# Summary of Risk Management Plan for Epidyolex® (cannabidiol)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Epidyolex is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.
Please note that the reference document which is valid and relevant for the effective and safe use of Epidyolex in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

DRAC AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Epidyolex.

**Summary of Risk Managment Plan for Epidyolex (cannabidiol)**

This is a summary of a risk management plan (RMP) for Epidyolex. The RMP details important risks of Epidyolex, risk minimisation measures, and how more information will be obtained about Epidyolex's risks and uncertainties (missing information).

Epidyolex's Information for healthcare professionals (summary of product characteristics / SmPC) and its Patient Information (package leaflet) give essential information to healthcare professionals and patients on how Epidyolex should be used.

This summary of the RMP for Epidyolex should be read in the context of all this information including the assessment report of evaluation and its plain-language summary all of which are part of the Swiss Public Assessment Report (Swiss PAR).

## I. The medicine and what it is used for

Epidyolex is indicated for the adjunctive therapy of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 2 years of age and older.

It contains CBD as the active substance and it is given as an oral solution (CBD-OS).

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

The important risks of Epidyolex, together with measures to minimise such risks and the proposed studies for learning more about Epidyolex's risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

If important information that may affect the safe use of Epidyolex is not yet available, it is listed under 'missing information' below.

## II.A List of important risks and missing information

Important risks of Epidyolex are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Epidyolex. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

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| **Important identified risks** | • Hepatocellular injury<br>• Somnolence and sedation<br>• Lethargy<br>• Pneumonia<br>• Rash hypersensitivity reactions |
| **Important potential risks** | • Suicidality (class effect)<br>• Seizure worsening<br>• Aggression<br>• Euphoria<br>• Impact on cognitive development<br>• Urinary retention |
| **Missing information** | • Exposure during pregnancy and lactation<br>• Long-term safety |

## II.B Summary of important risks

| **Important Identified Risk 1: Hepatocellular injury** | |
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| Evidence for linking the risk to the medicine | Clinical trial results have shown that CBD-OS is associated with dose-related alanine aminotransferase (ALT) elevations in a subset of patients. Aspartate aminotransferase (AST) elevations have also been observed, but to a lesser extent than ALT.<br><br>No severe liver injury has been observed.<br><br>However as elevated ALT and AST can be the first sign of a drug-induced liver injury (DILI) this would affect how CBD-OS may be used in a patient. |
| Risk factors and risk groups | Elevations in liver enzymes called transaminases (such as ALT and AST) appear to be more frequent in patients taking higher doses of CBD-OS.<br><br>Patients who are also using valproate (VPA), a commonly used drug in epilepsy, were at an increased risk of developing elevated transaminases during treatment.<br><br>Patients with higher levels of ALT at the beginning of treatment were at an increased risk developing elevated transaminases.<br><br>The majority of elevations in transaminases occurred within the first 60 days of commencing CBD-OS. Some patients had elevations after this time and therefore periodic monitoring is recommended. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section 'Contraindications'<br>Information for Professionals section 'Warnings and precautions'<br>Information for Professionals section: 'Undesirable effects'<br><br>Package Leaflet<br><br>Available by prescription only |
| Additional pharmacovigilance activities | Specific detailed adverse reaction follow-up for significant liver abnormality reports.<br><br>Post-marketing cohort study PASS GWEP21042.<br><br>Long-term Safety Study to Assess the Potential for Chronic Liver Injury GWEP19022. |

| **Important Identified Risk 2: Somnolence and Sedation** | |
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| Evidence for linking the risk to the medicine | In clinical trials conducted in patients with DS, LGS or TSC, somnolence was a common AE, and was consistently more frequent in patients treated with CBD-OS compared with placebo.<br><br>Sedation occurred less frequently than somnolence, but is a medically similar event. For both events, some were serious or led to discontinuation and also occurred in both the long and short-term trials. |
| Risk factors and risk groups | Patients most often first reported somnolence by their second week of treatment with CBD-OS. Sedation was reported at a much lower rate than somnolence but again the greatest number of events were reported within the first 2 weeks of treatment.<br><br>The incidence of somnolence or sedation is considered to be dose-related.<br><br>The incidence of somnolence or sedation was higher in patients taking CLB alongside CBD-OS, compared with those who were not. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section 'Warnings and precautions'<br>Information for Professionals section: 'Undesirable effects'<br><br>Package Leaflet<br><br>Available by prescription only |

| **Important Identified Risk 3: Lethargy** | |
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| Evidence for linking the risk to the medicine | In clinical trials conducted in patients with DS, LGS or TSC, lethargy was consistently more frequent in patients treated with CBD-OS compared with placebo.<br><br>Lethargy events were considered dose related. Some events were serious or led to discontinuation and also occurred in both the long and short-term trials. |
| Risk factors and risk groups | Most events of lethargy were reported within the first 2 weeks of treatment with CBD-OS.<br>The incidence of lethargy is considered to be dose-related.<br>The incidence of lethargy was higher in patients taking CLB alongside CBD-OS, compared with those who were not. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section: 'Undesirable effects'<br><br>Package Leaflet<br><br>Available by prescription only |

| **Important Identified Risk 4: Pneumonia** | |
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| Evidence for linking the risk to the medicine | Clinical trial results have shown that more patients receiving CBD-OS experienced pneumonia-type events compared with those who received placebo. It is noted that these events are common in the target patient populations and there was no increase in incidence with increasing CBD-OS dose. |
| Risk factors and risk groups | The incidence of pneumonia does not appear to be dose related.<br>More patients experienced pneumonia if they were also taking CLB, compared to if they were not taking CLB. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section: 'Undesirable effects'<br><br>Available by prescription only |
| Additional pharmacovigilance activities | Specific detailed adverse reaction follow-up for pneumonia reports. |

| Important Identified Risk 5: Rash Hypersensitivity Reactions | |
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| Evidence for linking the risk to the medicine | Clinical trial results have shown that more patients receiving CBD-OS experienced events of rash compared with those who received placebo. Healthy subjects as well as patients with epilepsy have experienced rash events. These rashes have not been associated with serious outcomes.<br>However, based on what has been observed, serious rashes may be seen in post-marketing. |
| Risk factors and risk groups | The occurrence of all rash events was approximately twice as high in epilepsy patients who were also taking CLB along with CBD-OS, in the pivotal trials. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section: 'Undesirable effects'<br><br>Available by prescription only |
| Additional pharmacovigilance activities | Specific detailed adverse reaction follow-up for rash hypersensitivity reactions. |

| Important Potential Risk 1: Suicidality (Class Effect) | |
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| Evidence for linking the risk to the medicine | Suicidality-related events have been reported more often in people with epilepsy, than in the general population.<br><br>Suicidality-related events have also been reported more often in people taking any epilepsy medication.<br><br>From the clinical development programme, there is no evidence that CBD-OS increases the risk of patients experiencing suicidality-related events.<br><br>However, taken together, suicidality has been added as an important potential risk for CBD-OS in the indications of DS, LGS and TSC. |
| Risk factors and risk groups | Having epilepsy and using antiepileptic drugs (AEDs) means that the target population already have risk factors for developing suicidality-related events.<br>From the clinical trials there is no evidence that CBD-OS increases the risk of patients experiencing suicidality-related events. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section 'Warnings and precautions'<br><br>Package Leaflet<br><br>Available by prescription only |

| **Important Potential Risk 2: Seizure Worsening** | |
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| Evidence for linking the risk to the medicine | Based on seizure count data in the LGS trials, some patients receiving 20 mg/kg/day CBD-OS, in the absence of CLB were more likely to experience a ≥ 25% increase in primary seizure frequency, compared to those receiving placebo. This was not the case in the 10mg/kg/day CBD-OS groups. This did not occur in the DS or TSC trials.<br><br>Based on AE reporting, there was no difference in the frequency of seizure worsening type events between patients receiving CBD-OS and placebo.<br><br>Seizure worsening can occur when patients do not respond to an AED, particularly in severe, difficult-to-treat epilepsies such as DS, LGS or TSC. It is also possible that an AED may worsen certain seizure types.<br><br>Taken together, seizure worsening has been considered as an important potential risk. |
| Risk factors and risk groups | In the LGS trials, in the absence of CLB, patients taking 20 mg/kg/day CBD-OS were more likely to experience seizure worsening (≥ 25% increase from the number of seizures experienced prior to starting CBD-OS) than those taking placebo. In such patients taking concomitant CLB, the opposite trend was seen. Seizure worsening ≥ 25% was not seen in patients on 10mg/kg/day CBD-OS as compared to placebo.<br><br>Patients with a greater number of seizures prior to starting CBD-OS tended to be more likely to experience a ≥ 25% increase in the number of seizures on treatment with CBD-OS and may be at greater risk.<br><br>Patients with DS and TSC appear to have less risk as in the DS and TSC trials, the frequency of patients with ≥ 25% seizure increases was no greater with CBD-OS treatment groups, compared with placebo. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section ‘Dosage/Administration’<br>Information for Professionals section ‘Warnings and precautions’<br><br>Available by prescription only |

| **Important Potential Risk 3: Aggression** | |
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| Evidence for linking the risk to the medicine | Clinical trial results have shown that more patients receiving CBD-OS experienced aggression compared with those who received placebo. Most events of aggression were mild or moderate in intensity. There have been isolated individual reports of aggression which suggest that aggression-type events could potentially result in important outcomes. There is already a risk of patients with epilepsy such as DS, LGS and TSC to have behaviour problems such as aggression. For these reasons, aggression is an important potential risk. |
| Risk factors and risk groups | No clear risk factors or risk groups for aggression have been identified. Aggression is a comorbidity in the target population. Although not data-driven, a history of aggression and/or behavior problems would likely confer an increased risk of aggression on CBD-OS. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section: 'Undesirable effects'<br><br>Available by prescription only |

| **Important Potential Risk 4: Euphoria** | |
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| Evidence for linking the risk to the medicine | Clinical trials in DS, LGS and TSC patients suggest that the presence of euphoria-related events with CBD-OS was minimal.<br><br>More patients receiving CBD-OS compared with those who received placebo experienced euphoric mood during a Phase 1 study in recreational polydrug users. All events were reported as mild in intensity and none were serious AEs. However, in this study CBD-OS was not "liked" by the users of CBD-OS as much as other drugs with known abuse potential. |
| Risk factors and risk groups | No clear risk factors or risk groups have been identified in the target patient population. It is possible that the euphoria events seen in a study in polydrug abusers were only seen due to the nature of these patients. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section 'Properties/Effects - further information - abuse'<br><br>Available by prescription only |

| **Important Potential Risk 5: Impact on cognitive development** | |
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| Evidence for linking the risk to the medicine | In the clinical trials, the available data makes the assessment of a possible decrease in cognitive function impossible. Some adverse event reports have been received that may potentially indicate a change in some aspects of cognitive function, although patients with DS, LGS or TSC often have impaired cognitive function. It should also be noted that CBD-OS is an anti-epileptic drug, and reduction of seizure may help improve cognitive function.<br><br>However, taken together, a possible decrease in cognitive function has been added as an important potential risk for CBD-OS. |
| Risk factors and risk groups | No clear risk factors or risk groups for a negative impact on cognitive development have been identified.<br><br>Patients with a higher numbers of seizures and those experiencing somnolence and/or sedation may be at a higher risk. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Available by prescription only |
| Additional pharmacovigilance activities | Post-marketing cohort study PASS GWEP21042 |

| **Important Potential Risk 6: Urinary retention** | |
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| Evidence for linking the risk to the medicine | Clinical trial results have shown that more patients receiving CBD-OS experienced urinary retention compared with those who received placebo. |
| Risk factors and risk groups | Adverse events are likely linked to the complex medical history and physical characteristics of the population in which CBD is being administered, although it is noted that the occurrence of urinary symptoms occurred predominantly in CBD-OS patients administering 20mg/kg/day. |
| Risk minimisation measures | Routine Risk Minimisation:<br><br>Available by prescription only |

| Missing Information 1: Exposure During Pregnancy and Lactation | |
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| Risk minimisation measures | Routine Risk Minimisation:<br><br>Information for Professionals section 'Pregnancy, Lactation'<br><br>Available by prescription only |
| Additional pharmacovigilance activities | Participation in Antiepileptic Drug Pregnancy Registries including:<br><br>European and International Registry of Antiepileptic Drugs and Pregnancy<br><br>and<br><br>North American Antiepileptic Drug Pregnancy Registry |

| Missing Information 2: Long-term Safety | |
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| Risk minimisation measures | Routine Risk Minimisation:<br><br>Available by prescription only |
| Additional pharmacovigilance activities | Post-marketing cohort study PASS GWEP21042. |

## II.C Post-authorisation development plan

### II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Epidyolex.

### II.C.2 Other studies in post-authorisation development plan

**European and North American Antiepileptic Pregnancy Registries**
Purpose of the studies:
These registries will be used to collect data on the use of the product in pregnancy and lactation.

**Prospective, Observational Cohort Study to Assess Long-term Safety in Patients Prescribed Epidyolex with a Focus on Drug-induced Liver Injury (DILI) – PASS – GWEP21042**
Purpose of the study:
Evaluate the long-term safety profile of Epidyolex when used under conditions of routine clinical care. To assess drug-induced liver injury (DILI) and adverse effects on cognitive development/behaviour.

**Long-term Safety Study to Assess the Potential for Chronic Liver Injury in Participants Treated with Epidiolex (Cannabidiol) Oral Solution – GWEP19022**
Purpose of the study:
To assess the potential for chronic liver injury and liver fibrosis, in participants undergoing long-term treatment with Epidiolex. The study will also monitor the overall long-term safety of Epidiolex.