Approved indications for Cannabinoids

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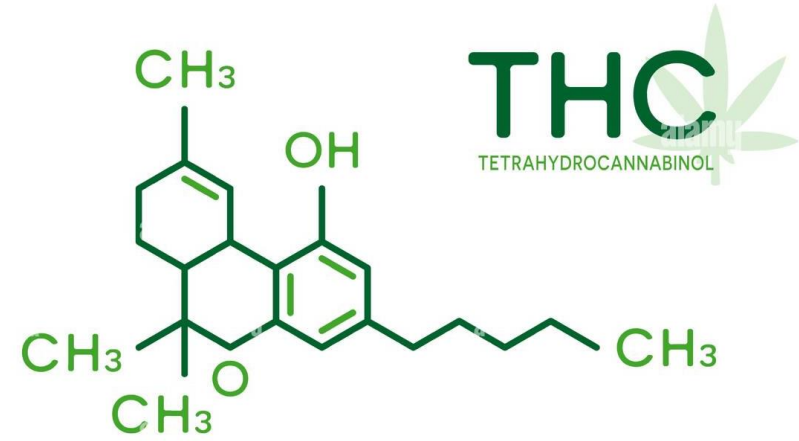
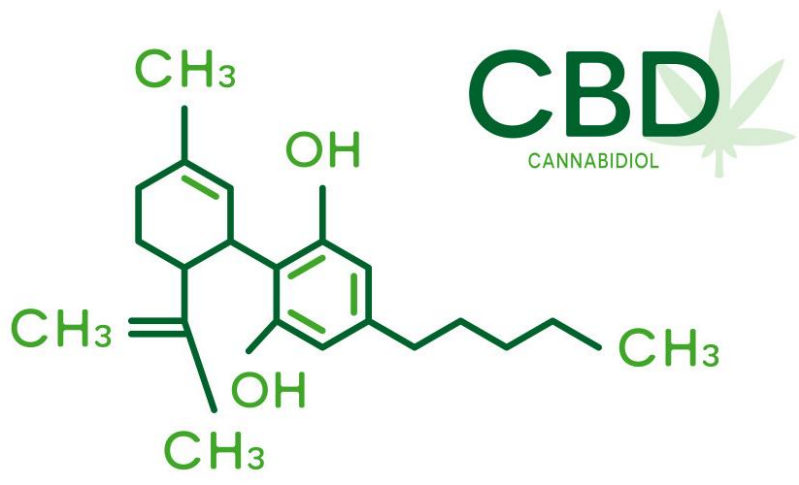
Cannabinoids





Cannabis plant

Cannabinoids are the active substances derived from cannabis plant, usually cannabis flowers

Medicine based evidence for use of cannabinoids

- Cannabis preparations are widespread products used to treat various painful and pathogenic conditions
- Due to legal and ethical reasons, the clinical use of cannabis preparations in many countries is limited
- Lack of evidence-based medicine with which the benefit of therapy can be reiterated

Medicine based evidence for use of cannabinoids

- The use of these preparations has been increasing in the last ten years
- There is a huge evidence that cannabinoids can help in treatment of different pathogenic conditions
- Not enough yet for finishing the process of marketing authorization

Mechanism of action of Cannabinoids

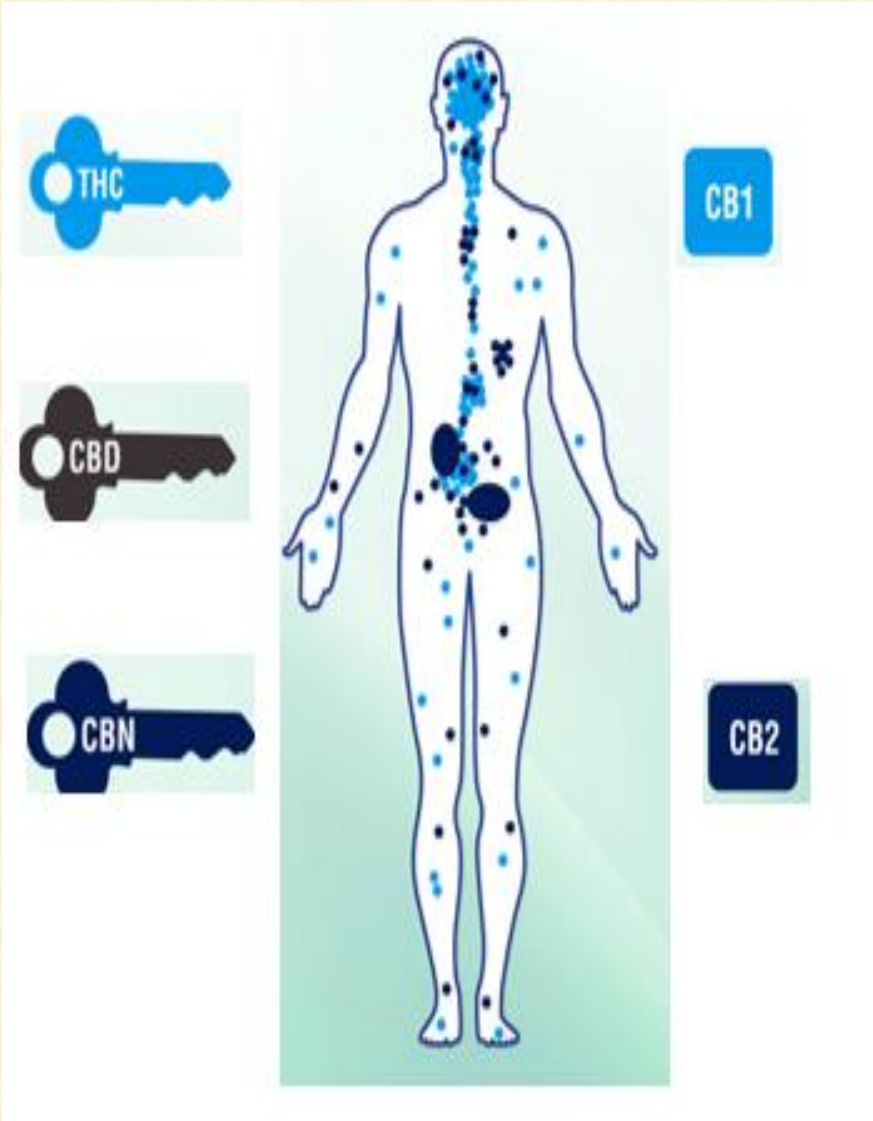
THE ENDOCANNABINOID SYSTEM

The endocannabinoid system consists of three major parts:

- the signaling molecules (endocannabinoids)
- their receptors
- the enzymatic machinery that synthesizes and degrades endocannabinoids

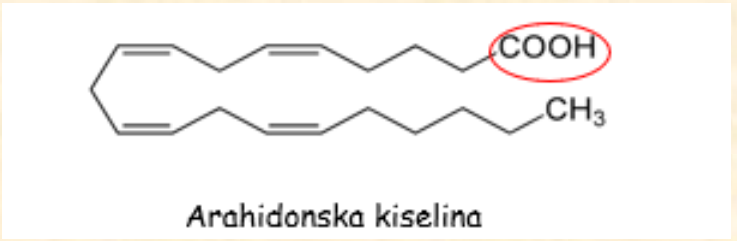
Endocannabinoids are recognized by two G-protein coupled receptors:

- CB1 - predominantly located in CNS (neurons)
  - ✓ Cortical areas & Limbic system – high conc.
  - ✓ Basal ganglia – high conc.
  - ✓ Cerebellum – high conc.
  - ✓ Hypothalamus – moderate conc.
- CB2 - peripherally located
  - ✓ Tonsils – high conc.
  - ✓ Thymus – high conc.
  - ✓ Spleen – high conc.
  - ✓ Blood cells & mast cells – moderate conc.



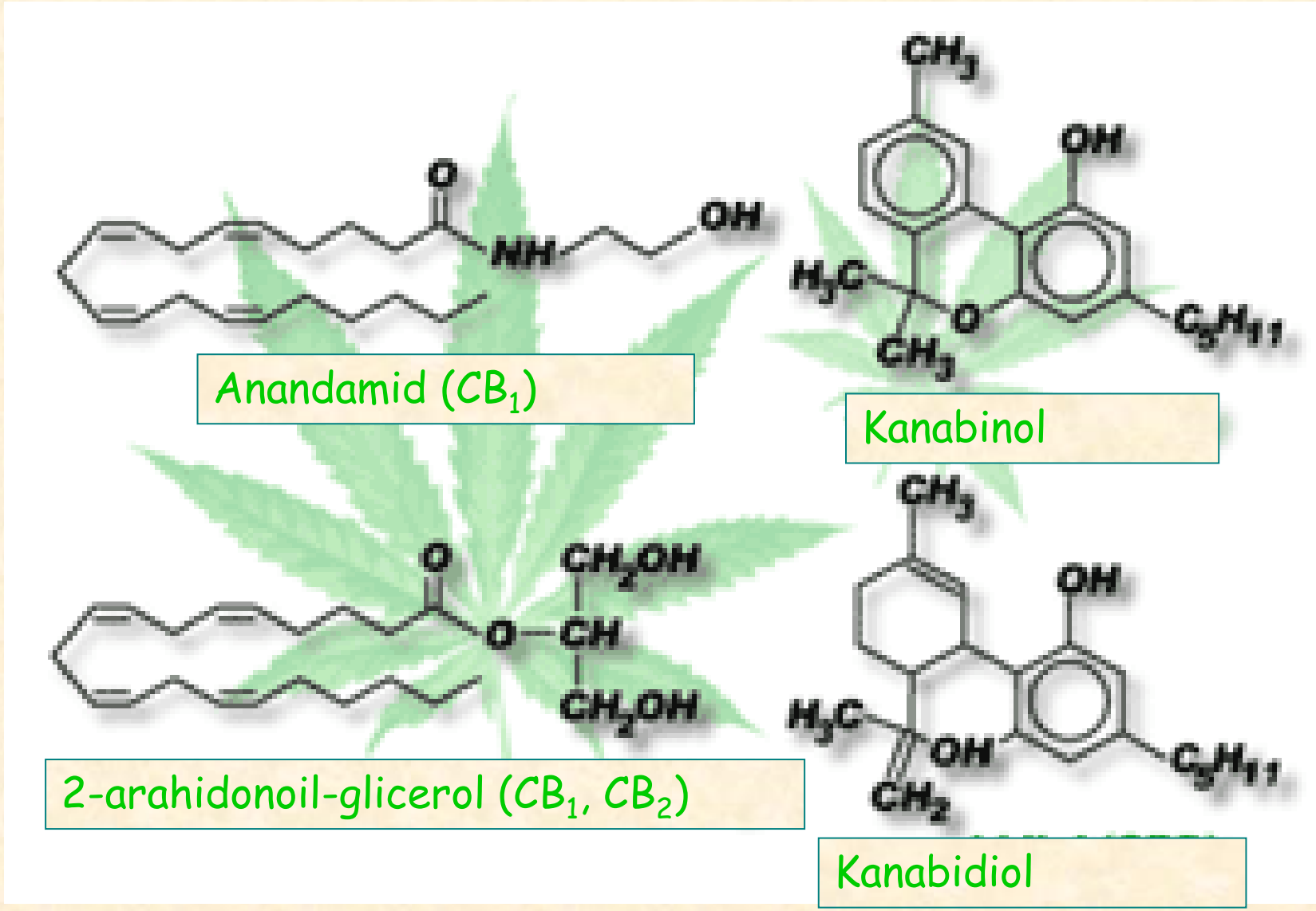
THE ENDOCANNABINOID SYSTEM

- **The first discovered and best studied endocannabinoids**



synthesized from arachidonic acid

Endogenous (left) vs exogenous (right) ligands for cannabinoid receptors



- Phytocannabinoids are completely different (chemically, structurally) than endocannabinoids
- They bind to the same receptors and cause the same effects

Approved indication for Cannabinoids by FDA

FDA approved cannabis based preparations

- **Nabilone (Cesamet®) capsules 1mg (synthetic cannabinoid, an analogue of dronabinol)**
- **Manufacturer Valeant Pharmaceuticals International.**
- **Approved by FDA for 2 indications:**
  - ✓ **treatment of chemotherapy-induced nausea and vomiting in patients who do not respond adequately to conventional antiemetics**
  - ✓ **as an adjunctive analgesic for neuropathic pain**
- **Numerous trials and case studies have demonstrated effectiveness for relieving chronic pain in multiple sclerosis**

FDA approved cannabis based preparations

- **Dronabinol (Marinol®) capsules of 2.5mg, 5mg and 10mg (synthetic THC)**
- **Manufacturer Solvay Pharmaceuticals**
- **Approved by FDA for 2 indications:**
  - ✓ **treatment of chemotherapy-induced nausea and vomiting in patients who do not respond to conventional antiemetic**
  - ✓ **treatment of anorexia or weight loss in people associated with syndrome of Acquired Immune Deficiency (AIDS)**

PHCANN - cannabis based preparations

=

FDA approved cannabis based preparations

- **EPIDYOLEX (cannabidiol - CBD) solution for oral use 100mg / ml (nature origin)**
- **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**
  - ✓ **Dravet's syndrome for patients 2 years of age and older**

PHCANN - cannabis based preparations

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PHCANN - cannabis based preparations

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What happens when we stimulate CB_1 receptors?

What happens when we stimulate CB_1 receptors?

↓↓ Release of 5-HT @ CTZ

↓

↓↓ Stimulation of 5-HT_3 receptor

↓

Nausea
Vomiting

↓↓ release of Leptin @ Hypothalamus

↓

↑↑Appetite

↓

Anorexia
Cachexia

INDICATIONS

- **Neuromuscular disease – Spasticity – Why?!** ↓↓ **Ach, Glutamate, GABA, Glycine**
- **Pain (Analgesics) ... Why?!**

Cannabinoids

- ↓↓**Release of neuropeptide @ spinal core** → ↓↓**pain**
- **Activate TRRV$_1$ receptor** → ↓↓**pain**

↑

Capsaicin

- **Glaucoma**
- **Asthma**

Approved indication for Cannabinoids by EMA

EMA approved cannabis based preparations

- only one cannabis-based medicine authorized for use in the European Union – Epidyolex
- 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
- It is also approved by EMA to be used for treatment of tuberous sclerosis.

Medicine based evidence for use of cannabinoids by EMA

- That is the reason why The Committee for Orphan Medicinal Products (COMP) for these preparations gave opinion to grant an orphan designation status for treatment of some life-threatening or very serious rare diseases for which:

there was no alternative therapy available in that moment

patients have not responded adequately to it

for other reasons like: adverse effects or allergic reactions to the conventional medicines, patients are not able to receive approved therapy

An orphan designation is not a marketing authorisation

- The European Commission decides whether to grant an orphan designation for the medicine based on the The Committee for Orphan Medicinal Products (COMP's) opinion

Medicine based evidence for use of cannabinoids by EMA

- identified 3 approved cannabinoids
  - ✓ Cannabidiol
  - ✓ cannabinol-9-carboxylic acid (resunab and lenabasum)
  - ✓ 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
  - ✓ fragile X syndrome

Key words:

Dronabinol
Cannabidiol
Cannabinoid
Cannabinol
Cannabidivarin

Medicine based evidence for use of cannabinoids by EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 November 2014
EMA/COMP/557465/2014
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation
Cannabidiol for the treatment of Dravet syndrome

On 15 October 2014, orphan designation (EU/3/14/1339) was granted by the European Commission to GW Pharma Ltd, United Kingdom, for cannabidiol for the treatment of Dravet syndrome.

An orphan designation is not a marketing authorisation

- **Dravet syndrome, also called severe myoclonic epilepsy of infancy (SMEI), is a severe form of epilepsy that affects children and adults. It is caused by defects in genes required for the proper function of brain cells**
- **At the time of designation, the medicine Diacomit (stiripentol) was authorised in the EU as add-on treatment for generalised tonic-clonic seizures**

Medicine based evidence for use of cannabinoids by EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 August 2015
EMA/COMP/427063/2015
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Cannabidiol for the treatment of perinatal asphyxia

On 28 July 2015, orphan designation (EU/3/15/1520) was granted by the European Commission to GW Pharma Ltd, United Kingdom, for cannabidiol for the treatment of perinatal asphyxia.

An orphan designation is not a marketing authorisation

- **Perinatal asphyxia happens when babies are born without enough oxygen in their blood**
- **At the time of orphan designation, there was no treatment for perinatal asphyxia authorised in the EU.**

Medicine based evidence for use of cannabinoids by EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 November 2015
EMA/COMP/607076/2015
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Dronabinol and cannabidiol for the treatment of glioma

On 9 October 2015, orphan designation (EU/3/15/1564) was granted by the European Commission to GW Research Ltd, United Kingdom, for dronabinol and cannabidiol for the treatment of glioma.

Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in November 2015 on request of the Sponsor.

EUROPEAN MEDICINES A
SCIENCE MEDICINES H

31 March 2016
EMA/COMP/72100/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan

Delta-9-tetrahydrocannabinol and cannabidiol fror
sativa L. plant for the treatment glioma

On 17 February 2016, orphan designation (EU/3/16/1621) was granted by the European Commission to GW Research Ltd, United Kingdom, for delta-9-tetrahydrocannabinol and cannabidiol from extracts of the ***Cannabis sativa*** L. plant for the treatment of glioma.

Last updated: 15 June 2023

Glioma is a type of brain tumour that affects the 'glial' cells (the cells that surround and support the nerve cells).

Medicine based evidence for use of cannabinoids by EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 May 2016
EMA/COMP/252372/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan

Cannabidiol for the prevention of graft-versus-host

On 28 April 2016, orphan designation (EU/3/16/1645) was granted by the European Commission to Richardson Associates Regulatory Affairs Ltd, UK, for cannabidiol for the prevention of graft-versus-host disease.

22 September 2016
EMA/COMP/505608/2016
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Cannabidiol for the treatment of graft-versus-host disease

On 29 August 2016, orphan designation (EU/3/16/1718) was granted by the European Commission to Richardson Associates Regulatory Affairs Ltd, United Kingdom, for cannabidiol for the treatment of graft-versus-host disease.

Graft-versus-host disease is a complication that can affect patients who have received allogeneic haematopoietic (blood) stem-cell transplantation to treat diseases of the blood such as leukaemia (a cancer of the white blood cells)

Medicine based evidence for use of cannabinoids by EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3 May 2017
EMA/143020/2017
Committee for Orphan Medicinal Products

Last updated: 14 June 2023

Public summary of opinion on orphan designation

Cannabidiol for the treatment of Lennox-Gastaut syndrome

On 20 March 2017, orphan designation (EU/3/17/1855) was granted by the European Commission to GW Research Ltd, United Kingdom, for cannabidiol for the treatment of Lennox-Gastaut syndrome.

An orphan designation is not a marketing authorisation

- **Lennox-Gastaut syndrome is a severe form of epilepsy that starts in childhood between 2 and 5 years of age**
- **At the time of designation, several epilepsy medicines were authorised in the EU for treatment of seizures in children with Lennox-Gastaut syndrome, including clonazepam, felbamate, lamotrigine, rufinamide, and topiramate**

Medicine based evidence for use of cannabinoids by EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 January 2018
EMA/625004/2017

Last updated: 15 June 2023

Public summary of opinion on orphan designation

Cannabidiol for the treatment of West syndrome

On 16 October 2017, orphan designation (EU/3/17/1920) was granted by the European Commission to GW Research Ltd, United Kingdom, for cannabidiol for the treatment of West syndrome.

An orphan designation is not a marketing authorisation

West syndrome is an epilepsy disorder in which young children have regular seizures (fits) called 'infantile spasms'

Medicine based evidence for use of cannabinoids by EMA

An orphan designation is not a marketing authorisation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 March 2018
EMA/5287/2018

Public summary of opinion on orphan designation

Cannabidiol for the treatment of tuberous sclerosis

On 17 January 2018, orphan designation (EU/3/17/1959) was granted by the European Commission to GW Research Ltd, United Kingdom, for cannabidiol for the treatment of tuberous sclerosis.

- **Tuberous sclerosis is a genetic disease that causes growth of benign (non-cancerous) tumours in different organs of the body, including the brain, lungs, heart, kidneys, skin and eyes**
- **At the time of designation, the medicine Votubia (everolimus) was authorised in the EU for the treatment of certain tumours caused by tuberous sclerosis**

Medicine based evidence for use of cannabinoids by EMA

EU/3/21/2522 - orphan designation for treatment of complex regional pain syndrome

Cannabidiol
Dronabinol

Orphan | Human

Overview

This medicine was designated as an orphan medicine for the treatment of complex regional pain syndrome in the European Union on 12 November 2021.

Key facts

Active substance	• Cannabidiol • Dronabinol
Intended use	Treatment of complex regional pain syndrome
Orphan designation status	Positive
EU designation number	EU/3/21/2522
Date of designation	12/11/2021

Medicine based evidence for use of cannabinoids by EMA

EU/3/22/2583 - orphan designation for treatment of fragile X syndrome (FXS)

Cannabidiol

Orphan Human

Overview

This medicine was designated as an orphan medicine for the treatment of fragile X syndrome (FXS) in the European Union on 24 February 2022.

Medicine based evidence for use of cannabinoids by EMA

EU/3/22/2609 - orphan designation for treatment of epidermolysis bullosa

Cannabidiol

Orphan Human

Overview

This medicine was designated as an orphan medicine for the treatment of epidermolysis bullosa in the European Union on 16 May 2022.

Medicine based evidence for use of cannabinoids by EMA

EU/3/22/2718 - orphan designation for treatment of 22q11.2 deletion syndrome

Cannabidiol

Orphan Human

Overview

This medicine was designated as an orphan medicine for the treatment of 22q11.2 deletion syndrome in the European Union on 11 November 2022.

Medicine based evidence for use of cannabinoids by EMA

EU/3/22/2600 - orphan designation for treatment of epilepsy with myoclonic-atonic seizures

Cannabidiol

Orphan Human

Overview

This medicine was designated as an orphan medicine for the treatment of epilepsy with myoclonic-atonic seizures in the European Union on 13 April 2022.

Medicine based evidence for use of cannabinoids by EMA

EU/3/23/2800 - orphan designation for treatment of Leigh syndrome

Cannabidiol

Orphan Human

Overview

This medicine was designated as an orphan medicine for the treatment of Leigh syndrome in the European Union on 25 July 2023.

Leigh syndrome is a severe neurological disorder that usually becomes apparent in the first year of life. This condition is characterized by progressive loss of mental and movement abilities (psychomotor regression) and typically results in death within two to three years, usually due to respiratory failure

Active substance		Used for treatment of	Overview	Status “orphan designation” approved on
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 causes muscle weakness and severe skin rash	26 October 2018 EU/3/18/2070
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

Approved cannabis based preparations in EU

Approved in Germany, Italy, Denmark, Sweden, Austria and Czech Republic

- first medicine in the world that is based on natural extracts of cannabis
- contains THC and CBD (2.7mg THC + 2.5mg CBD/ml)
- is on the market in Germany, Austria, England, Denmark, Canada and Switzerland - it is registered with the MRP procedure
- intended for the treatment of spasticity and relief of neuropathic pain in patients with multiple sclerosis

Medicine based evidence for use of cannabinoids by EMA

SATIVEX

- **Sativex® oral spray – manufacturer GW Pharmaceuticals from England**

  - ✓ **Approved clinical trial P/0290/2012) for spasticity**
  - ✓ **Approved pediatric investigation plan (EMEA-000181-PIP01-08-M06) for neurology**
  - ✓ **Approved pediatric investigation plan (EMEA-000181-PIP02-13-M01) for pain**

SAFETY

Cannabinoids do NOT cause:

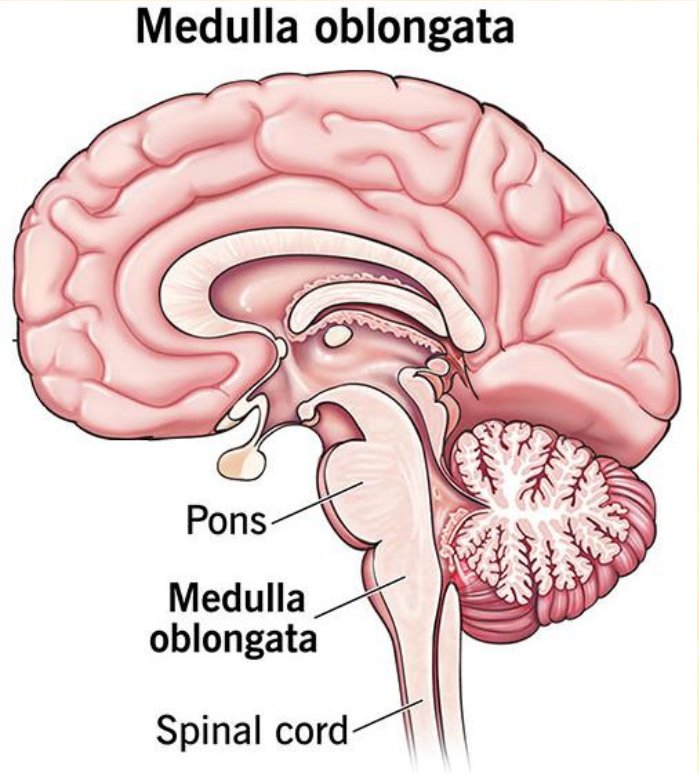
- ✓ **Cardia suppression &**
- ✓ **Respiratory suppression**

WHY NOT ?!

Because there are NO CB receptors @ the medulla oblongata

Medulla has 4 centers

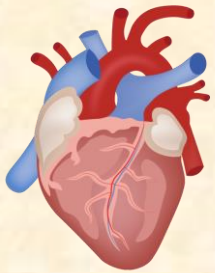
- ✓ **KVS**
- ✓ **Respiratory**
- ✓ **Swallowing**
- ✓ **Womiting**



SIDE EFFECTS

Cannabinoids

In patients with



BP = Dizziness
Reflex tachycardia
Palpitations

Patients who are

Euphoria
Confusion

In patients with

Can precipitate or aggrevates psychosis
Paranoia
Hallucinations

Pharmacology

- **Synergy: 1+1=3 e.g. Penicillin + Aminoglycosides**
- **Additive: 1+1=2 e.g. Ciprofloxacin + Metronidazol (good)**
  Loop diuretic 9furosemide) + Aminoglycosides (ototoxicity)
- **Antagonism: 1+1=0 e.g. Penicillin + Tertacycline**

BAD ADDITIVES

Cannabinoids + Opioids =
Cannabinoids + Alcohol =
} Additive CNS depression

Cannabinoids + ANTI-depressant (TCAs) =
Cannabinoids + ANTI-psychotic =
Cannabinoids + ANTI-muscarinic =
Cannabinoids + Amphetamines =
} Additive hearth & blood (on vessel) toxicity

Cannabinoids + Beta-blockers = Antagonism = ↑↑ Risk of IHD

SAFETY

CANNABINOIDS CAN BE SAFELY COMBINED WITH ALL OTHER MEDICINES AS AN “ADD ON” THERAPY

Thank you for your attention

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