Summary of the Risk Management Plan (RMP)
for

MAVENCLAD®

Cladribine 10 mg, tablets

Marketing Authorization Number 66831

RMP Summary:	Version 3.0, dated 03 August 2022
Based on EU RMP:	Version 1.7, dated 22 October 2021 (DLP: 08 Oct 2020)

Marketing Authorisation Holder: Merck (Schweiz) AG, Zug

Disclaimer:
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 **Mavenclad** 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 **Mavenclad** in Switzerland is the "Arzneimittelinformation/Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Merck (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of **Mavenclad**.

Part VI: Summary of the Risk Management Plan

Summary of the Risk Management Plan for MAVENCLAD (cladribine)

This is a summary of the risk management plan (RMP) for MAVENCLAD. The RMP details important risks of MAVENCLAD, how these risks can be minimized, and how more information will be obtained about MAVENCLAD's risks and uncertainties (missing information).

MAVENCLAD's summary of product characteristics (SmPC) and its package leaflet provide essential information to healthcare professionals and patients on how MAVENCLAD should be used.

This summary of the RMP for MAVENCLAD should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of MAVENCLAD's RMP.

I. The Medicine and What it is used for

MAVENCLAD is authorised for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features. It contains cladribine as the active substance and it is taken orally.

Further information about the evaluation of MAVENCLAD's benefits can be found in MAVENCLAD's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/assessment-report/mavenclad-epar-public-assessment-report_en.pdf

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of MAVENCLAD, together with measures to minimize such risks and the proposed studies for learning more about MAVENCLAD'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 authorized pack size - the amount of medicine in a pack chosen 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 the case of MAVENCLAD, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

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 MAVENCLAD is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of MAVENCLAD 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 MAVENCLAD. 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);

List of important risks and missing information	
Important identified risks	Severe (Grade ≥ 3) lymphopenia
	Herpes zoster
	Tuberculosis
	Liver injury
Important potential risks	Severe infections
	Progressive Multifocal Leukoencephalopathy (PML)
	Opportunistic infections (other than tuberculosis and PML)
	Malignancies
	Teratogenicity/adverse pregnancy outcomes
	Seizures
Missing information	Sequential use of other immunosuppressive or immunomodulatory agents after cladribine treatment
	Impact of exposure to prior immunomodulatory/immunosuppressive agents on subsequent risks following cladribine exposure
	Long-term safety data in particular for malignancy risk

II.B Summary of Important Risks

Important identified risk: Severe (Grade ≥ 3) lymphopenia	
Evidence for linking the risk to the medicine	The safety of cladribine was studied in all clinical trials that evaluated oral cladribine monotherapy 3.5 mg/kg (923 patients) and in all Phase II and Phase III studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1976 patients). Severe lymphopenia is considered an important identified risk as it may increase the risk of infections, especially for herpes zoster, and needs to be managed in clinical practice through lymphocyte count monitoring before, during and after cladribine treatment. Data from clinical trials can provide an accurate estimate of the frequency and nature of severe (Grade ≥ 3) lymphopenia that is expected to occur in clinical practice.
Risk factors and risk groups	Because of the dose-response observed in the clinical trials, doses higher than 3.5 mg/kg of cladribine appear to be associated with a higher risk of severe lymphopenia. Higher incidences of severe lymphopenia were also seen in combination treatment with interferon (IFN) β.
Risk minimisation measures	Routine risk minimisation measures *Lymphopenia is described as an adverse reaction (EU Summary of Product Characteristics (SmPC) section 4.8; Package Leaflet (PL) section 4)* *Monitoring recommendations are provided together with an algorithm for initiating and continuing treatment based on lymphocyte counts (EU SmPC section 4.2, 4.4; PL section 2)* *A recommendation for active monitoring for infections in case of ALC ≥ Grade 3 is provided (EU SmPC section 4.4)* *An interaction statement for combination with other products that may affect the hematological profile is provided (EU SmPC section 4.5; PL section 2)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *Prescriber Guide* *Patient Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLARION Study (long-term Post-Authorization Safety Study (PASS))* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Herpes zoster	
Evidence for linking the risk to the medicine	The safety of cladribine was studied in all clinical trials that evaluated oral cladribine monotherapy 3.5 mg/kg (923 patients) and in all Phase II and Phase III studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1976 patients). Herpes zoster is considered an important identified risk as the pain associated with herpes zoster can be debilitating, particularly in the elderly. Data from clinical trials can provide an accurate estimate of the frequency and nature of herpes zoster that is expected to occur in clinical practice.
Risk factors and risk groups	Advanced age, immunosuppressive treatment
Risk minimisation measures	Routine risk minimisation measures *Herpes zoster is described as an adverse reaction (EU SmPC section 4.8; PL section 4)* *Initiation of cladribine treatment in immunocompromised patients is contraindicated (EU SmPC section 4.3; PL section 2)* *Prophylactic measures including vaccination and consideration of anti-herpes prophylaxis in patients with grade 4 lymphopenia, as well as treatment recommendations in case of occurrence of herpes zoster are provided (EU SmPC section 4.4; PL section 2)* *Legal status: subject to restricted medical prescription*

Important identified risk: Herpes zoster	
	Additional risk minimisation measures *Prescriber Guide* *Patient Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLARION Study (long-term PASS)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Tuberculosis	
Evidence for linking the risk to the medicine	The safety of cladribine was studied in all clinical trials that evaluated oral cladribine monotherapy 3.5 mg/kg (923 patients) and in all Phase II and Phase III studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1976 patients). Tuberculosis is considered an important identified risk as it is a potentially serious infectious disease that may be activated by cladribine in patients with the latent infection. For rare events such as tuberculosis further long-term data are required for an accurate assessment of the risk; these will be collected in the CLARION study (long-term PASS).
Risk factors and risk groups	Age, immunosuppressive treatment, presence of latent tuberculous infection
Risk minimisation measures	Routine risk minimisation measures *Tuberculosis is described as an adverse reaction (EU SmPC section 4.8; PL section 4)* *Initiation of cladribine treatment in immunocompromised patients is contraindicated (EU SmPC section 4.3; PL section 2)* *Use in patients with active chronic infections (tuberculosis or hepatitis) is contraindicated (EU SmPC section 4.3; PL section 2)* *Screening for latent infections (e.g. hepatitis, tuberculosis) is required with a delay of cladribine initiation until such infection has been adequately treated (EU SmPC section 4.4; PL section 2)* *Monitoring recommendations are provided together with an algorithm for initiating and continuing treatment based on lymphocyte counts to avoid severe lymphopenia as a risk factor for opportunistic infections (EU SmPC section 4.2, 4.4; PL section 2)* *Recommendations for identification and management of patients with acute infections are provided (EU SmPC section 4.4; PL section 2)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *Prescriber Guide* *Patient Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLARION Study (long-term PASS)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Liver injury	
Evidence for linking the risk to the medicine	Several individual case safety reports from post-approval sources, which indicate a potential for cladribine to cause or contribute to mild and moderate liver injuries, mainly in patients who experienced similar and transient events previously with other drugs.
Risk factors and risk groups	Patients with a history of abnormal liver tests

Important identified risk: Liver injury	
Risk minimisation measures	Routine risk minimisation measures *Liver injury is described as an adverse drug reaction (EU SmPC section 4.8, PL section 4)* *Precautions are provided to evaluate the patient's medical history regarding previous episodes of liver injury with other drugs or underlying liver pathologies (EU SmPC section, 4.4; PL section 2)* *Monitoring recommendations are provided (EU SmPC section, 4.4; PL section 2)* *Recommendations for identification and management of patients with liver injury are provided (EU SmPC section 4.4; PL section 2)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures: *Prescriber Guide* *Patient Guide* *DHPC*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *None*

Important potential risk: Severe infections	
Evidence for linking the risk to the medicine	The safety of cladribine was studied in all clinical trials that evaluated oral cladribine monotherapy 3.5 mg/kg (923 patients) and in all Phase II and Phase III studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1976 patients). Severe infections are considered an important potential risk as they can result in hospitalization, turn into a chronic infection, potentially be life-threatening and result in death. Data from clinical trials can provide an accurate estimate of the frequency and nature of severe infections that may occur in clinical practice.
Risk factors and risk groups	Advanced age, immunosuppressive treatment
Risk minimisation measures	Routine risk minimisation measures *Initiation of cladribine treatment in immunocompromised patients is contraindicated (EU SmPC section 4.3; PL section 2)* *Use in patients with HIV infection is contraindicated (EU SmPC section 4.3; PL section 2)* *Use in patients with active chronic infections (tuberculosis or hepatitis) is contraindicated (EU SmPC section 4.3; PL section 2)* *Screening for latent infections (e.g. hepatitis, tuberculosis) is required with a delay of cladribine initiation until such infection has been adequately treated (EU SmPC section 4.4; PL section 2)* *Recommendations for identification and management of patients with acute infections are provided (EU SmPC section 4.4; PL section 2)* *Prophylactic measures including vaccination and consideration of anti-herpes prophylaxis in patients with grade 4 lymphopenia, as well as treatment recommendations in case of occurrence of herpes zoster are provided (EU SmPC section 4.4; PL section 2)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *Prescriber Guide* *Patient Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLARION Study (long-term PASS)*

Important potential risk: Severe infections	
	See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	The safety of cladribine was studied in all clinical trials that evaluated oral cladribine monotherapy 3.5 mg/kg (923 patients) and in all Phase II and Phase III studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1976 patients). PML is considered an important potential risk as it can result in hospitalization, potentially be life-threatening and result in death. While PML was not observed in these clinical trials, cases of PML were reported for parenteral cladribine in patients treated for hairy cell leukemia with a different treatment regimen. For rare events such as PML further long-term data are required for an accurate assessment of the risk; these will be collected in the ongoing CLARION long-term PASS).
Risk factors and risk groups	Age, immunosuppressive treatment, presence of latent infections such as tuberculosis, John Cunningham Virus (JCV), Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infections
Risk minimisation measures	Routine risk minimisation measures *Initiation of cladribine treatment in immunocompromised patients is contraindicated (EU SmPC section 4.3, PL section 2)* *Monitoring recommendations are provided together with an algorithm for initiating and continuing treatment based on lymphocyte counts to avoid severe lymphopenia as a risk factor for opportunistic infections (EU SmPC section 4.4, PL section 2)* *Recommendations for identification and management of patients with acute infections are provided (EU SmPC section 4.4, PL section 2)* *Precautions are provided that a baseline MRI should be performed before initiating cladribine (EU SmPC section 4.4, PL section 2)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *Prescriber Guide* *Patient Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLARION Study (long-term PASS)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Opportunistic infections (other than tuberculosis and PML)	
Evidence for linking the risk to the medicine	The safety of cladribine was studied in all clinical trials that evaluated oral cladribine monotherapy 3.5 mg/kg (923 patients) and in all Phase II and Phase III studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1976 patients). Opportunistic infections (other than tuberculosis and PML) are considered an important potential risk as they can result in hospitalization and may potentially be life-threatening and result in death. For uncommon events such as opportunistic infections further long-term data are required for an accurate assessment of the risk; these will be characterized in the ongoing CLARION (long-term PASS).
Risk factors and risk groups	Age, immunosuppressive treatment, presence of latent infections such as tuberculosis, JCV, HBV or HCV infections
Risk minimisation measures	Routine risk minimisation measures *Initiation of cladribine treatment in immunocompromised patients is contraindicated (EU SmPC section 4.3; PL section 2)*

Important potential risk: Opportunistic infections (other than tuberculosis and PML)	
	Use in patients with HIV infection is contraindicated (EU SmPC section 4.3; PL section 2) *Monitoring recommendations are provided together with an algorithm for initiating and continuing treatment based on lymphocyte counts to avoid severe lymphopenia as a risk factor for opportunistic infections (EU SmPC section 4.2, 4.4; PL section 2)* *Recommendations for identification and management of patients with acute infections are provided (EU SmPC section 4.4; PL section 2)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *Prescriber Guide* *Patient Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLARION Study (long-term PASS)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	The safety of cladribine was studied in all clinical trials that evaluated oral cladribine monotherapy 3.5 mg/kg (923 patients) and in all Phase II and Phase III studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1976 patients). Malignancies are considered an important potential risk as they are severe illnesses with potentially a fatal outcome. For rare events such as malignancies further long-term data are required for an accurate assessment of the risk; these will be characterized in the ongoing (long-term PASS).
Risk factors and risk groups	Advanced age, immunosuppressive treatment, exposure to biological, chemical or physical oncogenic factors (e.g. some viruses, tobacco use, sunbathing, ionizing radiation), genetic/familial disposition
Risk minimisation measures	Routine risk minimisation measures *Observation of malignancy events is described (EU SmPC section 4.4, 4.8; PL section 2)* *Use in patients with active malignancies is contraindicated (EU SmPC section 4.3; PL section 2)* *An individual benefit-risk evaluation is recommended in patients with prior malignancy (EU SmPC section 4.4; PL section 2)* *Patients will be advised to follow standard cancer screening guidelines (EU SmPC section 4.4; PL section 2)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *Prescriber Guide* *Patient Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLARION Study (long-term PASS)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Teratogenicity/adverse pregnancy outcomes	
Evidence for linking the risk to the medicine	Cladribine interferes with DNA synthesis and could cause congenital malformations when used during pregnancy based on human experience

Important potential risk: Teratogenicity/adverse pregnancy outcomes	
	with other substances inhibiting DNA synthesis. Non-clinical studies have also shown reproductive toxicity in the offspring of cladribine treated animals. Despite precautionary measures to prevent pregnancy in clinical trials, pregnancies did occur during cladribine treatment and in female partners following paternal exposure to cladribine. There was no imbalance in pregnancy outcomes between cladribine- and placebo-treated subjects and there were no congenital malformations in pregnancies which occurred during cladribine treatment or within 6 months after last dose. Teratogenicity/adverse pregnancy outcomes are considered an important potential risk as a teratogenic medicine may cause growth retardation, delayed mental development or other congenital disorders. The ongoing CLEAR study (pregnancy PASS) will provide data on pregnancies and infant outcomes in pregnant women with MS and in pregnancies fathered by men with MS exposed to oral cladribine treatment in routine clinical practice.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures *Embryolethal and teratogenic effects as well as chromosomal damage observed in animals are described (EU SmPC section 4.6, 5.3; PL section 2)* *Cladribine must not be used in pregnant women (EU SmPC section 4.3; PL section 2)* *In women of childbearing potential, exclusion of pregnancy prior to treatment is required (EU SmPC section 4.6; PL section 2)* *Use of effective contraception in both male and female patients during treatment and for at least 6 months after the last dose is required. Women using systemically acting hormonal contraceptives will be advised to add a barrier method during cladribine treatment and for at least 4 weeks after the last dose in each treatment year. (EU SmPC section 4.4, 4.6; PL section 2)* *At the beginning of each treatment year, counselling of patients regarding the potential risk to the fetus and the need for effective contraception is recommended (EU SmPC section 4.4, 4.6)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *Prescriber Guide* *Patient Guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLEAR Study (Pregnancy PASS)* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Seizures	
Evidence for linking the risk to the medicine	Individual case safety reports from post-approval sources; in few cases with a close temporal association to Mavenclad treatment. Neurotoxicity was observed in patients receiving parenteral cladribine; seizures were observed with other halogenated nucleoside analogues.
Risk factors and risk groups	Currently not known.
Risk minimisation measures	Routine risk minimisation measures: *Legal status: subject to restricted medical prescription*
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLARION Study (Long-term PASS)*

Important potential risk: Seizures	
	See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Sequential use of other immunosuppressive or immunomodulatory agents after cladribine treatment	
Risk minimisation measures	Routine risk minimisation measures *Prescribers and patients are advised to consider a potential additive effect on the immune system when immunosuppressive/immunomodulatory agents are used after treatment with cladribine (EU SmPC section 4.4; PL section 2)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *CLARION Study (Long-term PASS)* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Impact of exposure to prior immunomodulatory/immunosuppressive agents on subsequent risks following cladribine exposure	
Risk minimisation measures	Routine risk minimisation measures *Prescribers and patients are advised to consider mode of action and duration of effect of the other medicinal product if cladribine is used after treatment with an immunosupressive/immunomodulatory agent (EU SmPC section 4.4; PL section 2)* *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *CLARION Study (Long-term PASS)* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety data in particular for malignancy risk	
Risk minimisation measures	Routine risk minimisation measures *Legal status: subject to restricted medical prescription* Additional risk minimisation measures *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *CLARION Study (Long-term PASS)* See section II.C of this summary for an overview of the post-authorisation development plan.

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 MAVENCLAD.

II.C.2 Other Studies in the Post-authorisation Development Plan

CLARION (Long-term PASS)

Purpose of the study:

A long term, prospective, observational cohort study evaluating the safety profile, in terms of incidence of adverse events of special interest, in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine or fingolimod. The study also assesses the impact of prior and subsequent use of immunomodulatory/immunosuppressive agents on the incidence of adverse events of special interest.

CLEAR (Pregnancy PASS)

Purpose of the study:

A multi-country, cohort database study to investigate whether the exposure to oral cladribine before or during pregnancy, in women treated with oral cladribine or in pregnancies fathered by patients treated with cladribine, is associated with adverse pregnancy outcomes in the women and in their child