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.

Jazz Pharmaceuticals Switzerland GmbH 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 the 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).

Important identified risks	• Hepatocellular injury
Important potential risks	• Suicidality (class effect) • Seizure worsening • Impact on cognitive development
Missing information	• Exposure during pregnancy and lactation • Long-term safety

II.B Summary of important risks

Important Identified Risk 1: Hepatocellular injury	
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. No severe liver injury has been observed. 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. Patients who are also using valproate (VPA), a commonly used drug in epilepsy, were at an increased risk of developing elevated transaminases during treatment. Patients with higher levels of ALT at the beginning of treatment were at an increased risk developing elevated transaminases. 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: Information for Professionals section 'Contraindications' Information for Professionals section 'Warnings and precautions' Information for Professionals section: 'Undesirable effects' Package Leaflet Available by prescription only
Additional pharmacovigilance activities	Specific detailed adverse reaction follow-up for significant liver abnormality reports. Post-marketing cohort study PASS GWEP21042. Long-term Safety Study to Assess the Potential for Chronic Liver Injury GWEP19022.

Important Potential Risk 1: Suicidality (Class Effect)	
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. Suicidality-related events have also been reported more often in people taking any epilepsy medication. From the clinical development programme, there is no evidence that CBD-OS increases the risk of patients experiencing suicidality-related events. 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. 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: Information for Professionals section 'Warnings and precautions' Package Leaflet Available by prescription only

Important Potential Risk 2: Seizure Worsening	
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. Based on AE reporting, there was no difference in the frequency of seizure worsening type events between patients receiving CBD-OS and placebo. 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. 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. 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. 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.

Important Potential Risk 2: Seizure Worsening	
Risk minimisation measures	Routine Risk Minimisation: Information for Professionals section 'Dosage/Administration' Information for Professionals section 'Warnings and precautions' Available by prescription only

Important Potential Risk 3: Impact on cognitive development	
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. 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. 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: Available by prescription only
Additional pharmacovigilance activities	Post-marketing cohort study PASS GWEP21042

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

Missing Information 2: Long-term Safety	
Risk minimisation measures	Routine Risk Minimisation: Available by prescription only
Additional pharmacovigilance activities	Post-marketing cohort study PASS GWEP21042. Long-term Safety Study to Assess the Potential for Chronic Liver Injury GWEP19022.

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.