

## Approved indications for cannabis-based preparations

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Received 15 September 2021; Accepted 30 September 2021

### ABSTRACT

In traditional medicine, cannabis-based preparations have been used for a thousand of years for treatment of various diseases. The clinical use of cannabis-based preparations is limited due to legal and ethical reasons, and therefore there is a lack of data for the therapeutic potential of cannabinoids. By searching the FDA site, we identified three approved cannabis-based medicines for treatment of anorexia, nausea and vomiting caused by chemotherapy and two particularly severe forms of child epilepsy (Lennox-Gastaut and Dravet's syndrome). By searching the EMA site, we identify only one cannabis-based medicine authorized for use in the European Union – Epidyolex. But, EMA recognized possible positive therapeutic outcome of three cannabinoids (cannabidiol, cannabitol-9-carboxylic acid (resunab and lenabasum) and cannabidivarin) for which by the European Commission was granted status "Orphan designation" for 12 different indications: treatment of: tuberous sclerosis, West syndrome, Drave's syndrome, Lennox-Gastaut's syndrome, graft-versus-host disease, perinatal asphyxia, glioma, systemic sclerosis, cystic fibrosis, dermatomyositis, Rett syndrome and fragile X syndrome. The adverse effects of cannabis preparations are primarily due to THC, which has psychotropic effects and used in higher doses can cause certain central nervous system (CNS) disorders. Chronic use of THC may cause an excessive hyperemetic syndrome, which is always weaker than the side effects that cause chemotherapy. For many patients who do not respond adequate to conventional therapy, cannabis preparations are the only possible option even if cannabinoids are less potent than conventional therapy.

**KEYWORDS:** Approved cannabis-based medicines, Tetrahydrocannabinol (THC), Cannabidiol (CBD), Cannabitol (CBN), Cannabidivarin

### I. INTRODUCTION

About 30 million people living in the European Union (EU) suffer from a rare disease. For the patients who suffer from a debilitating rare disease, finding of effective treatment is a huge challenge. The European Medicines Agency (EMA) plays a central role in facilitating the development and authorization of medicines for rare diseases [1].

The Committee for Orphan Medicinal Products (COMP) is the EMA committee established in 2000 in line with Regulation (EC) No 141/2000, responsible for evaluating applications and recommending orphan designation of medicines for rare diseases [1].

Cannabinoids are the active substances derived from cannabis plant, usually cannabis flowers. Cannabis preparations are widespread products used to treat various painful and pathogenic conditions [2]. Due to legal and ethical reasons, the clinical use of cannabis preparations in many countries is limited, so there is a lack of evidence-based medicine with which the benefit of therapy can be reiterated [3]. But the use of these preparations has been increasing in the last ten years. So, there is a huge evidence that cannabinoids can help in treatment of different pathogenic conditions, but not enough yet for finishing the process of marketing authorization. That is the reason why COMP for these products gave opinion to grant an orphan designation for treatment of some life-threatening or very serious rare diseases for which there was no alternative therapy available in that moment or patients have not responded adequately to it or for other reasons (adverse effects, allergies) patients are not able to receive approved therapy. The European Commission decides whether to grant an orphan designation for the medicine based on the COMP's opinion [1].

For the first time, a cannabis extract was approved for clinical use in Germany in 2011 for the

treatment of moderate to severe refractory spasticity in multiple sclerosis. Later, National Association of Statutory Health Insurance Physicians, and the Drug Commission of the German Medical Association issued the following statement: “The benefit of treatment with cannabinoids for a number of medical indications has been shown in controlled trials in which predominantly standardized and/or synthetic cannabinoid preparations were used. The use of such preparations may therefore be reasonable for patients in whom conventional treatment does not achieve adequate relief of symptoms such as spasticity, pain, nausea, vomiting, or loss of appetite” [4].

## **II. APPROVED INDICATIONS FOR CANNABIS-BASED PREPARATIONS**

The purpose of this research was to identify all approved indications for cannabis-based preparations by the US Food and Drug Administration (FDA) and by the EMA.

The systematic review was made by searching using key words: cannabinoids, THC, CBD, CBN, cannabidiol, approved cannabis-based medicines and Randomized Clinical Trials (RCT).

Standard electronic literature search published on Medline / Pubmed, Embase, The Cochrane Controlled Trials Register, certain websites dedicated to cannabis and official websites of EMA and FDA was used.

### Approved indications for cannabis-based medicines by FDA [5]

According to the FDA, any product intended for use in the diagnosis, treatment, or prevention of a disease, is classified as a medicine. When approving a marketing authorization, the FDA considers the following essential information about the medicine: indications for what that medicine has been shown that is effective, information on whether the medicine has been tested in children, which side effects have been reported, preclinical and clinical data on the proposed use of the medicine.

Three cannabis-based medicines are approved by FDA:

- 1) Nabilone (Cesamet<sup>®</sup>) capsules 1mg, manufacturer Valeant Pharmaceuticals International. Nabilone is a synthetic cannabinoid, an analogue of dronabinol (tetrahydrocannabinol -THC) and it is approved by FDA for 2 indications: treatment of chemotherapy-induced nausea and vomiting in patients who do not respond adequately to conventional antiemetics and as an adjunctive analgesic for neuropathic pain [6]. Although its antiemetic action is not yet fully understood, it is apparent that there are several points in the control systems of the body at which nabilone could block the emetic mechanism. Numerous trials and case studies have demonstrated effectiveness for relieving chronic pain in multiple sclerosis [7].
- 2) Dronabinol (Marinol<sup>®</sup>) capsules of 2.5mg, 5mg and 10mg, manufacturer Solvay Pharmaceuticals. Dronabinol is a synthetic THC and it is approved by FDA for 2 indications: treatment of chemotherapy-induced nausea and vomiting in patients who do not respond to conventional antiemetics and for the treatment of anorexia or weight loss in people associated with syndrome of Acquired Immune Deficiency (AIDS) [8].
- 3) EPIDYOLEX (cannabidiol - CBD) solution for oral use 100mg / ml, manufacturer GW Pharmaceuticals. CBD in Epidyolex is a purified liquid cannabis extract approved by the FDA in June 2018 as adjunctive therapy in conjunction with clobazam for the treatment of two particularly severe forms of childhood epilepsy: Lennox-Gastaut and Dravet's syndrome for patients 2 years of age and older [9]. The precise mechanisms by which cannabidiol exerts its anticonvulsant effects in humans are unknown. But it is known that cannabidiol does not exert its anticonvulsant effect through interaction with cannabinoid receptors. Cannabidiol reduces neuronal hyper-excitability through modulation of intracellular calcium via G protein-coupled receptor 55 (GPR55) and transient receptor potential vanilloid 1 (TRPV-1) channels, as well as modulation of adenosine-mediated signaling through inhibition of adenosine cellular uptake via the equilibrative nucleoside transporter 1 (ENT-1) [9].

### Approved indications for cannabis-based medicines by EMA [1]

By the EMA there is only one cannabis-based medicine authorized for use in the European Union – Epidyolex. Same as FDA, this medicine is approved as an ‘orphan medicine’ to be used in addition to clobazam, to treat patients from two years of age with Lennox-Gastaut or Dravet syndrome (rare types of epilepsy that begin in childhood). It is also approved by EMA to be used for treatment of tuberous sclerosis.

By searching the EMA site, we identified 3 approved cannabinoids (cannabidiol, cannabitol-9-carboxylic acid (resunab and lenabasum) and cannabidivarin) with status "Orphan designation" for 12 different indications for treatment of: tuberous sclerosis, West syndrome, Drave's syndrome, Lennox-Gastaut's syndrome, graft-versus-host disease, perinatal asphyxia, glioma, systemic sclerosis, cystic fibrosis, dermatomyositis, Rett syndrome and fragile X syndrome (see Table 1).

It is important to emphasize that the status of “orphan designation” is not the same with marketing authorization. To qualify medicine as orphan designation, the medicine must meet a number of criteria: it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically

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debilitating, the prevalence of the condition must not be more than 5 in 10,000, no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.

These cannabis-based preparations are expected to work by three different mechanisms:

- Cannabidiol (CBD) act on targets that play a role in the movement of calcium in the cells, which in turn is important for the transmission of electrical signals in some nerve cells. Altering the movement of calcium is expected to reduce or prevent the seizures. Cannabidiol is also thought to act on adenosine, a chemical messenger in the brain that plays an important role in suppressing seizures
- Cannabinol-9-carboxylic acid (resunab and lenabasum) attaches to receptors called cannabinoid type 2 receptors (CB2) found on immune cells. By attaching to these receptors, it is expected to control the body's immune system better reducing inflammation and so improving symptoms of the condition
- Cannabidivarin works is not clearly understood. It is thought to help reduce inflammation and damage to glial cells (a type of brain cell that supports and protects nerve cells), to preserve the function of mitochondria (the energy producing components of cells), and to have an effect on the transmission of electrical signals in nerve cells

Active substance		Used for treatment of	Overview	Status “orphan designation” approved on
Cannabidiol (CBD)		Dravet syndrome	Severe myoclonic epilepsy of infancy (SMEI)	15 October 2014 EU/3/14/1339
		Perinatal asphyxia	Happens when babies are born without enough oxygen in their blood	28 July 2015 EU/3/15/1520
		Glioma (in combination with THC)	A type of brain tumor that affects the 'glial' cells	09 October 2015 EU/3/15/1564
		Graft vs host disease	Complication that can affect patients who have had allogeneic hematopoietic (blood) stem-cell transplantation to treat diseases of the blood such as leukemia	29 August 2016 EU/3/16/1718
		Lennox-Gastaut syndrome	Severe form of epilepsy that starts in childhood between 2 and 5 years of age	20 March 2017 EU/3/17/1855
		West syndrome	Epilepsy disorder in which young children have regular seizures (fits) called 'infantile spasms'	16 October 2017 EU/3/17/1920
		Tuberous sclerosis	Genetic disease that causes growth of benign tumors in different organs of the body (brain, lungs, heart, kidneys, skin and eyes)	17 January 2018 EU/3/17/1959
Cannabinol-9-carboxylic acid	also known as JBT-101 or resunab	Cystic fibrosis	Hereditary disease that affects the cells in the lungs, and the glands in the gut and pancreas, that secrete fluids	14 October 2016 EU/3/16/1736
		Systemic sclerosis (also known as scleroderma)	Complex disease in which the immune system is overactive, causing inflammation and excessive production of some proteins, particularly collagen	12 January 2017 EU/3/16/1808
	also known as lenabasum	Dermatomyositis	Inflammatory disease of the muscles and the skin which	26 October 2018 EU/3/18/2070

			causes muscle weakness and severe skin rash	
Cannabidivarin	Rett syndrome		genetic disease characterised by intellectual disability as well as by loss of speech and regression of acquired skills between 6 and 18 months of age	16 October 2017 EU/3/17/1921
	Fragile X syndrome		Inherited disease characterized by learning disability	22 February 2018 EU/3/18/1977

**Table 1.** Cannabinoids approved by EMA for treatment of rare diseases as “orphan designation” medicines

### III. DISCUSSION

Changes in laws in many countries to allow the legalization and use of cannabis for medical purposes are a sign that cannabis is becoming globally recognized and accepted among people as something that can help to improve their health. For these reasons, it is especially important for people to be informed about the possible therapeutic benefits, dosage and adverse effects associated with the use of cannabis-based preparations.

By the FDA three cannabis-based medicines are authorized for use[5]. By the EMA there is only one cannabis-based medicine authorized for use in the European Union – Epidyolex. But, EMA recognized possible positive therapeutic outcome of three cannabinoids (cannabidiol, cannabinol-9-carboxylic acid (resunab and lenabasum) and cannabidivarin) for which by the European Commission was granted status "Orphan designation" for 12 different indications[1].

Data conducted in one clinical study, support the medicinal potential of Cannabinol (CBN) in anti-cancer therapy and provides evidence that CBN inhibits proliferation and induces cell cycle arrest and apoptosis in glioblastoma, hepatocellular carcinoma, and breast cancer cells in a dose- and time-dependent manner [10].

Human clinical trials (randomized controlled trials and open-label trials) evaluating the efficacy of CBD as a therapeutic were identified for various medical conditions. There is clear evidence supporting the use of CBD for treatment of epilepsy. But, for other health conditions evidences are with general lack of data to draw definitive conclusions [11-12]. Lack of efficacy of CBD for relieving pain is also reported [13-17].

In a situation where we have sufficient evidence for the therapeutic potential of cannabis-based preparations for certain indications, monitoring the adverse effects of these preparations compared with the adverse effects of medicines used as conventional therapy for the treatment of same conditions is of great importance.

The side effects of cannabis-based preparations are primarily due to THC, which has psychotropic effects, so higher doses may cause certain disorders in CNS associated with abnormal psychomotor behavior, drowsiness, short-term memory impairment, and intoxication[18]. Chronic use of THC can cause excessive hyperemic syndrome characterized by cyclic vomiting, without any other recognizable cause. However, it should be kept in mind that these side effects are always less severe than the side effects of chemotherapy[19].

Literary data confirm that the therapeutic ratio between lethal and effective dose for cannabinoidosis 1000: 1, vs analgesics that have a therapeutic ratio of 20: 1 and antineoplastics that have a therapeutic ratio of 1.5:1. However, due to psychotropic effects, the total daily dose of THC should generally be limited to 30 mg/day or less, preferably in combination with CBD, to avoid psychoactive effects and the development of tolerance[20].

For all risk / benefit researchers using cannabis-based preparations, a special, simple, "online" scale of 25 questions was designed to determine the clinical benefit and side effects of cannabis use. The questions were divided into 5 groups, each of which has 5 questions. All questions in a particular group are either "positive" (ie best score is 4) or "negative" (ie best score is 0), with a total potential score between 0-100. The nature and design of the scale involves the use of internal logic to minimize the problems of automatic answering and giving contradictory answers to similar questions. A high score indicates a well-tolerated and effective product, while low results indicate significant side effects and / or a lack of positive clinical experience[21].

### IV. CONCLUSION

In traditional medicine, cannabis-based preparations have been used for a thousand of years for treatment of various diseases. By the FDA three cannabis-based medicines are authorized for use. EMA recognized possible positive therapeutic outcome of three cannabinoids that granted status "Orphan designation" for 12 different indications.

It is important to note that for many patients who do not respond appropriately to conventional therapy, cannabis-based preparations have a strong advantage even in the case where cannabinoids may be less potent

than conventional therapy. For these patients, cannabis-based preparations are the only possible option, especially for the patients who suffer from a debilitating rare disease. Changes in laws in many countries to allow the legalization and use of cannabis for medical purposes are a sign that cannabis is becoming globally recognized and accepted among people as something that can help improve their health.

#### ACKNOWLEDGEMENTS

All authors contributed toward data analysis, drafting, and critically revising the paper

**Disclosure statement:** The authors report no conflicts of interest in this work.

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