "Cannabinoids inhibit N- and P/Q-type calcium channels in cultured rat hippocampal neurons". J. Neurophysiol. 78 (1): 43-50. PMID 9242259. (1997).
41. R. Mechoulam, E. Fride and V. Di Marzo. Endocannabinoids. Eur. J. Pharmacol. 359, 1-18 (1998).
42. Wayne Hall, Nadia Solowij. Adverse effects of cannabis. Lancet. 352, 1611-16 (1998).
43. Zuo-Feng Zhang et al. Marijuana Use and Increased Risk of Squamous Cell Carcinoma of the Head and Neck. Cancer Epidemiology Biomarkers 8' prevention. 8, 1071-8 (1999).
44. W.Y. Ong, K. Mackie. A light and electron microscopic study of the CB1 cannabinoid receptor in the primate spinal cord. Journal of Neurocytology. 28 (1), 39-45 (1999).
45. A.M. Malfait, R. Gallily, P.F. Sumariwalla, A.S. Malik, E. Andreakos, R. Mechoulam, M. Feldmann. The non- psychoactive cannabis-constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc. Natl. Acad. Sci (USA) 97, 9561-9566 (2000).
46. McGee R. et al. Longitudinal study of cannabis use and mental health from adolescence to early adulthood. Addiction. 95, 491-503 (2000).
47. Ashton, C. Heather. Pharmacology and effects of cannabis: a brief review. The British Journal of Psychiatry, Volume 178, pp 101-106. (2001)
48. Disdier P. et al. Cannabis arteritis revisited-ten new case reports. Angiology. 52 (7), 505-6 (2001).
49. D. Panikashvili, C. Simeonidou, S. Ben-Shabat, L. Hanus, A. Breuer, R. Mechoulam and E. Shohami. An endogenous cannabinoid (2-AG) is neuroprotective after brain injury. Nature 413, 527-531 (2001).
50. E. Fride, Y. Ginzburg, A. Breuer, T. Bisogno, V. Di Marzo and R. Mechoulam. Critical role of the endogenous cannabinoid system in mouse pup suckling and growth. Eur. J. Pharmacol. 419, 207-214 (2001).

51. J.M. McPartland, E.B. Russo. Cannabis and Cannabis Extracts: Greater Than the Sum of Their Parts? J Cannabis Ther. (3/4), 103-132 (2001).
52. Pertwee RG. Cannabinoid receptors and pain. Prog Neurobiol. 63(5), 569-611 (2001).
53. Tramer MR. et al. Cannabinoids for control of chemotherapy induced nausea and vomiting quantative systemic review, BMJ. 323, 16-21 (2001).
54. A.C. Howlett, F. Barth, T.I. Bonner, G.Cabral, P. Casellas, W.A. Devane, C.C. Felder, M. Herkenham, K. Mackie, B.R. Martin, R. Mechoulam and R.G. Pertwee. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol. Rev. 54, 161-202, (2002).
55. Arseneault et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 325, 1212 (2002).
56. Berry EM Mechoulam R: tetrahydrocannabinol and endocannabinoids in feeding and appetite. Pharmacol. 95-185-190 (2002).
57. J. Van Os. Et al. Cannabis Use and Psychosis: A Longitudinal Population-based Study. Am J Epidemiol. 156 (4), 319-327 (2002).
58. Abrams DI et al. short term effects of cannabinoids in patients with HIV-1 infection: a randomized placebo controlled clinical trial. Ann. Inter. Med. 139, 258-66 (2003).
59. Baker D et al. Therapeutic potential of cannabis. Lancet Neurol. 2, 291-8 (2003).
60. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinetiks. 42, 327-360 (2003).
61. Cota D, Marsicano G, Tschop M, Grubler Y, Flachskamm C, Schubert M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest. 112, 423431 (2003).
62. Iversen L. cannabis and the brain. Brain, 126, (pt6) 1252-1270 (2003).
63. Freund TF, Katona I, Piomelli D ; "Role of endogenous cannabinoids in synaptic signaling". Physiol. Rev. 83 (3): 1017-66. doi:10.1152/physrev.00004.2003 (inactive 2015-01-09). PMID 12843414. (2003).
64. Grotenhermen. Clinical Pharmacokinetics 42(4):327-360, (2003)
65. Walter L, Franklin A, Witting A, Wade C, Xie Y, Kunos G, et al. Nonpsychotropic cannabinoid receptors regulate microglial cell migration. J Neurosci. 23, 1398-1405 (2003).
66. Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nat Rev Drug Discov. 3(9), 771-84 (2004).
67. Gregory T Carter, Patrick Weydt, Muraco Kyashna-Tocha, Donald I Abrams. Medicinal cannabis: Rational guidelines for dosing. IDrugs. 7(5), 464-470 (2004).
68. a b Guo J, Ikeda SR ; "Endocannabinoids modulate N-type calcium channels and G-protein-coupled inwardly rectifying potassium channels via CB1 cannabinoid receptors heterologously expressed in mammalian neurons". Mol. Pharmacol. 65 (3): 665-74. doi:10.1124/mol.65.3.665. PMID 14978245 (2004).

69. L.A. Parker, M. Kwiatkowska, P. Burton and R. Mechoulam. Effect of cannabinoids on lithium-induced vomiting in the Suncus murinus (house musk shrew). Psychopharmacol. 171, 156-161 (2004).
70. M. Kwiatkowska, L.A. Parker, P. Burton and R. Mechoulam. A comparative analysis of the potential cannabinoids and ondansetron to suppress cisplatin-induced emesis in the Suncus murinus (house musk shrew). Psychopharmacol. 174, 254-259 (2004).
71. N. Kogan, R. Rabinowitz, P. Levi, D. Gibson, P. Sandor, M. Schlesinger and R. Mechoulam. Synthesis and antitumor activity of quinonoid derivatives of cannabinoids. J. Med. Chem. 47, 3800-3806 (2004).
72. P.F. Sumariwalla, R. Gallily, S. Tchilibon, E. Fride, R. Mechoulam and M. Feldmann. A novel synthetic, nonpsychoactive cannabinoid acid (HU-320) with anti-inflammatory properties in murine collagen-induced arthritis. Arthritis & Rheumatism 50, 985-998 (2004).
73. Vincenzo Di Marzo1, Maurizio Bifulco3 & Luciano De Petrocellis. The endocannabinoid system and its therapeutic exploitation. Nature Reviews Drug Discovery. 3, 771-784 (2004)
74. Andersson, M. et al. Cannabinoid Action Depends on Phosphorylation of Dopamine-and cAMP-Regulated Phosphoprotein of 32 kDa at the Protein Kinase A Site in Striatal Projection Neurons. Journal of Neuroscience. 25 (37), 8432-8 (2005).
75. Ashton CHet al. cannacinoidsin bipolar affective disorder: a review and discussion of their therapeutic potential. J Psychopharmacol,.19, 293-300 (2005).
76. D. Panikashvili, R. Mechoulam, S. M. Beni, A. Alexandrovitch and E. Shohami. CB1 cannabinoid receptors are involved in neuroprotection via NF-kB inhibition. J. Cerebral Blood Flow Metabolism 25, 477-484 (2005).
77. Hert CL. Increasing treatment options for cannabis dependence: a review of potential pharmacotherapies. Drug and Alcohol dependence. 80, 147-159 (2005).
78. Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp pharmacoli. 168, 299-325 (2005).
79. Mechoulam, Editor, Birkhauser Verlag, Basel. Author - with L.Hanus. "Cannabinoids as Therapeutics" of Cannabinoid chemistry, an overview. 1, 23-46 (2005).
80. Osei-Hyiaman D, DePetrillo M, Pacher P, Liu J, Radaeva S, Batkai S, et al. Endocannabinoid activation at hepatic CB1 receptors stimulates fatty acid synthesis and contributes to diet-induced obesity. J Clin Invest.115, 1298-1305 (2005).
81. Shufman E, et al. depersonalization after withdrawal from cannabis usage. Harefua. 144, 249-251 (2005).
82. Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 310, 329-332 (2005).
83. D.Panikashvili, N.A.Shein, R.Mechoulam, V.Trembovler, R.Kohen, A.Alexandrovitch, E.Shohami. The endocannabinoid 2-AG protects the blood brain barrier after closed head injury and inhibits mRNA expression of proinflammatory cytokines. Neurobiol. Disease, 22, 257-264 (2006).

84. E.Murillo-Rodriguez, D.Millan-Aldaco, M. Palomero-Rivero, O. Prospero-Garcia, R. Mechoulam, R.Drucker- Colin. Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats. FEBS Letters, 580, 4337-4345 (2006).
85. Binzen U, Greffrath W, Hennessy S, Bausen M, Saaler-Reinhardt S, Treede RD ; "Co-expression of the voltage-gated potassium channel Kv1.4 with transient receptor potential channels (TRPV1 and TRPV2) and the cannabinoid receptor CB1 in rat dorsal root ganglion neurons". Neuroscience 142 (2): 527-39. doi:10.1016/j.neuroscience.2006.06.020. PMID 16889902. (2006).
86. Linszen D, van Amelsvoort T. Cannabis and psychosis: an update on course and biological plausible mechanisms. Curr Opin Psychiatry; 20(2):116-20. Review. (2007).
87. G.Milman, Y.Maor, S.Abu-Lafi, M.Horowitz, R.Gallily, S.Batkai, F-M. Mo, L. Offertaler, P. Pacher, G. Kunos, R. Mechoulam. N-Arachidonoyl L-serine, a novel endocannabinoid-like brain constituent with vasodilatory properties. PNAS, 103, 2428-2433 (2006).
88. J.Tam, O.Ofek, E.Fride, C.Ledent, Y. Gabet, R. Muller, A.Zimmer, K.Mackie, R. Mechoulam, E. Shohami, I. Bab. Involvement of neuronal cannabinoid receptor, CB1, in regulation of bone mass and bone remodeling. Mol. Pharmacol. 70, 4337-4345 (2006).
89. L. Weiss, M. Zeira, S.Reich, M.Har-Noy, R. Mechoulam, S.Slavin, R.Gallily. Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. Autoimmun. 39, 143-151 (2006).
90. Messinis et al. Neuropsychological deficits in long-term frequent cannabis users. Neurology. 66, 737-739 (2006).
91. N.M. Kogan, C. Blasquez, L.Alvarez, R.Gallily, M. Schlesinger, M.Guzman, R. Mechoulam. A cannabinoid quinone inhibits angiogenesis by targeting vascular endothelial cells. Mol. Pharmacol. 70, 51-59 (2006).
92. Pacher P. et al. The endocannabinoid system as an emerging target of pharmaco-therapy. Pharmacological reviews. 58, 389-462 (2006).
93. Cannabinoids Inhibit Nucleoside Transporter to Mediate Immunosuppression; Vol. 2006, Issue 336, pp. tw169. Science's STKE 23 May (2006).
94. Ryberg E, Larsson N, Sjogren S, Hjorth S, Hermansson NO, Leonova J, Elebring T, Nilsson K, Drmota T, Greasley PJ. The orphan receptor GPR55 is a novel cannabinoid receptor. Br J Pharmacol. 152(7), 1092-101 (2007).
95. M.Garcia-Arencibia, S.Gonzalez, E. de Lago, J.A.Ramos, R.Mechoulam, J.Fernandez-Ruiz, Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. Brain Research 1134, 162-170 (2007).
96. Moor TH. Et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systemic review. Lancet. 370, 319-28 (2007).
97. Marilyn A. Huestis PhD, Michael L. Smith PhD, DABFT, Human Cannabinoid Pharmacokinetics and Interpretation of Cannabinoid Concentrations in Biological Fluids and Tissues. Marijuana and the Cannabinoids. Forensic Science And Medicine, pp 205-235 (2007).

98. N.M. Kogan, M.Schlesinger, E, Priel, R.Rabinowitz, E. Berenshtein, M.Chevion, R.Mechoulam. HU-331, a novel cannabinoid-based anticancer topoisomerase inhibitor. Molecular Cancer Therapeutics 6, 173-183 (2007).
99. R. Durst, H. Danenberg, R. Gallily, R. Mechoulam, K. Meir, E. Grad, E., R. Beeri, T. Pugatsch, E.Tarsish, C. Lotan. Cannabidiol, a non-psychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury. Am J Physiol Heart Circ Physiol. 293, H3602-H3607 (2007).
100. T.Aguado, A. Carracedo, B. Julien, G. Velasco, G. Milman, R. Mechoulam, L. Alvarez, M. Guzman, I. Galve- Roperh. Cannabinoids induce glioma stem-like cell differentiation and inhibit gliomagenesis. J. Biol. Chem. 282, 6854-6862 (2007).
101. A. Strougo et al. Modelling of the concentration-effect relationship of THC on central nervous system parameters and heart rate – insight into its mechanisms of action and a tool for clinical research and development of cannabinoids. J Psychopharmacol. vol. 22 no. 7 717-726 (2008).
102. Battista N et al. interplay between endocannabinoids steroids and cytokines in the control of human reproduction. J neuroendocrinal.20, supp 1 (2008).
103. Cohen et al. Cerebellar grey-matter deficits, cannabis use and first-episode schizophrenia in adolescents and young adults. Australian New Zealand J Psychiatry. 42, 357-368 (2008).
104. D. McHugh, C. Tanner, R. Mechoulam, R. G. Pertwee, R. A. Ross. Inhibition of human neutrophil chemotaxis by endogenous cannabinoids and phytocannabinoids: evidence for a site distinct from CB1 and CB2. Mol. Pharmacol. 73, 441-450 (2008).
105. L.Weiss, M.Zeira, S.Reich, S. Slavin, I. Raz, R.Mechoulam, R. Gallily. Cannabidiol arrests onset of autoimmune diabetes in NOD mice. Neuropharmacol. 54, 244-249 (2008).
106. Murat Yiicel et al. Regional Brain Abnormalities Associated with Long-term heavy Cannabis Use. Arch Gen Psychiatry.65, 694-701 (2008).
107. Wang Tongtong et al. Adverse effects of medical cannabinoids: a systematic review. CMAJ (Canadian Medical Association). Vol. 178 no. 13 (2008).
108. R G Pertwee; The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: A9-tetrahydrocannabinol, cannabidiol and A9-tetrahydrocannabivarin. Br J Pharmacol.; 153(2): 199-215. (2008)
109. Cooper ZD et al. Action of delta -9- tetra-hydro-Cannabinol in cannabis: relation to use, abuse, dependence. Int Rev Psychiatry. 21, 104-112 (2009).
110. D'Souza DC et al. Cannabis and psychosis/schizophrenia: human studies. Eur Arc Psych Clin Neurosci. 8, 117-123(2009).
111. Sewell RA, etal. The effect of cannabis compared with alcohol on driving. Am J Addict. 18, 185-193 (2009).
112. Storr et al. Activation of cannabinoid 2 receptor (CB2) protects against experimental colitis. Inflam/bowel dis. 15, 1678-85 (2009).

113. Zimmermann U. S. Et al. Withdrawal phenomena and dependence syndrome after the consumption of 'Spice Gold'. Dtsh Artzebl Int 2009; 106: 464-67 (2009)

114. L. Zuurman, A. E. Ippel, E. Moin, J. M. A. van Gerven. Biomarkers for the effects of cannabis and THC in healthy Volunteers. Br J Clin Pharmacol. 67(1), 5-21. (2009)

115. Dehert M et al. Effects of cannabis use associated with age of onset of high risk symptoms for psychosis. Canad J of psychiatry. 55, 165-171 (2010).

116. Every-Palmer S. Warning: Legal synthetic cannabinoid-receptor agonists such as JWH-018 may precipitate psychosis in vulnerable individuals. Addiction, 105/10, 1859-1860 (2010).

117. Muller H. et al. The synthetic cannabinoid Spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes. Schizophr Res 2010; 118: 309-10 (2010).

118. Sadiye Amcaoglu Rieder, Ashok Chauhan, Ugra Singh, Mitzi Nagarkatti, and Prakash Nagarkatti*; Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. Immunobiology. Aug; 215(8): 598-605. (2010)

119. Naftali T. Treatment of Crohn's disease with cannabis an observational study. IMAJ. 13, 455-8 (2011).

120. Laura M. Borgelt, Kari L. Franson, Abraham M. Nussbaum, George S. Wang. The Pharmacologic and Clinical Effects of Medical Cannabis. Pharmacotherapy, 33(2):195-209 (2013).

121. T. Docimo, R. Consonni, I. Coraggio, and M. Mattana. Early Phenylpropanoid Biosynthetic Steps in Cannabis sativa: Link between Genes and Metabolites. Int J Mol Sci. 14(7): 13626-13644. (2013).

122. Arias F, Szerman N, Vega P, Mesias B, Basurte I, Morant C, Ochoa E, Poyo F, Babin F. Abuse or dependence on cannabis and other psychiatric disorders. Madrid study on dual pathology prevalence. Actas Esp Psiquiatr; 41(2):122-9. Epub (2013).

123. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The Pharmacologic and Clinical Effects of Medical Cannabis. Pharmacotherapy. 33(2), 195-209 (2013).

124. S. Vathi, S. Schimmenti. Endocannabinoid system: key regulatory enzymes and physio-pathological implications. Int. flipper e nuvola, http://flipper.diff.org/app/pathways/info/6112 (2014)

125. C. Itin, N.M. Azulay, Y. Ratz, S.Y. Superstein, I Shuemacher. Main side effects and interactions for the use of Medical Cannabis. The pharmaceutical society of Israel. January (2014)

126. C. Conrad. Cannabis Yields and Dosage. PO Box 21106, El Sobrante CA 94820 www.chrisconrad.com 510-275-931. Eighth updated edition (2015)

127. McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and A(9) - tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol. 172(3), 737-53. doi: 10.1111/bph.12944. (2015).

128. Fundacion CANNA website. The Endocannabinoid System. http://www.fundacion canna.es/en/endocannabinoid-system. Figures and citations were taken on June 18, (2015).

129. Yafa Tsubary, Israel Anti-Drug Authority. Synthetic Cannabis. http://www.antidrugs.gov.il/pages/1624.aspx

130. Nora D. Volkow, MD; JamesM. Swanson, PhD; A. Eden Evins, MD; Lynn E. DeLisi, MD; Madeline H. Meier, PhD; Raul Gonzalez, PhD; Michael A. P. Bloomfield, MRCPsych; H. Valerie Curran, PhD; Ruben Baler, PhD; Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. JAMA Psychiatry. doi:10.1001/jamapsychiatry.2015.3278 Published online February 3, (2016).

131. Carlos Blanco; Deborah S. Hasin; Melanie M. Wall; Ludwing Florez-Salamanca; Nicolas Hoertel; Shuai Wang; Bradley T. Kerridge; Mark Olfson; Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence From a US National Longitudinal Study. doi:10.1001/jamapsychiatry.2015.3229 JAMA Psychiatry. Published online February 17, (2016).

132. An American postgraduate medical study group, TheAnswerPage, has kindly allowed us to use their summaries on medical cannabis in specific diseases. These summaries include a general background and specific use and doses.

Israeli physicians interested in any of these summaries can receive copies by applying to TheAnswerPage through the Cannabis Unit at the Ministry of Health.