EU Risk Management Plan (RMP) for Mavenclad® (Cladribine)

Active substance(s) (INN/Trade Name):	Cladribine
Name of Company:	**Merck Healthcare KGaA** **Frankfurter Straße 250** **D-64293 Darmstadt** **Germany** **Telephone +49 61 51-72 0** **Telefax +49 61 51-72 69 14** **e-mail: GlobalDrugSafety@merckgroup.com**

RMP version to be assessed as part of this application:

RMP version number:	2.2
Data lock point (DLP) for this RMP:	07 Jul 2023
Date of final sign-off:	Document signed electronically, see date of eSignature at the end of the document.
Rationale for submitting an updated RMP:	Update of Company Core Data Sheet (CCDS) Version 13.0 and corresponding update of Summary of Product Characteristics.
Summary of significant changes in this RMP:	Update of text regarding pregnancy prevention in order to align with CCDS Version 13.0 which reflects results from a drug-drug interaction study between cladribine and oral hormonal contraceptives. Update of safety data with a new DLP 07 Jul 2023 (which is the DLP of recently submitted PBRER).

Other RMP versions under evaluation:

RMP version number:	NA
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Details of the currently approved RMP:	
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Signatures

Name:	Dr. Sabine Hackel, MD
Title:	Qualified Person responsible for Pharmacovigilance in European Economic Area (EEA QPPV), PPD and QPPV QPPV oversight declaration: The content of this RMP has been reviewed and approved by the Marketing Authorization Holder's QPPV. The electronic signature is available on file
Signature	**Document signed electronically by the EEA QPPV**
Name:	PPD Global Patient Safety, PPD (contact person for this RMP)
E-mail:	PPD
Signature:	**Document signed electronically**

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List of Abbreviations

5'-NTase	5'-nucleotidase
ACE	Angiotensin Converting Enzyme
Adj-AE	Observation-Adjusted Adverse Event Incidence Rate
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
Cd-ATP	2-Chlorodeoxyadenosine Triphosphate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIOMS	Council for International Organization of Medical Sciences
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPMS	Chronic Progressive Multiple Sclerosis
CRL	Complete Response Letter
CYP	Cytochrome
DC	Dynamic Cohort
DCK	Deoxycytidine Kinase
DDI	Drug-Drug Interaction
DILI	Drug-Induced Liver Injury
DMD	Disease Modifying Drug
DNA	Deoxyribonucleic Acid
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU QPPV	Qualified Person responsible for Pharmacovigilance in European Economic Area
EXT	Extension
FDA	Food and Drug Administration
GPS	Global Patient Safety
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
HPβCD	Hydroxypropyl-β-cyclodextrin
ICSR	Individual Case Study Report

IFN	Interferon
INN	International Non-proprietary Name
ISS	Integrated Summary of Safety
IV	Intravenous
JCV	John Cunningham Virus
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NARCOMS	North American Research Committee on Multiple Sclerosis
NCA	National Competent Authority
NDA	New Drug Application
NICE	National Institute for Health and Care Excellence
NOAEL	No-Observed-Adverse-Effect Level
PASS	Post-Authorization Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PL	Package Leaflet
PML	Progressive Multifocal Leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
PY	Patient-years
REM	Rapid Eye Movement
RMP	Risk Management Plan
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Events
SC	Subcutaneous
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SPMS	Secondary Progressive Multiple Sclerosis
TB	Tuberculosis
ULN	Upper Limit of Normal
Vs	Versus
yr	Year

Part I: Product(s) Overview

Product Overview

Active substance (INN or common name)	Cladribine
Pharmacotherapeutic group (ATC Code)	Selective Immunosuppressants (L04AA40)
Marketing Authorization Holder	Merck Europe B.V. Gustav Mahlerplein 102 1082 MA Amsterdam Netherlands Tel. +31 (0) 207 235 230 Fax +31 (0) 207 235 239 e-mail: GlobalDrugSafety@merckgroup.com
Medicinal products to which this RMP refers	Mavenclad® 10 mg tablets
Invented name in the European Economic Area (EEA)	Mavenclad
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Chlorinated purine nucleoside analogue A chlorine substitution in the purine ring protects cladribine from degradation by adenosine deaminase, increasing the intracellular residence time of the cladribine prodrug
	Summary of mode of action: Cladribine is a prodrug that has to be phosphorylated intracellularly to become biologically active. Phosphorylation of cladribine to its active triphosphate form, 2-chlorodeoxyadenosine triphosphate (Cd-ATP), is particularly efficiently achieved in lymphocytes, due to their constitutively high deoxycytidine kinase (DCK) and relatively low 5'-nucleotidase (5'-NTase) levels. A high DCK to 5'-NTase ratio favors the accumulation of Cd-ATP, making lymphocytes particularly susceptible to cell death. As a result of a lower DCK/5'-NTase ratio other bone marrow derived cells are less affected than lymphocytes. DCK is the rate limiting enzyme for conversion of the cladribine prodrug into its active triphosphate form, leading to selective depletion of dividing and non-dividing T and B cells. The primary apoptosis-inducing mechanism of action of Cd-ATP has direct and indirect actions on DNA synthesis and mitochondrial function. In dividing cells, Cd-ATP interferes with DNA synthesis via inhibition of ribonucleotide reductase and competes with deoxyadenosine triphosphate for incorporation into DNA by DNA polymerases. In resting cells cladribine causes DNA single-strand breaks, rapid nicotinamide adenine dinucleotide consumption, ATP depletion and cell death. There is evidence that cladribine can also cause direct caspase-dependent and -independent apoptosis via the release of cytochrome c and apoptosis-inducing factor into the cytosol of non-dividing cells. Multiple sclerosis (MS) pathology involves a complex chain of events in which different immune cell types, including autoreactive T and B cells play a key role. The mechanism by which cladribine exerts its therapeutic effects in MS is not fully elucidated but its predominant effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to MS.

Hyperlink to the Product Information	Mavenclad Product Information
Indication in the EEA	Current: Mavenclad is indicated for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended cumulative dose of Mavenclad is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. Following completion of the 2 treatment courses, no further cladribine treatment is required in years 3 and 4. Route of administration: Oral
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Tablet. White, round, biconvex tablets of 8.5 mm diameter, engraved with 'C' on one side and '10' on the other side. Each tablet contains 10 mg of cladribine
	Proposed: Not applicable
Is the product subject to additional monitoring in the EU?	No

Part II: Safety Specification

Part II: Module SI - Epidemiology of the Indication(s) and Target Population

Indication

Mavenclad® is indicated for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features.

Incidence

Multiple sclerosis is a complex demyelinating disease of the central nervous system (CNS) and represents the most common cause of acquired neurological disability in young adults in developed countries (Compston and Coles 2008).

Regionally, the median estimated incidence is greatest in Europe (3.8 per 100,000 person-years), followed by the Americas (2.5), the Eastern Mediterranean (2), the Western Pacific (0.9), and Africa (0.1). No data are available from countries in South-East Asia.

The epidemiology of multiple sclerosis in European and other non-European countries is presented in Table 1. European countries with highest incidence of MS are Bosnia and Herzegovina (12 per 100,000 person-years), Latvia (11.6 per 100,000 person-years), Czech Republic (11 per 100,000 person-years), Estonia, Hungary, and Iceland (each at 10 per 100,000 person-years).

Prevalence

Globally, the median estimated prevalence of MS is 30.1 MS patients per 100,000 population. The age-standardized prevalence estimates had increased by 22.47 cases (95% UI 20.5–24.61) per 100,000 population or 10·4% (9.1–11.8) between 1990 and 2016 (GBD 2016 Multiple Sclerosis Collaborators, 2019). It is not clear if this increase is due to better diagnosis and reporting, or to other causes.

MS median estimated prevalence varies substantially across regions. Age-standardized prevalence is greater than 120 cases per 100,000 population in North America and some northern European countries, moderate (60–120 per 100,000) in some countries in Europe and Australia, and lowest (<60 per 100,000 population) in North Africa and the Middle East, Latin America, Asia, Oceania, the Caribbean, and sub-Saharan Africa (GBD 2016 Multiple Sclerosis Collaborators 2019).

European countries with the highest prevalence of MS are Denmark (227 MS patients per 100,000 population), Sweden (189 MS patients per 100,000 population), Hungary (176 MS patients per 100,000 population), and Cyprus (175 MS patients per 100,000 population) (see Table 1) (Multiple Sclerosis International Federation, Atlas of MS 2013).

Table 1 Epidemiology of Multiple Sclerosis in European and Other Non-European Countries

Country	Incidence (per 100,000 person-years)	Prevalence (per 100,000 persons)
Europe		
Eastern Europe		
Albania	unknown	22
Bosnia and Herzegovina	12	60
Bulgaria	3.5	39.1
Croatia	unknown	59
Cyprus	6	175
Czech Republic	11	160
Estonia	10	82
Greece	7	70
Hungary	10	176
Latvia	11.6	89.9
Lithuania	8	78
Poland	unknown	64
Romania	0.75	30
Serbia	2	65
Slovenia	1.8	120
Turkey	unknown	55
Macedonia	2	31

Country	Incidence (per 100,000 person-years)	Prevalence (per 100,000 persons)
Western Europe		
Austria	unknown	140
Belgium	4	100
Denmark	7.89	227
Finland	9	105
France	7.6	94.7
Germany	5	149
Iceland	10	140
Ireland	unknown	140
Italy	4	113
Netherlands	5	88
Norway	7	160
Portugal	unknown	56.2
Spain	4	100
Switzerland	4	110
Sweden	5	189
United Kingdom	4	164
Africa		
Algeria	unknown	20
Egypt	unknown	25
Lybia	1	5.9
Morocco	unknown	20
South Africa	1	5
Tunisia	1.34	20.1
Asia		
Central Asia		
Bahrain	unknown	35
Iran	4	45
Iraq	1.5	5
Israel	5.4 [a)]	62.5
Jordan	1.14 [b)]	39
Kuwait	8	83
Lebanon	unknown	45
Qatar	6.9	64.6
Russia	1.75	50
Oman	2	22
Saudi Arabia	7.5	30
United Arab Emirates	7	55

Country	Incidence (per 100,000 person-years)	Prevalence (per 100,000 persons)
China Region		
China	0.11 [c)]	1.5
Hong Kong	unknown	4.8 [e)]
Japan	0.77 [d)]	8
Singapore	unknown	3.9
South Korea	0.5	3.5
South East Asia		
Taiwan	0.63	2.96
Thailand	unknown [e)]	0.75
The Americas		
Central America and Caribbean		
Costa Rica	unknown	5.4
Cuba	unknown	14
Guatemala	0.07	3.3
Mexico	unknown	15
Nicaragua	0.5	2
Panama	0.6	5.2
North America		
Canada	13.4	291
United States	3.2	219.5 [h)]
South America		
Argentina	1	18
Bolivia	0.25	1.5
Brazil	unknown	15
Chile	0.9 [f)]	5.69 [g)]
Colombia	unknown	4.9
Ecuador	unknown	3.2
Paraguay	0.6	5.7
Peru	unknown	5
Uruguay	2.5	26
Venezuela	unknown	6.9
Oceania		
Australia	3.8	103.7 [i)]

[a)] Siegel 2012, [b)] Heydarpour 2015 , [c)] Shandong province, Liu 2016 [d)] Houzen 2012 [e)] Eskandarieh 2016 [f)] Díaz 2012; [g)] Correa 2016; [h)] Briggs 2019 [i)] Campbell 2019

Note: No data on incidence and prevalence were available for Luxembourg, Macau, Moldavia, Ukraine, Slovakia, Syria

Demographics of the population in the authorized indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Typically, symptoms of MS begin in the third and fourth decade of life and extend over many years (Coyle 2014). Studies have shown a lower prevalence of MS in African American, Japanese and Chinese populations, and a higher prevalence in European and American populations (Oreja-Guevara 2014). In addition, a female:male ratio of approximately 2.5:1 has been demonstrated (Oreja-Guevara 2014).

The exact cause of MS is unknown. Risk factors for MS include genetic predisposition and environmental factors and a complex interaction of both genetic and environmental factors is probably involved in the etiology of MS:

- Approximately 15% of patients with MS have a positive family history. Recurrence among monozygotic twins is approximately 35%, reflecting the extent of genetic predisposition. The estimated risk to the siblings of a proband is 3–5%, increasing to 29.5% if one or both parents have MS. Risk to the offspring of a patient with MS is 2–3% and higher if both parents have MS (20%) (Oreja-Guevara 2014).
- Several genes are associated with susceptibility for MS, most importantly HLA-DRB1, IL7R (CD127), IL2R, and SOCS1 (Oreja-Guevara 2014).
- Environmental factors associated with the development of MS are vitamin D deficiency, low exposure to sunlight, cigarette smoking, and Epstein−Barr virus infection. However, no single environmental factor appears to be sufficient for the etiology of MS (Oreja-Guevara 2014).
- Other viruses are also implicated in the etiology of MS, although this has not been unequivocally confirmed (George 2012).

The main existing treatment options

Treatment options for relapsing MS include disease modifying therapies, medications used to treat relapses and symptomatic treatments. Disease modifying agents impact the underlying disease by targeting some aspect of the inflammatory process of MS, and reducing the frequency of relapses, decreasing the development of new CNS lesions as seen on Magnetic Resonance Imaging (MRI), and slowing the accumulation of disability. These treatments include injectable medications (i.e. interferon (IFN) β-1a, IFN β-1b, glatiramer acetate); oral medications (i.e. teriflunomide, fingolimod, ozanimod, dimethyl fumarate) and infusion medications (i.e. alemtuzumab, ocrelizumab, mitoxantrone, and natalizumab). Treatment options for acute relapses include corticosteroids.

Generally, concomitant medications in MS patients aim at alleviating symptoms that affect the ability of MS patients to carry out normal activities of daily life and/or minimizing risk factors for an acute exacerbation (Ziemsen 2011, Thompson 2010). These medications may be used to treat a variety of different impairments, e.g. fatigue, spasticity, bladder dysfunction, pain, mood disorders, depression, ameliorate involuntary and uncontrollable episodes of laughing and/or crying, known as the ‘pseudobulbar affect’ (Damal 2013), changes in cognitive function or memory, sexual dysfunction, tremor, urinary tract infections, and others.

Table 2 displays the most common concomitant medications used in the target population of MS patients to alleviate symptoms/complications of MS (source: National Institute for Health and Care Excellence (NICE) guideline 186 on the management of multiple sclerosis in primary and secondary care, issued on October 2014, other NICE guidelines, literature, and information from the National Multiple Sclerosis Society). Other medications commonly used in the target population are those commonly prescribed in co-morbidities found in MS (see Table 3).

Table 2 Most Common Concomitant Medications in the Target Population to Alleviate Symptoms/Complications of Multiple Sclerosis

Symptoms	Treatment	Comments/Recommendations from the NICE
Fatigue (National Clinical Guideline Centre 2014)	Amantadine, modafinil	No medicines targeted at fatigue should be used routinely. Other factors causing fatigue, such as disturbed sleep, chronic pain and poor nutrition, should be identified and treated if possible.
Bladder dysfunction (National Clinical Guideline Centre 2012)	Anticholinergic medicines such as oxybutinin or tolterodine; desmopressin	Any person who wishes to control urinary frequency during the day (for example, when traveling), and who has failed with other measures, should be offered desmopressin, but desmopressin should never be used more than once in 24 hours.
Urinary tract infections	Antibiotics such as sulfamethoxazole, ciprofloxacin, nitrofurantoin, methenamine, depending on the germ	Any person with MS with more than three confirmed episodes of urinary tract infection in a period of 1 year should be assessed by a continence specialist for residual urine and other evidence of risk factors, and offered appropriate treatment and guidance.
Bowel problems	Docusate, bisacodyl, sodium phosphate, mineral oil, psyllium hydrophilic musilloid, glycerin suppository	If a person with MS has apparent constipation despite treatment with oral laxatives, he or she should be considered for the routine use of suppositories or enemas.
Spasticity and spasms (National Clinical Guideline Centre 2014)	Baclofen, gabapentin, tizanidine, diazepam, clonazepam, dantrolene	Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin. The other drugs cited should be given only if treatment with baclofen or gabapentin is unsuccessful or side effects are not tolerated. Combinations of medicines, and other medicines such as anticonvulsants, should only be used after seeking further specialist advice.
Walking impairment (National Clinical Guideline Centre 2014)	Dalfampridine	The 2014 Clinical Guidelines of the National Institute for Health and Care Excellence, does not recommend the use of fampridine to treat lack of mobility in people with MS because it is not a cost effective treatment.
Contractures at joints	Local botulinum toxin injection	-
Ataxia and tremor (National Clinical Guideline Centre 2014)	Isoniazid	-
Pain, including musculoskeletal and neuropathic pain	Analgesics or opioids, anticonvulsants such as carbamazepine or gabapentin, antidepressants such as amitriptyline	-

Symptoms	Treatment	Comments/Recommendations from the NICE
Emotionalism (National Clinical Guideline Centre, 2014)	Tricyclic antidepressants or selective serotonin re-uptake inhibitor such as duloxetine	If the emotionalism causes concern or distress to the person with MS or the family, then treatment with an antidepressant should be offered.
Depression/anxiety (National Collaborating Centre for Mental Health 2010, National Collaborating Centre for Mental Health 2011)	Antidepressants and/or benzodiazepine such as duloxetine, venlafaxine, paroxetine, fluoxetine, bupropion, sertraline	In the North American Research Committee on Multiple Sclerosis (NARCOMS) patient registry, half of the patients reporting depression received treatment for it, namely: fluoxetine (21%), sertraline (19%) paroxetine (12%), amitriptyline (11%), venlafaxine (5%) (Lo 2005). In Denmark, 11% of the MS patients take antidepressants (Svendsen 2003).
Sexual dysfunction (Tsertsvadze 2009)	Male: Phosphodiesterase-5 inhibitors (sildenafil, vardenafil, tadalafil, avanafil)	
Oscillopsia (National Clinical Guideline Centre 2014)	Gabapentin, memantine	Refer the person with MS for specialist advice if there is no improvement of oscillopsia after treatment with gabapentin and memantine or side effects prevent continued use.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Multiple sclerosis is an inflammatory disorder of the brain and spinal cord in which focal lymphocytic infiltration leads to damage of myelin and axons (Compston 2008). The initial symptoms often include weakness or diminished dexterity in one or more limbs, a sensory disturbance, optic neuritis, diplopia, gait instability, and ataxia (Hunter 2016). As MS progresses, bladder dysfunction, fatigue, and heat sensitivity occur in many patients. Additional symptoms include Lhermitte's sign, facial weakness or pain, vertigo, brief tonic spasms, and other paroxysmal symptoms, which are believed to represent discharges along demyelinated axons. Cognitive deficits are common, particularly in advanced cases, and include memory loss, impaired attention, problem-solving difficulties, slowed information processing, and difficulties in shifting between cognitive tasks. The disease pathology is characterized by multifocal lesions within the CNS, in both the white matter and gray matter, with perivenular inflammatory cell infiltrates, demyelination, axonal transection, neuronal degeneration, and gliosis (Hunter 2016).

During the early course of the disease inflammation is transient and remyelination occurs, leading to episodes of neurological dysfunction that usually recover (Compston 2008). However, over time, widespread microglial activation is associated with extensive and chronic neurodegeneration leading to progressive accumulation of disability. Clinically, MS is characterized by discrete episodes (attacks or relapses) of neurologic dysfunction (Gelfand 2014). Commonly, patients may experience numbness, tingling, weakness, vision loss, gait impairment, incoordination, imbalance, and bladder dysfunction. In between these attacks, at least during the remitting periods of the illness, patients have fairly stable neurologic function although patients experience fatigue or heat sensitivity in the interval between attacks. Over several years to decades, many patients who begin with relapsing-remitting MS (RRMS) evolve to the secondary progressive features of illness, in which they experience an insidious worsening of function and accumulation of neurologic disability.

A review of frequency and symptom severity of domain-specific impairments conducted using the North American Research Committee on Multiple Sclerosis (NARCOMS) Registry data from over 35,000 patients found that of the 11 domains commonly affected in MS (mobility, hand function, vision, fatigue, cognition, bowel/bladder function, sensory, spasticity, pain, depression, and tremor/coordination), the severity of impairment increases with disease duration across all domains, but the patterns of disability accumulation differ (Kister 2013). In the mobility, hand function, bowel/bladder function, and spasticity domains, worsening impairment was observed over the three decades of disease, whereas for other domains such as vision, cognition, sensory, pain, and depression there was little change after 15 years of disease.

Mortality due to MS is difficult to determine because of poor data collection and reporting. Nevertheless, the following reports illustrate that mortality is increased in patients with MS:

Globally, age-standardized death rates have decreased significantly (change –11.5%, 95% UI – 35.4 to –4.7) between 1990 and 2016 (GBD 2016 Multiple Sclerosis Collaborators, 2019). A review of large MS cohort registries assessing mortality found that, compared with the general healthy population, life expectancy in patients with MS was reduced by 7 to 14 years (Scalfari 2013). A more recent study using population-based administrative data of 5,797 persons with MS and 28,807 controls matched according to sex, year of birth, and region, showed that the median survival from birth in the MS population was lower (75.9 years versus 83.4 years) compared to the matched controls (Marrie 2015h).

Complications of MS account for 50-75% of the deaths among patients with MS (Scalfari 2013). The large variation of the proportion of "deaths due to MS" (50% to 75%) may be related to the fact that the definition of death due to MS can be variably interpreted by doctors or be entirely unknown for those not familiar with MS. Deaths not related to MS are mainly attributable to the common causes of death in the non-MS population: cardiovascular disease (range from 13.1% to 26%), cancer (range from 9.5% to 35%), infectious and respiratory disease (range from 1.5% to 5.4%), and accidents or suicide (range from 0% to 28%) (Scalfari 2013).

A meta-analysis of 12 studies including data from over 28,000 patients with MS revealed that the pooled all-cause standardized mortality ratio was 2.8 (95% Confidence Interval (CI) 2.7-2.9). Compared with the general population, patients with MS had increased death rates from infection and respiratory diseases, suicide, and cardiovascular disease (Manouchehrinia 2016).

In another study the mortality rate from MS (per 100,000 persons) in Europe ranged from 0.36 in Spain to 1.48 in Norway for the period 1990 to 1994 (Ekestern 2004). In the US, mortality rate was 1.44 deaths per 100,000 persons from 1990 to 2001 (Redelings 2006).

Important co-morbidities

A comprehensive review of the literature of co-morbidities in MS reveals that treating physicians need to be aware of specific co-morbid conditions in MS patients and need to ensure appropriate screening and treatment (Marrie 2015). The authors reviewed over 7,000 studies of the incidence and prevalence of co-morbidities in MS including 249 studies, from 1905 through 2012, which underwent detailed review and on which the six reported meta-analyses were based (Marrie 2015). Only 32% of studies were considered as of moderate to good quality and heterogeneity was high.

Despite these limitations some general conclusions can be drawn from this body of work (Culpepper 2015):

- the five most prevalent co-morbidities in MS were: depression (Marrie 2015b), anxiety (Marrie 2015b), hypertension (Marrie 2015c), hypercholesterolemia (Marrie 2015c) and chronic lung disease;
- autoimmune thyroid disease and psoriasis were the most frequent co-morbid autoimmune diseases (Marrie 2015e);
- the risk of meningiomas and urinary system cancers was greater and the risk of pancreatic, ovarian, prostate and testicular cancers was lower than expected compared to the general population (Marrie 2015f);
- several co-morbid conditions were found to occur more frequently than previous research had suggested, such as stroke (Marrie 2015c), heart disease (Marrie 2015c), congestive heart failure (Marrie 2015c), arthritis (Marrie 2015d), inflammatory bowel disease (Marrie 2015e), irritable bowel syndrome (Marrie 2015d), seizure disorders (Marrie 2015g), sleep disorders (Marrie 2015g), bipolar disorder (Marrie et al., 2015b), and alcohol abuse (Marrie 2015b).

The epidemiology of disease specific co-morbidities and other conditions frequently observed in MS patients should be taken into consideration for assessment of adverse event (AE) causality as summarized in Table 3. The main co-medications prescribed for these co-morbidities are also presented in the table.

Table 3 Epidemiology of Co-morbidities in the Target Multiple Sclerosis Population

Co-morbidity in the Target Population	Depression, Anxiety
Incidence/prevalence	**Depression:** Incidence: from 4.0% in one year to 34.7% over a five-year period. Prevalence: The summary estimate was 23.7% (95% CI: 17.4%-30.0%), based on 15 population-based studies. **Anxiety:** Incidence: Not reported Prevalence: The summary estimate was 21.9% (95% CI: 8.76%-35.0%), based on eight population-based studies. Source: meta-analysis of 118 studies on the epidemiology of psychiatric co-morbidity in MS patients (Marrie 2015b).
Mortality	No data identified
Main co-medications prescribed	Antidepressants and/or anxiolytics.
Co-morbidity in the Target Population	**Hypertension**
Incidence/prevalence	Incidence: 3.73% of an incident MS cohort developed hypertension over a maximum follow-up of 30 years. Prevalence: The summary estimate was 18.6% (95% CI: 13.9%-23.2%), based on two population-based studies. Source: meta-analysis of 20 studies on the epidemiology of hypertension in MS patients (Marrie 2015c).
Mortality	No data identified

Co-morbidity in the Target Population	Depression, Anxiety
Main co-medications prescribed	Antihypertensive drugs (diuretics, beta blockers, angiotensin receptor blockers, angiotensin converting enzyme [ACE] inhibitors)

Co-morbidity in the Target Population	Hyperlipidemia
Incidence/prevalence	Incidence: Not reported. Prevalence: The summary estimate was 10.9% (95% CI: 5.6%-16.1%), based on three population-based studies. When compared to the general population, most of the studies reported a higher prevalence of hyperlipidemia in the MS population (Kang 2010, Khan 2007, Sheu 2013, Lavela 2012, Sun 2014). Source: meta-analysis of 13 studies on the epidemiology of hyperlipidemia in MS patients (Marrie 2015c)
Mortality	No data identified
Main co-medications prescribed	Lipid lowering drugs (fibrates, statins)

Co-morbidity in the Target Population	Chronic Lung Disease
Incidence/prevalence	Incidence: 2.50% of an incident MS cohort developed chronic obstructive pulmonary disease (COPD) over a maximum of 30 years of follow-up. Prevalence: For asthma, the summary estimate was of 7.46% (95% CI: 2.50-12.4%), based on three population-based studies. For chronic lung disease, the summary estimate was 10.0% (95% CI: 0-20.9%), based on two population-based studies For COPD, one population-based study reported a prevalence of 1.2%. Source: meta-analysis of 22 studies on the epidemiology of chronic lung disease in MS patients (Marrie 2015d).
Mortality	No data identified
Main co-medications prescribed	Asthma: Systemic glucocorticoids (acute exacerbation), quick-acting inhaled beta-2-selective adrenergic agonist, inhaled beta agonist, inhaled glucocorticoids. COPD, chronic lung disease: Oxygen therapy, beta adrenergic agonists, anticholinergic agents, oral glucocorticoid therapy, antibiotics

Co-morbidity in the Target Population	Diabetes Mellitus Type II
Incidence/prevalence	Incidence: from 0.001% to 1.01%. Prevalence: One population-based study reported a prevalence of type II diabetes mellitus of 8.57%. Source: meta-analysis of 39 studies on the epidemiology of diabetes mellitus type II in MS patients (Marrie 2015c)
Mortality	No data identified
Main co-medications prescribed	Insulin, antidiabetic drugs

Co-morbidity in the Target Population	Irritable Bowel Syndrome
Incidence/prevalence	Incidence: Not reported. Prevalence: One population-based study reported a prevalence of irritable bowel syndrome of 12.2%. Irritable bowel syndrome affects the MS patients nearly twice as often as the general population (Marrie 2013). Source: meta-analysis of 11 studies on the epidemiology of gastrointestinal co-morbidity in MS patients (Marrie 2015d)
Mortality	No data identified
Main co-medications prescribed	Medication for constipation (osmotic laxatives, lubiprostone, guanylate cyclase agonists), antidiarrheal agents, antispasmodic agents

Co-morbidity in the Target Population	Musculoskeletal Disorders
Incidence/prevalence	**Arthritis:** Incidence: Not reported. Prevalence: from 2.97% to 26.0%. **Fibromyalgia:** Incidence: 0.12% annually Prevalence: 6.82% based on a population-based study, and higher than in the general population (Marrie 2012). **Bone/joint problems:** Incidence: Not reported. Prevalence: Knee replacement ranges from 0.99% to 1.52% while the prevalence of hip replacements ranges from 0.50% to 1.52%. MS patients have a higher risk of fractures, lower bone mineral density and osteoporosis than age-matched and gender-matched healthy individuals (Oreja-Guevara 2014). Fractures are more likely to occur in MS patients which is associated with vitamin D deficiency; these patients are also more prone to falling (from mobility problems caused by the disease). Source: meta-analysis of nine studies on the epidemiology of musculoskeletal disorders in MS patients (Marrie 2015d).
Mortality	No data identified
Main co-medications prescribed	Analgesics, anti-inflammatory drugs (e.g. nonsteroidal anti-inflammatory drugs)

Co-morbidity in the Target Population	Stroke
Incidence/prevalence	Incidence: The summary estimate for any stroke was 2.73% (95% CI: 2.51%-2.95%), based on two population-based studies. In the two comparative studies, the incidence of any stroke and ischemic stroke was greater in the MS population than in matched populations (Jadidi 2013, Christiansen 2010). Prevalence: The summary estimate was 3.28% (95% CI: 0%-8.98%), based on two population-based studies. When compared to the general population, most of the studies reported a higher prevalence of any stroke and ischemic stroke in the MS population (Allen 2008, Kang 2010, Khan 2007, Lavela 2012). Source: meta-analysis of 10 studies about the epidemiology of cerebrovascular disorders in MS patients (Marrie 2015c).
Mortality	No data identified.

Co-morbidity in the Target Population	Stroke
Main co-medications prescribed	Intravenous (iv) thrombolysis and interventions for ischemic stroke are associated with either reduced disability, complications, or stroke recurrence, including antithrombotic therapy, lipid lowering therapy, and blood pressure reduction.

Co-morbidity in the Target Population	Congestive Heart Failure
Incidence/prevalence	Incidence: from 0.89% to 2.86%. In two comparative studies (Christiansen 2010; Jadidi 2013), a nearly two-fold increased incidence of congestive heart failure in the incident MS population versus an age- and sex-matched cohort from the general population was found, but one study did not cover a 30-year follow-up period (Christiansen 2010). Prevalence: Ranges from 1.8% to 5.39%. Source: meta-analysis of four studies on the epidemiology of congestive heart failure in MS patients (Marrie 2015c).
Mortality	No data identified.
Main co-medications prescribed	Acute heart failure: Supplemental oxygen and assisted ventilation, diuretics, vasodilator therapy (nitroglycerin, nitroprusside, nesiritide), sodium and fluid restriction. Heart failure with preserved ejection fraction: Directed toward associated conditions (e.g. hypertension) and symptoms (e.g. edema). If reduced ejection fraction: Diuretics, ACE inhibitors, angiotensin II receptor blocker, and beta blockers.

Co-morbidity in the Target Population	Ischemic Heart Disease
Incidence/prevalence	Incidence: from to 2.36% to 2.75%. All of the studies that reported the incidence of ischemic heart disease also compared findings to matched populations and found elevated incidence rate ratios in their incident MS populations (Christiansen 2010, Jadidi 2013, Marrie 2013). Prevalence: The summary estimate of prevalence was 2.50% (95% CI: 0-5.77%), among three population-based studies. Source: meta-analysis of 14 studies on the epidemiology of ischemic heart disease in MS patients (Marrie 2015c).
Mortality	No data identified.
Main co-medications prescribed	Beta blockers, calcium channel blockers, and nitrates.

Co-morbidity in the Target Population	Autoimmune Diseases
Incidence/prevalence	**Psoriasis:** Incidence: from 0.17-1.63%. One comparative study reported a higher incidence of psoriasis in the MS population than expected for the Danish general population (Christiansen 2010). Prevalence: 7.74% based on one population-based study. None of the five comparative studies that used concurrent control populations note a difference in odds of psoriasis in the MS population as compared to the general population (Cendrowski 1989, Henderson 2000, Langer-Gould 2010, Midgard 1996, Percy 1971). **Thyroid disease:** **Incidence:** The summary incidence estimate was 0.17% (95% CI: 0-0.40%), among four studies. Three studies compared the incidence of

Co-morbidity in the Target Population	Autoimmune Diseases
	thyroid disease in the MS population to that in the general population, and none found a statistically significant difference (Nielsen 2008, Wynn 1990, Marrie 2012). **Prevalence:** The summary estimate was 6.44% (95% CI: 0.19-12.7%), based on two population-based studies. In comparative studies, about half of them (eight out of 13) found that the prevalence of disease was similar in the MS population (Marrie 2015e). I**nflammatory bowel disease:** Incidence: from 0.33-1.0%. Prevalence: 0.78% based in only one population-based study. In comparative studies, findings regarding inflammatory bowel disease were mixed, but most studies reported that the incidence and prevalence were higher in the MS population than in the general population before and after MS diagnosis (Marrie 2015e). Source: meta-analysis of 61 studies on the epidemiology of autoimmune diseases co-morbidity in MS patients (Marrie 2015e).
Mortality	No data identified
Main co-medications prescribed	Psoriasis: Topical corticosteroids, emollients, vitamin D analogs (calcipotriene, calcitriol), topical retinoids (tayarotene) ultraviolet B (UVB) phototherapy, systemic therapies (retinoids, methotrexate, cyclosporine, apremilast), or biologic immune modifying agents (e.g. anti-tumor necrosis factor [TNF] agents). Thyroid disease: Medication according to functional thyroid status. Inflammatory bowel disease: 5-aminosalicylic acid (5-ASA) and/or steroids

Co-morbidity in the Target Population	Malignancy
Incidence/prevalence	Incidence: The summary estimate for any cancer was 4.3% (2.67-6.1%), based on nine population-based studies, that presented large variability (I^2 statistic=99.8%). Findings regarding cancer risk in people with multiple sclerosis as compared to the general population have been inconsistent. The meta-analysis included 11 comparative studies of the risk of overall cancer in MS versus the general population (Marrie 2015f) with inconclusive results. Most of the studies (n=6) presented no statistical difference between the two groups (Achiron 2005; Midgard 1996b, Moller 1991, Nielsen 2008, Sumelahti 2004, Wynn 1990), while others found a higher or lower risk of malignancies in MS as compared to the general population (Christiansen 2010; Bahmanyar 2009; Kingwell 2012, Lebrun 2011). A nationwide Danish register-based study the incidence of cancer was 5.76 per 1,000 person-years (Norgaard 2019). MS patients did not have increased cancer incidence than general population, with a standardized incidence ratio of 0.98 (95% CI, 0.90–1.06) for any cancer (Norgaard 2019). In population-based studies, cancers that had the highest incidence were cervical (summary estimate: 2.95 [0.005-0.58], breast (summary estimate: 1.6 [0.98-2.30], and digestive cancers (summary estimate: 1.05 [0.098-2.01]. Prevalence: The summary estimate for any cancer was 2.23% (95% CI: 1.18-3.29%), among five population-based studies, that also had large variability (I^2 statistic=90.8%). In comparative studies, the risk of meningiomas and urinary system cancers appeared higher than expected, while the risks of pancreatic, ovarian, prostate and testicular cancer were lower than expected (Marrie 2015f)

Co-morbidity in the Target Population	Malignancy
	Source: meta-analysis of 38 studies on the epidemiology of malignancy in MS patients (Marrie 2015f).
Mortality	Ranges from 9.5% to 35% (Scalfari 2013).
Main co-medications prescribed	Surgery +/- chemotherapy +/- radiotherapy.

Co-morbidity in the Target Population	Fatigue
Incidence/prevalence	Incidence: Among 949 MS patients from Canadian Centers, 38.8% (95% CI: 32.7%-45.3%) experienced any fatigue over two years (Fiest 2016). Prevalence: In the same study, the prevalence of no fatigue was 21.8% (95% CI: 19.3%-24.6%); mild fatigue, 24.1% (95% CI: 21.5%-27.0%); moderate fatigue, 27.3% (95% CI: 24.5%-30.2%); and severe fatigue, 26.1% (95% CI: 23.4%-29.0%) (Fiest 2016)
Mortality	No data identified
Main co-medications prescribed	Amantadine, modafinil

Co-morbidity in the Target Population	Other Psychiatric Disorders: Bipolar Disorder, Alcohol Abuse
Incidence/prevalence	**Bipolar disorders:** Incidence: Not reported Prevalence: 5.83% based on one population-based study. **Alcohol abuse:** Incidence: Not reported. Prevalence: 14.8% based on one population-based study. Source: meta-analysis of 118 studies on the epidemiology of psychiatric co-morbidity in MS patients (Marrie 2015b)
Mortality	No data identified
Main co-medications prescribed	Bipolar disorders: Antipsychotic treatment. Alcohol abuse: Physician advice to stop or cut down on alcohol use

Co-morbidity in the Target Population	Seizure Disorder (Epilepsy)
Incidence/prevalence	Incidence: The summary estimate was 2.28% (95% CI: 1.11-3.44%), based on eight population-based studies. Most comparative studies (three out of four) found that the incidence of epilepsy was higher in the MS population than in the general population (Nicoletti 2003, Allen 2013, Nyquist 2002). One study found no difference (Olafsson 1999). Prevalence: The summary estimate of prevalence was 3.09% (95% CI: 2.01-4.16%), based in 11 population-based studies. In comparative studies, the prevalence of epilepsy was higher in the MS population than in the general population (Nicoletti 2003; Kang 2010; Marrie 2013). Source: meta-analysis of 32 studies on the epidemiology of epilepsy in MS patients (Marrie 2015g)
Mortality	No data identified
Main co-medications prescribed	Anti-epileptic medications

Co-morbidity in the Target Population	Sleep Disorders
	Restless legs syndrome: The prevalence ranges from 14.4% to 57.5%. Seven studies compared the prevalence of restless legs syndrome in the MS population to a control population, and all found a higher prevalence of the syndrome in the MS population (Deriu 2009, Ferini-Strambi 1994, Fragoso 2011, Gómez-Choco 2007, Kaminska 2012, Li 2012, Manconi 2008, Shaygannejad 2013, Auger 2005). Regarding other sleep disorders, prevalence ranges for sleep apnea from 7.14% to 58.1%, for narcolepsy from 0% to 1.6%, and for rapid eye movement (REM) behavior disorder from 2.2% to 3.2%. For periodic limb movements of sleep the prevalence was of 36% in one study Source: meta-analysis of 18 studies on the epidemiology of sleep disorder in MS patients (Marrie 2015g).
Mortality	No data identified.
Main co-medications prescribed	Restless legs syndrome, periodic limb movements of sleep: Anti-epileptic medications, anti-psychotics, centrally acting anti-histamines when needed. Sleep apnea: Positive airway therapy pressure when needed. Narcolepsy: modafinil, methylphenidate, amphetamines. REM behavior disorder: melatonin, clonazepam.

Part II: Module SII - Non-clinical Part of the Safety Specification

The key safety findings from the non-clinical program and their relevance to clinical use in humans are presented in Table 4.

Table 4 Key Safety Findings From Non-clinical Studies and Relevance to Human Usage

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
Single and repeat-dose toxicity: Toxicological evaluations of cladribine by the intravenous (iv), subcutaneous (sc) and oral routes revealed target organs of toxicity as expected from its pharmacological mode of action. The primary target organs at toxicologically relevant levels were tissues/organs in the lymphoid and myeloid system (spleen, thymus, lymph nodes, bone marrow) including decreases of lymphocytes and red blood cell parameters. No toxic effects were observed when cladribine was administered by oral route up to 20 mg/kg/day in mice and up to 6 mg/kg/day in monkeys, respectively, in chronic and sub-chronic studies. The daily exposure associated to these No-Observed-Adverse-Effect Levels (NOAELs) exceeded the daily human exposure at the maximum oral clinical dose (20 mg/day) of at least 1.95 fold based on area under the curve (AUC).	Single and repeat-dose toxicity: Based on the results from single and repeat-dose toxicity studies, no significant toxicity other than effects consistent with the mechanism of action of cladribine (e.g. lymphopenia) are anticipated.
Reproductive toxicity: Cladribine did not affect fertility in male or female mice. However, cladribine induced testicular changes (reduced testes weights and increased number of non-motile sperm) without detrimental effects on fertility. The NOAEL for testicular changes in the fertility study in male mice was set at CCI Testicular effects and changes in sperm parameters were also seen in monkey repeat-dose studies. Cladribine was shown to be embryolethal and induced fetal malformations in mice and rabbits after iv administration CCI The NOAEL for fetal effects in the embryofetal toxicity studies were 0.5 and 1.0 mg/kg/day respectively in mice and rabbits. Skeletal anomalies were also observed in the pre- and postnatal toxicity study in mice at ≥1.5 mg/kg/day by iv route (NOAEL for fetal effects was 0.5 mg/kg/day). No effects were detected on reproductive functions or general performance of the F1 generation. No effect was observed on the fetuses of the F2 generation. The NOAEL for maternal reproductive function and general toxicity was set at 3 mg/kg/day. The NOAEL for offspring development was set at 0.5 mg/kg/day.	Pregnancy, breastfeeding: Drugs that inhibit desoxyribonucleic acid (DNA) synthesis have been reported to be teratogenic in humans. Therefore and due to the teratogenicity observed with cladribine in animal studies, cladribine must not be used in pregnant women. In women of childbearing potential, pregnancy must be excluded before the initiation of cladribine in year 1 and year 2, and prevented by use of effective contraception during cladribine treatment and for at least 6 months after the last dose. On the basis of data from the reproductive toxicity studies in animals, potential consequences on human testes cannot be excluded. As cladribine interferes with DNA synthesis, adverse effects on human gametogenesis could be expected, male-mediated developmental toxicity cannot be ruled out. Male patients must take precautionary measures to prevent pregnancy of their partner during cladribine treatment and for at least 6 months after the last dose of cladribine.
Nephrotoxicity: Karyomegaly of renal tubular epithelium was observed in a one year subcutaneous toxicity study in monkeys at the dose of 1 mg/kg/day. Renal tubule degeneration /regeneration was seen in mice at the high dose of 30 mg/kg/day. With regards to the potential of HPβCD (excipient used in the proposed drug product formulation) to induce nephrotoxic effects, it is reported that many substituted cyclodextrins caused reversible vacuolation of the proximal renal tubular epithelium without evidence of kidney	Nephrotoxicity: Non-clinical findings from long-term treatment in monkeys and treatment with high doses in mice have little relevance for the proposed posology in patients. As no safety data are available in patients with moderate to severe renal impairment and renal elimination is a major contributor to cladribine clearance, cladribine is contraindicated in patients

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
damage or functional impairment indicating that this effect has few toxicological implications (Stella 2008). No toxicologically relevant effects were found in animals treated with hydroxypropyl-β-cyclodextrin (HPßCD) alone at 431 mg/kg in the transgenic tg.rasH2 mouse carcinogenicity study. HPßCD, when given to rats at oral dosages of 500 or 5000 mg/kg/day for 4 cycles (each cycle consisting of 5 days of dosing followed by a 23-day non-dosing period), followed by additional 5 days of dosing, did not cause adverse renal effects.	with moderate or severe renal impairment (creatinine clearance < 60 mL/min). There are no safety aspects from nonclinical studies on HPßCD that can be relevant to human usage.
<u>Hepatotoxicity:</u> Changes in liver function were observed in a sub-chronic toxicity study in mice by subcutaneous route at the doses of CCI [redacted] cladribine. These included mainly mild to moderately increased alanine aminotransferase (ALT), aspartate amino transaminase (AST) and/or alkaline phosphatase (ALP) activities.	<u>Hepatotoxicity:</u> Although the effects of the liver function after cladribine treatment is considered low in animals, based on the current accumulated clinical data, routine monitoring of liver parameters prior to start of Mavenclad in each treatment year is indicated. In case of signs or symptoms suggestive for a hepatic dysfunction, measurement of liver parameters is advised and Mavenclad treatment to be interrupted or discontinued as appropriate.
<u>Genotoxicity:</u> Cladribine is incorporated into DNA strands and inhibits DNA synthesis and repair. Cladribine did not induce gene mutation in bacteria or mammalian cells, but it was clastogenic causing chromosomal damage in mammalian cells in vitro at a concentration which was 17-fold above the expected clinical Cmax. In vivo clastogenicity in mice was detected at CCI [redacted] <u>Carcinogenicity:</u> The carcinogenic potential of cladribine was assessed in a long-term 22-month study with subcutaneous administration in mice and in a short-term 26-week study by oral route in transgenic mice. In the long-term carcinogenicity study in mice, the highest dose used was CCI [redacted] which seen to be genotoxic in the mouse micronucleus study CCI [redacted] No increased incidence of lymphoproliferative disorders or other tumor types (apart from Harderian gland tumors, predominantly adenomas) was seen in mice. Harderian gland tumors are not considered to be of clinical relevance, as humans do not have comparable anatomical structures. In the short-term carcinogenicity study in Tg rasH2 mice by oral route, no cladribine-related increase in incidence of lymphoproliferative disorders or other tumor types was seen at any dose tested up to 30 mg/kg per day (equivalent to approximately 25-fold the expected human exposure in AUC in patients taking the maximum daily dose of 20 mg cladribine). Cladribine was also assessed in a 1-year monkey study by the subcutaneous route. No increased incidence in lymphoproliferative disorders and no tumors were seen in this study. Although cladribine may have a potential for genotoxicity, long-term data in mice and monkeys did not provide any evidence of a relevant increased carcinogenicity risk in humans. Cyclodextrin (HPβCD): No toxicologically relevant effects were	<u>Malignancy:</u> Although cladribine may have a potential for genotoxicity, long-term study data in mice and monkeys did not provide evidence of an increased risk of malignancies in humans. Based on the preclinical studies, it is not anticipated that cladribine would pose a carcinogenic risk to humans at the intermittent and infrequent dose regimen foreseen in the MS indication. However, due to the mechanism of action leading to prolonged immune suppression, malignancy is considered a potential risk of cladribine.

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
found in animals treated with HPßCD alone at 431 mg/kg in the tg.rasH2 mouse carcinogenicity study.	
General and safety pharmacology: Safety pharmacology studies showed a favorable safety pharmacological profile of cladribine. In particular, no evidence was found that cladribine has any effect on the duration of the heart rate-corrected QT interval. In addition, the results of the 3 month toxicology study in monkeys did not show any effect on the duration of the heart rate-corrected QT interval (Bazett) following application of cladribine at doses of CCI [redacted] Moreover, the nonclinical safety pharmacological results indicated the absence of adverse events with respect to the CNS, which should translate into a safe clinical use of cladribine in patients. CCI [redacted]	Results of safety pharmacological studies do not indicate a risk for cardiovascular toxicity in humans in particular for Torsade-de-Pointes arrhythmias.
Mechanisms for drug interactions: In both rat and human hepatic S9 fractions and microsomes, cladribine metabolism was low. The in vitro metabolism of 14C-cladribine using primary hepatocyte cultures confirmed that cladribine was not substantially metabolized in humans. The metabolism routes in human hepatocytes were also the principal routes in all hepatocytes from the pre-clinical species and no unique human metabolite was found CCI [redacted] Using pooled human liver microsomes and cultured hepatocytes, there was no evidence of inhibition of major cytochrome (CYP) P450 enzyme activity by cladribine. In addition, cladribine has shown no clinically meaningful inductive effect on CYP1A2, CYP2B6 and CYP3A4 enzymes.	Non-clinical studies indicate hepatic metabolism as low; the compound is not a relevant substrate for CYP enzymes.

In conclusion the main toxicities observed in the non-clinical development program that have relevance for use in humans are:

Important identified risks

- Lymphopenia (based on non-clinical data; severe (≥grade 3) lymphopenia based on clinical data)

Important potential risks

- Teratogenicity/adverse pregnancy outcomes

Missing information

- None

Part II: Module SIII - Clinical Trial Exposure

The overview of studies conducted in the development program and included in the integrated safety analyses are provided in Table 5 below. Phase 1 studies are not included in the integrated safety analyses and hence not shown in the table.

Table 5 Overview of Studies in the Development Program Included in the Integrated Safety Analyses

Study	Indication	Type of Control / Blinding / Design	Total Number of Participants	
			Enrolled	At Least One Dose
CLARITY	RRMS	Phase 3: Randomized, placebo-controlled, double-blind, oral cladribine, MS disease modifying drug (DMD) allowed as rescue medication	1,326	1,319
CLARITY EXT	RRMS	Phase 3b: Randomized, placebo-controlled, double-blind, oral cladribine, MS DMD allowed as rescue medication. Extension study of CLARITY	867	806 (1)
ONWARD	RRMS/ Secondary Progressive Multiple Sclerosis (SPMS) with active disease	Phase 2: Randomized, placebo-controlled, double-blind, oral cladribine, INF-β as active background therapy for all participants	214	214
ORACLE-MS	Clinically Isolated Syndrome (CIS)	Phase 3: Randomized, placebo-controlled, double-blind, oral cladribine, MS DMD allowed as rescue medication	617	616
PREMIERE	RRMS/SPMS with active disease/CIS	Prospective observational long-term safety registry of participants who have participated in one of the 4 oral cladribine clinical trials (CLARITY, CLARITY EXT, ONWARD, ORACLE) or the Phase 1 pantoprazole drug-drug interaction (DDI, No 27967] study	1,183(2)	-
Scripps A	Chronic Progressive Multiple Sclerosis (CPMS)	Phase 2: open label proof-of-concept, iv cladribine	7	7
Scripps B	CPMS	Phase 2: Randomized, placebo-controlled, double-blind, SC cladribine and crossover retreatment phase	11	11

Study	Indication	Type of Control / Blinding / Design	Total Number of Participants	
			Enrolled	At Least One Dose
Scripps C	RRMS	Phase 2: 1.5 year (yr), randomized, placebo-controlled, double-blind, parallel group, SC cladribine and open label phase	49	49
MS-Scripps	CPMS	Phase 2: 2-yr, double-blind, placebo-controlled, randomized, crossover, single center, iv cladribine	49	49
MS-001	CPMS	Phase 3: Randomized, placebo-controlled, double-blind, parallel group, SC cladribine, long-term follow-up	159	159

(1) 61 of these participants were followed for safety only from the start of the study (i.e. these participants did not receive any treatment)

(2) 1,183 patients were enrolled; 1,148 patients were included in the safety set whereof 950 participants had been exposed to cladribine in previous studies and 198 patients were never exposed to cladribine; Clinical Trial Report for the PREMIERE Registry, dated 12 April 2019)

In general, the integrated safety analyses focused on specific cohorts (grouping of sets of studies) to characterize the safety profile of cladribine across all exposed participants and across a number of distinct populations. In this RMP, the frequencies and incidence rates of the important identified and potential risks as described in Part II, Module SVII.3 will be presented for the Monotherapy Oral cohort, focusing on the 3.5 mg/kg treatment group as this resembles most closely the target patient population and the posology according to the proposed labeling of cladribine. For the potential risks of malignancies and teratogenicity/adverse pregnancy outcomes, data from the All Exposed cohort are presented in addition.

These cohorts included the following safety data:

Monotherapy Oral cohort: includes safety data from all studies that used cladribine as oral monotherapy.

All Exposed cohort: includes safety data from all Phase 2/3 studies with any formulation of cladribine.

The following tables present the exposure to study drug for the Monotherapy Oral and the All Exposed cohorts.

Table 6 Duration of Exposure in the Monotherapy Oral Cohort (Integrated Analysis Population)

Parameter Statistic	Placebo	Cladribine 3.5 mg/kg
Monotherapy Oral, N	**641**	**923**
Time on study (weeks)		
Mean (SD)	197 ±139	223 ±132
Median	136	164
Min; Max	2; 471	1; 476
Patient-years	2421	3937

Parameter Statistic	Placebo	Cladribine 3.5 mg/kg
Number of weekly administration cycles, n		
Mean (SD)	5.4 (±1.2)	5.3 (±2.1)
Median	6.0	6.0
Min; Max	1.0; 6.0	1.0; 10.0
Cumulative dose (mg/kg)		
Mean (SD)	0	3.27 (±0.81)
Median	0	3.61
Min; Max	0	0.25; 4.00

Monotherapy Oral cohort includes data from CLARITY, CLARITY EXT, ORACLE-MS and PREMIERE Registry
Source: Integrated Summary of Safety (ISS) Update Analysis - Final version, Table ISS 1.4a

Table 7 Duration of Exposure in the All Exposed Cohort (Integrated Analysis Population)

Parameter Statistic	Placebo	Cladribine
All exposed, N	**802**	**1,976**
Time on study (weeks)		
Mean (Standard Deviation [SD])	181±135	260 ±139
Median	126	269
Min; Max	2; 723	1; 602
Patient-years	2782	9,855
Number of weekly administration cycles (n)		
Mean (SD)	5.5 (±1.4)	6.5 (±3.0)
Median	6.0	6.0
Min; Max	1.0; 8.0	1.0; 18.0
Cumulative dose (mg/kg)		
Mean (SD)	0	4.74 (±2.13)
Median	0	3.91
Min; Max	0	0.25; 13.02

All Exposed cohort includes data from CLARITY, CLARITY EXT, ONWARD, ORACLE-MS, PREMIERE Registry, Scripps A, Scripps B, Scripps C, MS-Scripps and MS-001
Source: ISS Update Analysis - Final version, Table ISS 1.1a

Table 8 **Exposure by Age Category and Gender: Cohort Monotherapy Oral (Integrated Analysis Population)**

Gender Age category	Placebo (N = 641)	Cladribine 3.5 mg/kg (N = 923)
	n (%)	n (%)
Total	641 (100.0)	923 (100.0)
Male	217 (33.9)	311 (33.7)
Female	424 (66.1)	612 (66.3)
<= 40 years	396 (61.8)	560 (60.7)
Male	149 (23.2)	211 (22.9)
Female	247 (38.6)	349 (37.8)
> 40 years	245 (38.2)	363 (39.3)
Male	68 (10.6)	100 (10.8)
Female	177 (27.6)	263 (28.5)

Source: ISS Update Analysis - Final version, Table ISS 2.4.1a

Table 9 **Exposure by Age Category and Gender: Cohort All Exposed (Integrated Analysis Population)**

Gender Age Category	Placebo (N = 802)	Cladribine (N = 1,976)
	n (%)	n (%)
Total	802 (100.0)	1,976 (100.0)
Male	267 (33.3)	670 (33.9)
Female	535 (66.7)	1,306 (66.1)
<= 40 years	457 (57.0)	1,092 (55.3)
Male	167 (20.8)	393 (19.9)
Female	290 (36.2)	699 (35.4)
> 40 years	345 (43.0)	884 (44.7)
Male	100 (12.4)	277 (14.0)
Female	245 (30.6)	607 (30.7)

Source: ISS Update Analysis - Final version, Table ISS 2.1.1a

Table 10 Exposure by Ethnic/Racial Origin: Cohort Monotherapy Oral (Integrated Analysis Population)

Ethnic/ Racial Origin	Placebo (N = 641)	Cladribine 3.5 mg/kg (N = 923)
	n (%)	n (%)
White	621 (96.9)	899 (97.4)
Black	2 (0.3)	5 (0.5)
Asian	12 (1.9)	13 (1.4)
Other	6 (0.9)	6 (0.7)
Total	641 (100.0)	923 (100.0)

Source: ISS Update Analysis - Final version, Table ISS 2.4.1a

Table 11 Exposure by Ethnic/Racial Origin: Cohort All Exposed (Integrated Analysis Population)

Ethnic/ Racial Origin	Placebo (N = 802)	Cladribine (N = 1,976)
	n (%)	n (%)
White	777 (96.9)	1,906 (96.4)
Black	5 (0.6)	23 (1.2)
Asian	12 (1.5)	24 (1.2)
Other	8 (1.0)	23 (1.2)
Total	802 (100.0)	1,976 (100.0)

Source: ISS Update Analysis - Final version, Table ISS 2.1.1a

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Pregnant or breastfeeding females

Reason for exclusion: Excluding pregnant or breastfeeding females is a standard precautionary measure that is often applied in clinical trials.

Is it considered to be included as missing information? No

Rationale: Cladribine was shown to be embryolethal when administered to pregnant mice, and the compound was teratogenic in mice and rabbits (Module SII). Furthermore, cladribine inhibits DNA synthesis and other drugs that inhibit DNA synthesis are known to be teratogenic. Therefore, use during pregnancy is contraindicated and use of effective contraception during treatment and for 6 months after the last dose of cladribine is recommended in women of childbearing potential and in male patients to prevent pregnancy of their partner. Breastfeeding is contraindicated during cladribine treatment and for 1 week after the last dose because of the potential for serious adverse reactions in breast-fed infants.

Teratogenicity/adverse pregnancy outcomes is considered an important potential risk of cladribine. The risk will be further quantified in the CLEAR study (Pregnancy Post-Authorization Safety Study [PASS]) (Part III) and the safety concern will continue to be monitored in clinical use.

Patients with renal impairment

Reason for exclusion: Patients with clinically significant renal disease were excluded as a precautionary measure considering the renal elimination of cladribine. No dedicated studies have been conducted in patients with renal impairment.

Is it considered to be included as missing information? No

Rationale: Renal clearance of cladribine has been shown to be dependent on creatinine clearance. While no dose adjustment is considered necessary in patients with mild renal impairment (creatinine clearance 60 to 89 mL/min), use of cladribine is contraindicated in patients with moderate or severe renal impairment (creatinine clearance <60 mL/min) and therefore use is not expected.

Pediatric patients (below 18 years)

Reason for exclusion: The target population in the clinical trials were adults of the age range 18 - 65 years.

Is it considered to be included as missing information? No

Rationale: In May 2009, the EU Pediatric Committee (PDCO) granted Merck a full waiver not to conduct studies in all categories of pediatric patients. This product specific waiver was confirmed by the Agency in April 2015.

Patients with compromised immunocompetences

Reason for exclusion: Patients with compromised immunocompetences were excluded from the clinical trials as a precautionary measure considering cladribine's immunosuppressive effect.

Is it considered to be included as missing information? No.

Rationale: Initiation of cladribine treatment is contraindicated in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy.

Patients with hypersensitivity to cladribine

Reason for exclusion: Excluding patients with hypersensitivity to the investigational medicinal product is a standard precautionary measure that is often applied in clinical trials.

Is it considered to be included as missing information? No

Rationale: Similar to all medicinal products use of cladribine is contraindicated in patients who are hypersensitive to the active substance or to any of the excipients. It is unlikely that patients with a known hypersensitivity will receive cladribine in clinical practice.

Patients with chronic infections

Reason for exclusion: Patients with chronic infections were excluded as a precautionary measure considering cladribine's immunosuppressive effect.

Is it considered to be included as missing information? No

Rationale: Cladribine is recognized to reduce the body's immune defense and may increase the likelihood of infections. Therefore, chronic infections are a recognized risk with cladribine and use of cladribine is contraindicated in patients with active chronic infection (tuberculosis or hepatitis) or with human immunodeficiency virus (HIV) infection. Tuberculosis is an important identified risk, and severe infections, PML and opportunistic infections (other than tuberculosis and PML) are important potential risks. All of these important risks will be further quantified in the CLARION study (long-term PASS) (Part III) and the safety concern will continue to be monitored in clinical use.

Patients with hepatic impairment

Reason for exclusion: Excluding patients with hepatic impairment is a standard precautionary measure that is often applied in clinical trials.

Is it considered to be included as missing information? No.

Rationale: Hepatic metabolism is considered negligible for cladribine; the clearance of cladribine in patients with hepatic impairment should not be impacted. Therefore, no studies have been conducted in patients with moderate to severe hepatic impairment. The product labeling provides this information along with a non-recommendation for the treatment of patients with moderate to severe hepatic impairment. No additional risk minimization measures are deemed necessary. Regarding pharmacovigilance, the number of patients with moderate to severe hepatic impairment in observational studies is expected to be low, and thus would not allow any meaningful analyses. Therefore, no additional pharmacovigilance measures seem feasible and no additional measures beyond routine risk management are planned.

Elderly (above 65 years)

Reason for exclusion: Elderly patients over the age of 65 years were excluded from the clinical trials to standardize the study population to adults so that efficacy and safety could be evaluated in this target population.

Is it considered to be included as missing information? No.

Rationale: No studies have been conducted in elderly patients. As per product labeling caution is recommended when Mavenclad is used in elderly patients, taking into account the potential greater frequency of decreased hepatic or renal function, concomitant diseases and other medicinal therapies in the older age group. The number of elderly patients currently included in the ongoing CLARION (long-term PASS) is low, and thus will not allow any meaningful analyses. However, a cumulative analysis of safety data in elderly from 817 individual case reports in the PBRER covering the period 08 July 2022 to 07 July 2023 showed that the pattern of AEs in elderly patients was consistent with the known safety profile of Mavenclad in the overall population. No additional measures beyond routine risk management are deemed necessary.

Patients with cardiac impairment

Reason for exclusion: Excluding patients with cardiac impairment is a standard precautionary measure that is often applied in clinical trials. The exclusion criterion for patients with cardiac impairment was not related to any cardiovascular toxicity of cladribine.

Is it considered to be included as missing information? No

Rationale: Cladribine is not known to be cardiotoxic based on non-clinical findings (Module SII) and experience in the clinical development program. The safety and efficacy of cladribine are not expected to be different in patients with cardiac impairment and accordingly no guidance is needed concerning use of cladribine in this population.

Patients at risk of malignancy

Reason for exclusion: As a precautionary measure considering the immunosuppressive effect of cladribine, patients with prior or current history of malignancy were excluded from the studies, with the exception of basal or squamous cell skin carcinoma in situ surgically removed without recurrence for at least five years prior to entry in the clinical studies.

Is it considered to be included as missing information? Yes. Long-term safety data in particular for malignancy risk is an area of missing information. Malignancies are also an important potential risk of cladribine. The risk will be further quantified in the CLARION study (Long-term PASS) (Part III) and will continue to be monitored in clinical use.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare or very rare adverse reactions or adverse reactions with a long latency such as malignancies.

A total of 1,976 patients received cladribine (all formulations, all Exposed Cohort) in Phase 2/3 studies to date, amounting to an exposure of 9,855 patient-years. The mean and median time on study for these patients was approximately 260 and 269 weeks, respectively. The sample size of 1,976 patients enables very common, common and uncommon adverse drug reactions (ADRs) to be detected. Across the MS program some of the patients have been followed up for more than 8 years, without evidence for an increased risk of ADRs with a long induction time such as malignancies.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 12 Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type Of Special Population	Exposure
Pregnant women	Despite precautionary measures to prevent pregnancy in clinical trials, pregnancies did occur in clinical trials with cladribine. The number of pregnancies reported including their outcome is provided in Table 13. Among 49 pregnancies in 43 women treated with cladribine 16 pregnancies occurred during administration of cladribine or within 183 days (i.e. 6 months) after last dose of cladribine. Three out of these 16 pregnancies resulted in 3 healthy newborns, 10 pregnancies were terminated by an induced abortion per decision of the patient, there were 2 spontaneous abortions and PPD . Overall, in the program 11 pregnancies were reported following paternal exposure to cladribine (reference: cohort All Exposed). Two pregnancies occurred in the placebo arm and 9 in the cladribine exposed arm. For 2 of the partner pregnancies the conception occurred during administration of cladribine or within 183 days (i.e. 6 months) after last dose of cladribine. These pregnancies resulted in 2 healthy newborns. Overall, there was no imbalances in pregnancy outcomes between cladribine- and placebo-treated participants. There were no congenital malformations in

<table>
<tr><th>Type Of Special Population</th><th>Exposure</th></tr>
<tr><td></td><td>pregnancies which occurred during cladribine treatment or within 6 months after the last dose.

Table 13 All Exposed Cohort – Pregnancy Outcomes (Female Trial Participants)

<table>
<tr><th></th><th>Placebo Number of Pregnancies (%), N=21 (100%)</th><th>Cladribine Number of Pregnancies (%), N=49 (100%)</th></tr>
<tr><td>Pregnancy outcome</td><td></td><td></td></tr>
<tr><td>Life birth</td><td>9 (43)</td><td>19 (39)</td></tr>
<tr><td>Induced abortion*</td><td>4 (19)</td><td>14 (29)</td></tr>
<tr><td>Spontaneous abortion</td><td>5 (24)</td><td>11 (22)</td></tr>
<tr><td>Medically indicated abortion</td><td>2 (9)</td><td>5 (10)</td></tr>
<tr><td>Unknown</td><td>1 (5)</td><td>0</td></tr>
</table>
*As per decision of the trial participants
ISS Update Analysis – Final version; Listing 3 and information from the Global Patient Safety (GPS) Database</td></tr>
<tr><td>Breast-feeding women</td><td>Not included in the clinical development program</td></tr>
<tr><td>Patients with relevant co-morbidities:
Patients with hepatic impairment
Patients with renal impairment
Patients with cardiovascular impairment
Immunocompromised patients
Patients with a disease severity different from inclusion criteria in clinical trials</td><td>Patients with hepatic impairment
Patients with moderate or severe hepatic impairment were not included in the clinical development program including patients with serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) or hepatic alkaline phosphatase (ALP) elevated to two and a half times the upper limit of normal (ULN) range. No dedicated studies have been conducted in patients with hepatic impairment. A small number of patients with some degree of hepatic impairment at baseline in the CLARITY study did not have any worse safety outcome as compared to the rest of the study population. Although the importance of hepatic function for the elimination of cladribine is considered negligible, its use is not recommended in patients with moderate or severe hepatic impairment.

Patients with renal impairment
Patients with a clinically significant renal disease were excluded from the studies. No dedicated studies have been conducted in patients with renal impairment. In patients with mild renal impairment (creatinine clearance 60 to 89 mL/min), no dosage adjustment is considered necessary. As the safety profile of cladribine in patients with moderate or severe renal impairment has not been established and renal elimination is a major contributor to cladribine clearance, cladribine is contraindicated in patients with moderate or severe renal impairment (creatinine clearance < 60 mL/min).</td></tr>
</table>

Type Of Special Population	Exposure
	Patients with cardiovascular impairment Patients with clinically significant cardiac disease, such as angina pectoris, congestive heart failure or arrhythmias, were not included in the clinical development program. As non-clinical safety data did not indicate a potential for cardiovascular toxicity and available clinical data does not provide evidence for a potential risk of cardiotoxicity, a contraindication /precaution is not warranted in patients with pre-existing cardiac disease. **Immunocompromised patients** Due to cladribine's immunosuppressive effect, patients with a history of active or chronic infectious disease or any disease that compromises immune function were excluded from the clinical development program. Prior or concomitant use of immunosuppressive therapy was also excluded during the clinical studies. Initiation of cladribine treatment is contraindicated in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy. Cladribine treatment is also contraindicated in patients with active chronic infections (tuberculosis or hepatitis) and with HIV infections. Screening for latent infections, in particular tuberculosis and hepatitis B and C, must be performed prior to initiation of therapy in year 1 and year 2. Initiation of cladribine should be delayed until the infection has been adequately treated. A delay in initiation of cladribine should also be considered in patients with an acute infection until the infection is fully controlled. **Patients with a disease severity different from inclusion criteria in clinical trials** Not applicable.
Population with relevant different ethnic origin	The majority of the patients enrolled in cladribine MS studies were of Caucasian origin (Table 10 and Table 11). There is currently no evidence to conclude that the safety profile would be different in patients of different racial and ethnic origin.
Subpopulations carrying relevant genetic polymorphisms	There was no testing for sub-populations with genetic polymorphisms.
Other	**Patients at risk of malignancy** Patients with prior or current history of malignancy were excluded from the studies, with the exception of basal or squamous cell skin carcinoma in situ surgically removed without recurrence for at least five years prior to entry into the clinical studies. Considering cladribine's immunosuppressive effects, the risk of a potential reactivation or development of a malignancy cannot be excluded. The use of cladribine in patients with active malignancies is contraindicated. An individual benefit-risk evaluation should be performed before initiating cladribine in patients with prior malignancy and standard cancer screening guidelines should be followed in patients treated with cladribine.

Part II: Module SV - Post-Authorisation Experience

In the US a New Drug Application (NDA) submission was made on 27 May 2010 for cladribine tablets with a proposed indication of the treatment of relapsing multiple sclerosis (RMS) (NDA 22-561), a Complete Response Letter (CRL) was received on 28 February 2011 and subsequently the NDA was withdrawn by the Sponsor on 19 August 2011. In addition, a negative opinion from the EU Committee for Medicinal Products for Human Use (CHMP) was received in January 2011. In June of that year, and in absence of additional data to allow regulatory agencies to re-assess the benefit/risk ratio, the Sponsor announced they would no longer pursue the worldwide approval of cladribine tablets. Consequently, the product under the tradename MOVECTRO was withdrawn from the approved markets, Australia and Russia, and all ongoing marketing authorization applications (MAAs) in other countries were withdrawn. However, the Sponsor decided to continue the Phase 2 and Phase 3 studies that were ongoing at the time, including the collection of long-term safety data to support a thorough characterization of the safety profile of cladribine, and thus establish a proper benefit/risk assessment for the treatment of RMS.

Following the availability of new clinical data, a new MAA was filed in the EU in June 2016 followed MAAs in other countries. Cladribine (Mavenclad) received approval from the European Commission on 22 August 2017 for the treatment of adult patients with highly active RMS as defined by clinical or imaging features (Mavenclad Summary of Product Characteristics [SmPC]).

Mavenclad was granted approval by the FDA on 29 March 2019. Mavenclad is currently authorized in 92 countries and marketed in 81 of these.

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Internal sales data have been used as the source to estimate the exposure of patients to cladribine.

A total 1,497,898 tablets were sold over the period from 01 September 2017 until 30 June 2023.

Taking the number of sold tablets into account, the patient exposure was calculated based on the following estimations:

- Patient compliance to cladribine is 98% during the first year course and 93% during the second-year course of treatment. Compliance is defined as completing treatment in the first treatment year and in the second treatment year. If a patient stops treatment, regardless of the reason, it is considered not compliant.
- Each patient receives a mean number of 11.2 tablets of 10 mg in the 2 weeks of treatment in Year 1 and as well in Year 2 considering that he/she is fully compliant.
- The 2 weeks treatment per yearly treatment take place during the same year.
- In the first year following the launch of Mavenclad, sold tablets were only used by patients in their first treatment year.

- In the second and following years after launch, sold tablets were used by patients in their first treatment year as well as by previously exposed patients who initiated their second treatment year.

For the calculation of the cumulative exposure in the period from 01 September 2017 until 30 June 2023 only the tablets sold for patients who initiated the first treatment year in that period are considered. The number of tablets used by patients who received their year 2 treatment are not considered, as they are related to returning patients already included in the calculation.

SV.1.2 Exposure

The cumulative post-authorization exposure to Mavenclad since marketing authorization in the EU (22 August 2017) until 30 June 2023 is estimated to be 78,613 patients (Periodic Benefit-Risk Evaluation Report [PBRER] for the period 08 July 2022 to 07 July 2023). As calculations are performed quarterly, this period does not entirely coincident with the reporting period; however, it provides an adequate estimation of patient exposure.

In addition, a maximum of 153 patients were exposed to cladribine when the product was marketed in Russia and Australia with the brand name MOVECTRO in the years 2011 and 2012 (Periodic Safety Update Reports [PSURs] no. 1-3). As these data are not reflective of Mavenclad, these data are not considered further.

Part II: Module SVI – Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Based on the available data (as included in the latest PBRER), the potential for misuse of cladribine is considered to be low. Even if accidentally obtained, illegal trafficking for commercial purposes is not anticipated.

Part II: Module SVII – Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable as this RMP version is not the initial submitted RMP.

SVII.1.1 Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

Safety data from the development program

Illustrations of AEs mainly focus on reporting by observation-adjusted adverse event incidence rates (Adj-AE) in the cladribine exposed participants compared to placebo group, defined as:

Adj-AE per 100-Patient-years (PY) = 100*(Number of participants with at least an AE)/ Sum of observation time in days among participants at risk for initial occurrence of an AE or time on study/365.25). Adj-AE will be expressed per 100 observation years, i.e. the Adj-AE for a specific AE will be multiplied by 100.

Incidence rates are generally reported for the Monotherapy Oral cohort, cladribine treatment group 3.5 mg/kg vs. placebo. (Please note, that with the availability of the final report of the PREMIERE registry in April 2019, the data in this section were recalculated) In addition, AE frequencies observed in the CLARITY trial are presented for the important identified risks as these frequencies served as reference for the assignment to frequency categories in the product labeling.

Accordingly, for the assessment of seriousness and severity of each identified and potential risk, the Monotherapy Oral cohort (cladribine treatment group 3.5 mg/kg vs placebo) has been used as reference.

For the potential risks of malignancies, teratogenicity/adverse pregnancy outcomes, data from the All Exposed cohort are provided in addition.

Safety data from postapproval sources

For each safety concern, safety data from postapproval sources is provided by the **cutoff date of 07 July 2023 (**as reported in recently submitted Mavenclad PBRER covering the period 08 July 2022 to 07 July 2023)**.**

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Severe (Grade ≥3) Lymphopenia	
Potential mechanism	The selective toxicity of cladribine in certain cell populations, in particular lymphocytes, can be explained by its mechanism of action.

<table>
<tr><th colspan="2">Important Identified Risk: Severe (Grade ≥3) Lymphopenia</th></tr>
<tr><td>Evidence source and strength of evidence</td><td>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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 and during 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.</td></tr>
<tr><td>Characterization of the risk</td><td><u>Frequency</u>

Clinical Data - Cohort Monotherapy Oral
Severe lymphopenia reported as AE
<table>
<tr><th></th><th>Placebo
(n=641)</th><th>cladribine 3.5 mg/kg (n=923)</th></tr>
<tr><td>No. of patients with adverse events of special interest (AESIs) of severe lymphopenia</td><td>0</td><td>24</td></tr>
<tr><td>Crude incidence rate</td><td>0</td><td>0.03</td></tr>
<tr><td>Adj-AE per 100-PY</td><td>0</td><td>0.62</td></tr>
<tr><td>95% CI</td><td>0.00; 0.15</td><td>0.42; 0.93</td></tr>
</table>
Source: ISS Update Analysis - Final version, Table ISS 15.1.6.1a

Note: As defined in the protocols and due to the mechanism of action of cladribine, lymphopenia was not routinely to be reported as AE.
Severe (Grade ≥3) lymphopenia from laboratory values.
<table>
<tr><th>Number (%) of participants with</th><th>Placebo
(n=641)</th><th>Cladribine 3.5 mg/kg (n=923)</th></tr>
<tr><td>ALC* at least one Grade 3</td><td>10 (1.6)</td><td>229 (24.8)</td></tr>
<tr><td>ALC at least one Grade 4</td><td>0</td><td>6 (0.7)</td></tr>
<tr><td>ALC missing (at all times)</td><td>0</td><td>2 (0.2)</td></tr>
</table>
Absolute Lymphocyte Count* postbaseline
Source: ISS Update Analysis - Final version, Table ISS 36.3.1a

CLARITY Trial
<table>
<tr><th>Number (%) of participants with</th><th>Placebo
(n=435)</th><th>Cladribine 3.5 mg/kg (n=430)</th></tr>
<tr><td>ALC Grade 3 or 4
at any time during the study</td><td>2 (0.5)</td><td>110 (25.6)</td></tr>
</table>
Source: CLARITY Clinical Trial Report, dated 18 May 2010, Table 25643-209

Postapproval Data
As of 07 Jul 2023, cumulatively, 151 cases with 152 AEs of serious lymphopenia in ~78,613 patients were reported (crude incidence: 0.002).</td></tr>
</table>

<table>
<tr><th colspan="2">Important Identified Risk: Severe (Grade ≥3) Lymphopenia</th></tr>
<tr><td></td><td>
Seriousness/outcomes

Clinical Data - Cohort Monotherapy Oral
Of 397 AEs of lymphopenia reported from 245 patients who received cladribine, only 4 were considered serious (1.0%). Of the 37 AEs of lymphopenia reported from 29 patients who received placebo, none were considered serious.
<table>
<tr><th>Duration (Recovery) of Grade 3 or 4 Lymphopenia episode</th><th>Placebo

(n=641)</th><th>Cladribine 3.5 mg/kg (n=923)</th></tr>
<tr><td>Number of episodes*</td><td>10 (100%)</td><td>283 (100%)</td></tr>
<tr><td>More than 2 months</td><td>6 (60.0)</td><td>215 (76.0)</td></tr>
<tr><td>More than 4 months</td><td>5 (50.0)</td><td>179 (63.3)</td></tr>
<tr><td>More than 9 months</td><td>4 (40.0)</td><td>107 (37.8)</td></tr>
<tr><td>More than 12 months</td><td>4 (40.0)</td><td>73 (25.8)</td></tr>
<tr><td>More than 24 months</td><td>3 (30.0)</td><td>29 (10.2)</td></tr>
<tr><td>More than 84 months</td><td>0</td><td>1 (0.4)</td></tr>
<tr><td>Number (%) of participants who left the study with unknown recovery (duration end date is missing)</td><td>5 (0.8)</td><td>45 (4.9)</td></tr>
</table>
* A Grade 3 or 4 lymphopenia episode is defined by a start/end date. Start= ALC>=Grade 3, postbaseline, end = following normal or Grade 1. A second episode can only occur if the first episode has ended (recovery). Source: ISS Update Analysis - Final version, Table ISS 36.3.4.5a

Postapproval Data
Cumulatively, among the 151 cases of serious lymphopenia (with 152 events), 46 cases were associated with infections (67 AEs [40 serious and 27 nonserious]). Serious coreported infections occurring more than once included COVID-19 (n=5), urinary tract infection (n=4), COVID-19 pneumonia, subcutaneous abscess and urosepsis (n=2, each). None of the coreported infections had a fatal outcome.
The outcome of serious lymphopenia events was reported as resolved (n=20), resolved with sequelae (n=2), resolving (n=33), not resolved (n=40), and unknown/not reported (n=57).
Note: Serious lymphopenia is provided instead of severe lymphopenia, as severity is often not reported in the postapproval setting.
</td></tr>
<tr><td>Risk factors and risk groups</td><td>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 IFN-β.</td></tr>
<tr><td>Preventability</td><td>While lymphopenia is essential for the therapeutic action of cladribine in MS, severe lymphopenia should be avoided. Severe lymphopenia may be preventable by careful monitoring of lymphocyte counts prior to each treatment course. Participants are only allowed to start cladribine treatment in Year 1 if they have normal lymphocyte counts. Cladribine treatment in Year 2 is restricted to participants with normal ALC or lymphopenia Grade 1. In case of lymphopenia Grade ≥2, treatment in Year 2 can be delayed for up to 6 months to allow for a recovery of lymphocyte counts.
Additional risk minimization measures are described in Part V, V.2.</td></tr>
</table>

Important Identified Risk: Severe (Grade ≥3) Lymphopenia	
Impact on the risk-benefit balance of the product	Patients with severe lymphopenia may be at an increased risk of infections especially for herpes zoster. Overall, the clinical benefit of cladribine for treating a debilitating condition is considered to outweigh the risk of severe (Grade ≥3) lymphopenia that can be managed in clinical practice through monitoring lymphocytes, actively monitoring for signs and symptoms suggestive of infections, and using prophylactic medications and/or treatment where indicated. The risk of severe (Grade ≥3) lymphopenia will be further characterized in patients exposed to cladribine in the ongoing CLARION study (long-term Post-Authorization Safety Study [PASS]) but this is unlikely to impact the risk-benefit balance of cladribine.
Public health impact	There is no public health risk posed.

Important Identified Risk: Herpes Zoster	
Potential mechanism	The risk of herpes zoster in patients treated with cladribine is likely related to the severity and duration of lymphopenia.
Evidence source and strength of evidence	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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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.
Characterization of the risk	Frequency *Clinical Data - Cohort Monotherapy Oral* **Placebo (n=641)** / **Cladribine 3.5 mg/kg (n=923)** No. of patients with any AESI: 4 / 28 Crude incidence rate: 0.006 / 0.03 Adj-AE per 100-PY: 0.2 / 0.7 95% CI: 0.1; 0.4 / 0.5; 1.1 Source: ISS Update Analysis - Final version, Table ISS 13.5.6.1a
	CLARITY Trial **Number (%) of participants with** / **Placebo (n=435)** / **Cladribine 3.5mg/kg (n=430)** Herpes zoster: 0 / 8 (1.9) Source: CLARITY Clinical Trial Report, dated 18 May 2010, Table 25643-130 *Postapproval Data* As of 07 Jul 2023, cumulatively, 665 ICSRs (670 AEs) of herpes zoster in ~78,613 patients were reported (crude incidence: 0.009).

Important Identified Risk: Herpes Zoster	
	Severity/Seriousness/outcomes *Clinical Data - Cohort Monotherapy Oral* Out of 31 AEs of herpes zoster reported for 28 participants treated with cladribine, 3 were considered serious; all of these events resolved. Of the 6 AEs of herpes zoster reported for 4 participants who received placebo, none were considered serious. One patient each in the placebo group and in the cladribine group experienced a severe AE of herpes zoster, otherwise herpes zoster was of mild to moderate severity. There was only one case of cladribine treatment discontinuation due to a herpes zoster in the Monotherapy Oral Cohort, cladribine treatment group 3.5 mg/kg. Across the program, there was also no case of systemic, serious disseminated herpes zoster. Three cases involving the skin only and coded as herpes zoster disseminated were received. All of them were reported as nonserious and nonsevere. Two of them were seen in participants treated with cladribine and 1 was reported for a participant on placebo. Overall, in participants exposed to cladribine, the incidence of herpes zosters was higher during the period of Grade 3 or 4 lymphopenia compared to the time when the participants were not experiencing Grade 3 or 4 lymphopenia. For the Monotherapy Oral Cohort, the Adj.-AE rate for the cladribine 3.5 mg/kg treatment group was 2.08 with Grade 3 or 4 lymphopenia and 0.63 without Grade 3 or 4 lymphopenia. Source: ISS Update Analysis - Final version, Tables ISS 13.5.6.1a and 39.10.2.3a. *Postapproval Data* Cumulatively, out of 670 AEs of herpes zoster in 665 ICSRs in the postapproval setting, mainly AE of herpes zoster (n=638) was reported, followed by ophthalmic herpes zoster (n=18), genital herpes zoster (n=6), herpes zoster reactivation (n=4), herpes zoster meningitis, herpes zoster oticus, herpes zoster meningitis and herpes zoster meningoencephalitis (n=1, each). Overall, 48 of these AEs were serious, of which 28 had outcome reported as resolved, 7 as resolving, 3 as not resolved, and for 10 outcome was unknown or not reported.
Risk factors and risk groups	Advanced age, immunosuppressive treatment.
Preventability	The risk of herpes zoster may be mitigated by early identification of severe lymphopenia with careful monitoring of lymphocyte counts prior to each treatment course; 2 and 6 months after start of treatment in each treatment year; if ALC is ≥Grade 3, patients should be actively monitored for lymphocyte counts and infections until values increase again. Participants are only allowed to start cladribine treatment in Year 1 if they have normal lymphocyte counts. Cladribine treatment in Year 2 is restricted to participants with normal ALC or lymphopenia Grade 1. In case of lymphopenia Grade ≥2, treatment in Year 2 can be delayed for up to 6 months to allow for a recovery of lymphocyte counts. The risk of herpes zoster can further be mitigated by vaccination and consideration of antiherpes prophylaxis in patients with Grade 4 lymphopenia. Additional risk minimization measures are described in Part V, V.2.

Important Identified Risk: Herpes Zoster	
Impact on the risk-benefit balance of the product	Dermatomal herpes zoster, identified as an adverse reaction of cladribine, is mainly non-serious and non-severe and manageable with standard of care treatment. Cladribine has been shown to be effective at treating adult patients with relapsing multiple sclerosis, through reducing relapse rates and delaying disease progression, especially in patients with highly active disease. Overall the clinical benefit of cladribine for treating a debilitating condition is considered to outweigh the risk of herpes zoster that can be managed in clinical practice through actively monitoring for signs and symptoms suggestive of infections and using anti-herpes prophylaxis medications and/or anti-infective treatment where indicated. The risk of herpes zoster will be further characterized in patients exposed to cladribine in the ongoing CLARION study (long-term PASS), but this is unlikely to impact the risk-benefit balance of cladribine.
Public health impact	There is no public health risk posed.

Important Identified Risk: Tuberculosis	
Potential mechanisms	The occurrence of tuberculosis as an opportunistic infection is dependent on immunosuppression. The risk of tuberculosis in patients treated with cladribine could be influenced by the severity and duration of lymphopenia as well as the proportion of CD4+/CD8+ T cells.
Evidence source and strength of evidence	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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 patients). Tuberculosis is considered an important identified risk as it is a serious infectious disease that might occur when patients are immunosuppressed. For rare events such as tuberculosis further long-term data are required for an accurate assessment of the risk; these will be characterized in the ongoing CLARION study (long-term PASS).
Characterization of the risk	<u>Frequency</u> *Clinical Data - Cohort Monotherapy Oral*

	Placebo (n=641)	**Cladribine 3.5 mg/kg (n=923)**
No. of patients with any AESI	0	2
Crude incidence rate	0	0.002
Adj-AE per 100-PY	0	0.05
95% CI	0.00; 0.15	0.01; 0.20

Source: ISS Update Analysis - Final version, Table ISS 46.1.6.1a

Note: Overall 3 cases of tuberculosis occurred during the clinical development program. All 3 patients were enrolled into the respective trials and received their first cladribine dose before implementation of the mandatory tuberculosis screening in the clinical trial program.

Postapproval Data

As of 07 Jul 2023, cumulatively, 26 ICSRs (26 AEs) of TB in ~78,613 patients were reported (crude incidence: 0.0003).

Important Identified Risk: Tuberculosis	
	Seriousness/outcomes *Clinical Data* Cohort Monotherapy Oral 2 participants assigned to the cladribine 3.5 mg/kg group experienced serious infections of tuberculosis. One case resulted in death. This participant died due to tuberculosis approximately 6 months after initial and last dose of cladribine (actual dose at onset of the event: 0.84 mg/kg). Prolonged use of solumedrol for MS was considered a contributing factor. The event occurred prior to the implementation of pre-screening for tuberculosis at baseline in the protocols. The second patient recovered from the tuberculosis infection. Overall, in the program, there was a third case of tuberculosis in patient treated with a cumulative dose of oral cladribine of 7.3 mg/kg. The event resolved. All the events of tuberculosis emerged from countries where tuberculosis is endemic. *Postapproval Data* Most TB events in the 26 cases (26 AEs) were nonserious (n=18) with no clinical signs or symptoms. The majority of events (n=19) were reported as Latent tuberculosis (2 were SAEs), while the 7 remaining events were coded to PT: Tuberculosis (6 serious and 1 nonserious [described as "suspected TB"]). Reactivation of TB was specified in 1 of the serious cases. The outcome of TB was reported as resolved for 5 AEs, resolving for 1 AE, not resolved for 5 AEs, and not reported/unknown for 15 AEs.
Risk factors and risk groups	Age, immunosuppressive treatment, presence of latent tuberculous infection.
Preventability	The risk of experiencing tuberculosis may be prevented by early identification of severe lymphopenia with careful monitoring of lymphocyte counts prior to each treatment course, 2 and 6 months after start of treatment in each treatment year; if ALC is ≥Grade 3, patients should be actively monitored for lymphocyte counts and infections until values increase again. Participants are only allowed to start cladribine treatment in Year 1 if they have normal lymphocyte counts. Cladribine treatment in Year 2 is restricted to participants with normal ALC or lymphopenia Grade 1. In case of lymphopenia Grade ≥2, treatment in Year 2 can be delayed for up to 6 months to allow for a recovery of lymphocyte counts. In addition, active tuberculosis is a contraindication for treatment with cladribine and must be excluded before initiation of cladribine. Therefore, screening for a latent infection of tuberculosis is mandatory prior to initiation of therapy in Year 1 and Year 2. Additional risk minimization measures are described in Part V, V.2.
Impact on the risk-benefit balance of the product	Taking into account the implemented preventive measures and the small number of TB cases in ~78,613 patients exposed to Mavenclad, the impact on the risk-benefit balance is currently considered as low.
Public health impact	There may be a public health risk posed in case of tuberculosis during exposure to cladribine.

Important Identified Risk: Liver injury	
Potential mechanism:	Not known; a direct liver injury can be excluded; an indirect or an idiosyncratic pathomechanism according to the CIOMS Working Group consensus report on drug-induced liver injury (DILI) (CIOMS 2020) is assumed.

Important Identified Risk: Liver injury	
Evidence source and strength of evidence	Several individual case safety reports from postapproval 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
Characterization of the risk	Frequency *Clinical trial data* Clinical trial data included only single cases suggestive for a cladribine induced liver injury with overall no imbalance between the placebo and the cladribine treatment group regarding hepatic disorders or liver parameters. *Postapproval Data* As of 07 Jul 2023, cumulatively, 488 cases (670 AEs) of liver injury in ~78,613 patients were reported (crude incidence: 0.006). Severity/Seriousness/outcomes *Postapproval Data* Of the 670 AEs reported in 488 ICSRs, 188 AEs (in 115 ICSRs) were serious, with increased alanine aminotransferase (n=40) and increased aspartate aminotransferase (n=31) being the most common. Nonserious AEs (n=482) mostly pertained to liver enzyme elevations. In several cases, a medical history of episodes of liver parameter elevations with other drugs was reported. Overall, the outcome was resolved (with or without sequelae) or resolving for 202 AEs, not resolved for 102 AEs, and unknown/not reported for 365 AEs. The remaining 1 event had a fatal outcome and was described as a drug-induced liver injury (verbatim term: liver failure likely secondary to isoniazid toxicity in a patient with pre-existing alcoholic liver impairment) unrelated to cladribine. Of note, details in most ICSRs are generally insufficient to assess the severity of liver injury according to the criteria set forth by the International DILI Expert Working Group (CIOMS 2020).
Risk factors and risk groups	Patients with a history of abnormal liver tests
Preventability	Evaluation of the patient's medical history regarding previous episodes of liver injury with other drugs or underlying liver pathologies prior to start of Mavenclad treatment. Routine monitoring of liver parameters prior to start of treatment in year 1 and year 2. In case of signs or symptoms suggestive for a hepatic dysfunction, measurement of liver parameters is advised and Mavenclad treatment to be interrupted or discontinued as appropriate.
Impact on the risk-benefit balance of the product	Taking into account the low number of serious cases in 78,613 patients exposed to Mavenclad, the impact on the risk-benefit balance is currently considered as low
Public health impact	None identified

<table>
<tr><th colspan="2">Important Potential Risk: Severe Infections</th></tr>
<tr><td>Potential mechanism</td><td>The risk of severe infections in patients treated with cladribine may be related to the severity and duration of lymphopenia.</td></tr>
<tr><td>Evidence source and strength of evidence</td><td>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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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.</td></tr>
<tr><td>Characterization of the risk</td><td><u>Frequency</u>

Clinical Data - Cohort Monotherapy Oral
<table>
<tr><th></th><th>Placebo
(n=641)</th><th>Cladribine
3.5 mg/kg
(n=923)</th></tr>
<tr><td>No. of unique AESI of severe infection</td><td>26</td><td>39</td></tr>
<tr><td>No. of patients with AESI of severe infection</td><td>19</td><td>29</td></tr>
<tr><td>Crude incidence rate</td><td>0.03</td><td>0.03</td></tr>
<tr><td>Adj-AE per 100-PY</td><td>0.8</td><td>0.8</td></tr>
<tr><td>95% CI</td><td>0.5; 1.3</td><td>0.5; 1.1</td></tr>
</table>
Source: ISS Update Analysis - Final version, Tables ISS 13.2.6.1a

Postapproval Data
As of 07 Jul 2023, cumulatively, 1,028 ICSRs of serious infections in ~78,613 patients were reported (crude incidence: 0.01).
Among the 1,028 ICSRs, 1,271 serious infections were reported. The most frequently reported events (>20 times) were COVID-19 (n=151), pneumonia (n=149), urinary tract infection (n=129), COVID-19 pneumonia (n=47), sepsis (n=43), lower respiratory tract infection (n=36), kidney infection (n=34), influenza (n=31), diverticulitis (n=29), herpes zoster (n=29), infection (n=22) and urosepsis (n=21).
Note: Serious infections are provided instead of severe infections, as severity is often not reported in the postapproval setting.</td></tr>
</table>

Important Potential Risk: Severe Infections	
	Seriousness/outcomes *Clinical Data - Cohort Monotherapy Oral* Of the 39 unique AEs of severe infections from patients who received cladribine 3.5 mg/kg, 29 (74%) were considered serious. Of the 26 unique AEs of severe infections in patients who received placebo, 12 (46%) were considered serious. The majority of participants recovered from severe infections, one case of tuberculosis in a participant treated with cladribine resulted in death (see above). There were no fatal outcomes in participants treated with placebo. *Postapproval Data* Of the 1,271 serious infection AEs reported cumulatively, 350 were reported as resolved, 11 as resolved with sequelae, 194 as resolving, 134 as not resolved, and 561 as unknown/not reported. The remaining 21 SAEs (in 14 ICSRs) were fatal: COVID 19, Pneumonia (n=4, each), Urosepsis (n=2), COVID-19 pneumonia, Endocarditis bacterial, Lower respiratory tract infection, Nocardiosis, Pharyngitis, Respiratory tract infection, Sepsis, Septic embolus, Septic shock, Urinary tract infection and Infection (each reported once). Overall, the nature and frequency of serious infections postapproval was generally similar to the nature and frequency observed during clinical development.
Risk factors and risk groups	Advanced age, immunosuppressive treatment
Preventability	The risk of experiencing severe infections may be prevented by early identification of severe lymphopenia with careful monitoring of lymphocyte counts prior to each treatment course, 2 and 6 months after start of treatment in each treatment year; if ALC is ≥Grade 3, patients should be actively monitored for lymphocyte counts and infections until values increase again. Participants are only allowed to start cladribine treatment in Year 1 if they have normal lymphocyte counts. Cladribine treatment in Year 2 is restricted to participants with normal ALC or lymphopenia Grade 1. In case of lymphopenia Grade ≥2, treatment in Year 2 can be delayed for up to 6 months to allow for a recovery of lymphocyte counts. In addition, active chronic infections of tuberculosis and hepatitis are contraindications for treatment with cladribine and must be excluded before initiation of cladribine. Latent infections may be activated, including tuberculosis and hepatitis. Therefore, screening for latent infections in particular tuberculosis and hepatitis B and C is mandatory prior to initiation of therapy in Year 1 and Year 2. A delay in initiation of cladribine treatment is recommended until the infection has been adequately treated. In patients experiencing Grade 4 lymphopenia, consideration of antiherpes prophylaxis is recommended. Additional risk minimization measures are described in Part V, V.2.
Impact on the risk-benefit balance of the product	Severe infections are an important potential risk. Cladribine has been shown to be effective at treating adult patients with relapsing multiple sclerosis, through reducing relapse rates and delaying disease progression, especially in patients with highly active disease. Overall the clinical benefit of cladribine for treating a debilitating condition is considered to outweigh the risk of severe infections that can be managed in clinical practice through actively monitoring for signs and symptoms suggestive of infections and and/or anti-infective treatment where indicated.
Public health impact	There may be a public health risk posed in case of contagious infectious AEs such as reactivated hepatitis B virus (HBV), hepatitis C virus (HCV) and tuberculosis infections (please see potential risk of opportunistic infections) during exposure to cladribine.

Important Potential Risk: Progressive Multifocal Leukoencephalopathy (PML)	
Potential mechanism	The occurrence of PML as an opportunistic infection is dependent on immunosuppression. The potential risk of PML in patients treated with cladribine could be influenced by the severity and duration of lymphopenia as well as the proportion of CD4+/CD8+ T cells.
Evidence source and strength of evidence	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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 characterized in the ongoing CLARION study (long-term PASS)
Characterization of the risk	Frequency *Clinical Data* In clinical trials of both, oral and parenteral cladribine in MS, no cases of PML were reported during a total observation period of more than 9,800 PYs. Source: ISS Update Analysis - Final version, Tables ISS 13.6.1.1 *Postapproval Data* As of 07 Jul 2023, cumulatively, 1 case of PML was reported in ~78,613 patients exposed to Mavenclad. The assessment of this case is hampered by unavailability of relevant data including an MRI examination shortly prior to the start of Cladribine treatment and lack of positivity of a CSF JC virus polymerase chain reaction test result. The case causality could also not definitely be attributed to cladribine since the patient was pretreated with other agents that are supposed to be involved in the occurrence of PML. Thus, the case has been classified as not suspected to be causally related to Mavenclad. PML cases have been reported in the past but these have been in the context of patients with leukemia treated with a parenteral formulation of cladribine (i.e. not Mavenclad) using a different treatment regimen.
Risk groups or risk factors	Age, immunosuppressive treatment, presence of latent infections such as tuberculosis, JC Virus, HBV, or HCV infections
Preventability	The risk of PML may be prevented by early identification of severe lymphopenia with careful monitoring of lymphocyte counts prior to each treatment, 2 and 6 months after start of treatment in each treatment year; if ALC is ≥Grade 3, patients should be actively monitored for lymphocyte counts and infections until values increase again. Participants are only allowed to start cladribine treatment in Year 1 if they have normal lymphocyte counts. Cladribine treatment in Year 2 is restricted to participants with normal ALC or lymphopenia Grade 1. In case of lymphopenia Grade ≥2, treatment in Year 2 can be delayed for up to 6 months to allow for a recovery of lymphocyte counts. A baseline MRI should be considered before initiating cladribine treatment. Additional risk minimization measures are described in Part V, V.2.
Impact on the risk-benefit balance of the product	As only 1 case of PML has been reported in ~78,613 exposed patients which could not be causally attributed to Mavenclad, the impact on the risk-benefit balance is currently considered as very low
Public health impact	Considering the specific nature of PML an impact on the public health is not assumed

<table>
<tr><th colspan="2">Important Potential Risk: Opportunistic Infections other than PML and Tuberculosis</th></tr>
<tr><td>Potential mechanism</td><td>The occurrence of opportunistic infections is dependent on immunosuppression. The potential risk of opportunistic infections in patients treated with cladribine could be influenced by the severity and duration of lymphopenia as well as the proportion of CD4+/CD8+ T cells.</td></tr>
<tr><td>Evidence source and strength of evidence</td><td>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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 study (long-term PASS).</td></tr>
<tr><td rowspan="2">Characterization of the risk</td><td><u>Frequency</u>

Clinical Data - Cohort Monotherapy Oral
<table>
<tr><th></th><th>Placebo
(n=641)</th><th>Cladribine
3.5 mg/kg
(n=923)</th></tr>
<tr><td>No. of patients with any AESI</td><td>4</td><td>10</td></tr>
<tr><td>Crude incidence rate</td><td>0.006</td><td>0.01</td></tr>
<tr><td>Adj-AE per 100-PY</td><td>0.17</td><td>0.26</td></tr>
<tr><td>95% CI</td><td>0.06; 0.44</td><td>0.14; 0.48</td></tr>
</table>
Source: ISS Update Analysis - Final version, Tables ISS 13.7.6.1a

Postapproval Data
As of 07 Jul 2023, cumulatively, 22 ICSRs with 22 AEs of opportunistic infections (other than PML and TB) in ~78,613 exposed patients were reported (crude incidence: 0.0003).</td></tr>
<tr><td><u>Severity/Seriousness/outcomes</u>

Clinical Data - Cohort Monotherapy Oral
Of the 22 unique AEs of opportunistic infections (other than tuberculosis and PML) reported from 10 patients who received cladribine 3.5 mg/kg, none were considered serious and none were severe. Of the 4 unique AEs of opportunistic infections reported from 4 patients who received placebo, none considered serious but one was considered severe.
The majority of events resolved.

Postapproval Data
Of the 22 events, 18 were serious and 4 were nonserious. For SAEs, the most common PTs were Herpes ophthalmic (n=6) and Infection susceptibility increased (n=2). Other SAEs were reported once each: meningomyelitis herpes, esophageal candidiasis, nocardiosis, ophthalmic herpes simplex, histoplasmosis disseminated, pneumonia cryptococcal, cytomegalovirus infection, pulmonary histoplasmosis, atypical mycobacterial pneumonia and meningitis cryptococcal.
The outcomes of the 22 total events were resolved (n=4), resolving, not resolved (n=3, each), fatal (n=1), and unknown/not reported (n=11).</td></tr>
</table>

Important Potential Risk: Opportunistic Infections other than PML and Tuberculosis	
Risk factors and risk groups	Age, immunosuppressive treatment, presence of latent infections such as tuberculosis, JCV, HBV, or HCV infections.
Preventability	The risk of experiencing opportunistic infections may be prevented by early identification of severe lymphopenia with careful monitoring of lymphocyte counts prior to each treatment course, 2 and 6 months after start of treatment in each treatment year; if ALC is ≥ Grade 3, patients should be actively monitored for lymphocyte counts and infections until values increase again. Participants are only allowed to start cladribine treatment in Year 1 if they have normal lymphocyte counts. Cladribine treatment in Year 2 is restricted to participants with normal ALC or lymphopenia Grade 1. In case of lymphopenia Grade ≥2, treatment in Year 2 can be delayed for up to 6 months to allow for a recovery of lymphocyte counts. In patients experiencing Grade 4 lymphopenia, consideration of antiherpes prophylaxis is recommended. Additional risk minimization measures are described in Part V, V.2.
Impact on the risk-benefit balance of the product	Taking into account the very small number of opportunistic infections in ~78,613 patients exposed to Mavenclad in the postapproval setting, the impact on the risk-benefit balance is currently considered as low.
Public health impact	There may be a public health risk in case of contagious infections acquired during exposure to cladribine.

Important Potential Risk: Malignancies	
Potential mechanism	Immunosuppression caused by sustained, severe lymphopenia.
Evidence source and strength of evidence	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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 CLARION study (long-term PASS).
Characterization of the risk	Frequency Clinical Data Cohort All Exposed

	Placebo (n=802)	Cladribine (n=1,976)
No. of unique AESI	4	35*
No. of patients with any AESI	4	34
Crude incidence rate	0.005	0.017
Adj-AE per 100-PY	0.14	0.35
95% CI	0.05; 0.38	0.25; 0.48

*in addition, there was 1 indeterminate case as adjudicated by an independent external review board.

Source: ISS Update Analysis - Final version, Table ISS 14.1.1.1

<table>
<tr><th colspan="2">Important Potential Risk: Malignancies</th></tr>
<tr><td></td><td>Cohort Monotherapy Oral
<table>
<tr><th></th><th>Placebo (n=641)</th><th>Cladribine 3.5 mg/kg (n=923)</th></tr>
<tr><td>No. of unique AESI</td><td>3</td><td>10</td></tr>
<tr><td>No. of patients with any AESI</td><td>3</td><td>10</td></tr>
<tr><td>Crude incidence rate</td><td>0.005</td><td>0.011</td></tr>
<tr><td>Adj-AE per 100-PY</td><td>0.12</td><td>0.26</td></tr>
<tr><td>95% CI</td><td>0.04; 0.39</td><td>0.14; 0.48</td></tr>
</table>
Source: ISS Update Analysis - Final version, Table ISS 14.1.6.1a</td></tr>
<tr><td></td><td>Postapproval Data
As of 07 Jul 2023, cumulatively, 285 ICSRs (with 314 AEs) of malignancies (i.e. “Malignant tumors [SMQ]-Narrow scope”) in ~78,613 exposed patients were reported from all postapproval sources and Phase 4 interventional studies (crude cumulative incidence: 0.004).
PTs for the most frequently reported malignant tumors (MedDRA PTs) were Breast cancer, Basal cell carcinoma (n=30, both), Neoplasm malignant (n=21), Skin cancer (n=18), Malignant melanoma (n=13), Invasive ductal breast carcinoma (n=10).
In addition, 37 cases (with 38 AEs) of unspecified tumors were reported (i.e. not specified if benign or malignant). Events reported at least twice included neoplasm (n=10), thyroid neoplasm, brain neoplasm (n=4, each), lung neoplasm (n=3), neoplasm skin, renal neoplasm and bladder neoplasm (n=2, each).</td></tr>
<tr><td></td><td><u>Severity/Seriousness/outcomes</u>
Clinical data
Malignancies in the clinical development program of oral cladribine were considered serious per protocol. Cancer outcome depends on e.g. the tumor type and location, stage at time of diagnosis, available treatment options, curability of the tumor etc.
The types of malignancies observed in the clinical program and postapproval were typical of those observed in the general population. There was no clustering of malignancies, no increase in virally induced malignancies, hematological malignancies, or nonmelanoma skin cancers observed.

Postapproval data
The outcome of the 314 malignancies in the 285 cases was resolved (n=32), resolved with sequelae (n=1), resolving (n=14), not resolved (n=70), fatal (n=6), and unknown/not reported (n=191). In 5 cases, the malignant tumor had a fatal outcome (PTs: Lung adenocarcinoma [n=2], Lung cancer metastatic, Lung neoplasm malignant, and Lung carcinoma cell type unspecified stage iv [n=1, each]).
The outcome of the 38 unspecified tumors in 37 additional cases was resolved (n=3), resolving (n=1), not resolved (n=9), and unknown/not reported (n=24). The remaining 1 unspecified tumor reported outcome as fatal (PT: Langerhans’ cell histiocytosis).</td></tr>
<tr><td>Risk factors and risk groups</td><td>Advanced age, immunosuppressive treatment, exposure to biological, chemical or physical oncogenic factors (e.g. some viruses, tobacco use, sunbathing, ionizing radiation), genetic/familiar disposition</td></tr>
</table>

Important Potential Risk: Malignancies	
Preventability	Cladribine is contraindicated in MS patients with active malignancies. An individual benefit-risk evaluation should be performed before initiating cladribine in patients with prior malignancy. Patients treated with cladribine should follow standard cancer screening guidelines. Additional risk minimization measures are described in Part V, V.2.
Impact on the risk-benefit balance of the product:	Malignancies are severe illnesses with potentially a fatal outcome. Cladribine has been shown to be effective at treating adult patients with relapsing multiple sclerosis, through reducing relapse rates and delaying disease progression, especially in patients with highly active disease. Overall the clinical benefit of cladribine for treating a debilitating condition is considered to outweigh the risk of malignancies. The risk of malignancies will be further characterized in patients exposed to cladribine in the ongoing CLARION study (long-term PASS), but this is unlikely to impact the risk-benefit balance of cladribine.
Public health impact	None identified

Important Potential Risk: Teratogenicity / Adverse Pregnancy Outcomes	
Potential mechanism:	Cladribine is known to inhibit DNA synthesis. Other drugs that inhibit DNA synthesis were reported to be teratogenic. Cladribine was shown to be embryolethal when administered in pregnant mice, and the compound was teratogenic in mice and rabbits.
Evidence source and strength of evidence	Cladribine interferes with DNA synthesis and could cause congenital malformations when used during pregnancy based on human experience 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 participants 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

Important Potential Risk: Teratogenicity / Adverse Pregnancy Outcomes	
Characterization of the risk	*Clinical Data* All Exposed Cohort Patients who were pregnant or lactating were excluded from all studies and the use of adequate contraception was required in study participants. Nonetheless, across the cladribine clinical program in MS, 62 female participants experienced 70 pregnancies of which 43 participants treated with cladribine had 49 pregnancies and 19 participants treated with placebo had 21 pregnancies. Many of the pregnancies, which occurred during the study, were voluntarily terminated without any further information on the fetus. Among 49 pregnancies in 43 women treated with cladribine 16 pregnancies occurred during administration of cladribine or within 183 days (i.e. 6 months) after last dose of cladribine. 3 out of these 16 pregnancies resulted in 3 healthy newborns, 10 pregnancies were terminated by an induced abortion per decision of the patient, in addition there were 2 spontaneous abortions and 1 medically indicated abortion. In addition, 11 female partners of male study participants experienced 11 pregnancies, of which 9 participants were treated with cladribine and 2 participants received placebo. Two of the 9 male participants treated with cladribine fathered a child during administration of cladribine or within 183 days (i.e. 6 months) after last dose of cladribine. These pregnancies resulted in 2 healthy newborns. Source: ISS Update Analysis - Final version, Table 3: Pregnancies including female partner of male patients and information from the GPS Database Overall, there was no imbalance in adverse pregnancy outcomes (e.g. spontaneous abortions) in cladribine- and placebo-treated participants. There were no congenital malformations in pregnancies which occurred during cladribine treatment or within 6 months after last dose. *Postapproval Data* Cumulatively, 333 unique pregnancy reports were received (300 cases of maternal exposure and 33 cases of pregnancies in women whose partner was treated with cladribine [paternal exposure]) for patients exposed to cladribine during pregnancy or within 6 months prior to pregnancy. In cases of maternal exposure, pregnancy outcomes were last reported as follows: unknown/other (n=77), pending (n=105), live birth without congenital anomaly (CA) (n=70), live birth with CA (n=4, 1 major and 3 minor), spontaneous abortion (n=19), ectopic pregnancy (n=2), PPD and elective termination without fetal defects or unknown (n=22). In the 33 cases of paternal exposure, pregnancy outcomes were last reported as follows: pending (n=16), unknown (n=8), spontaneous abortion (n=2), and live birth without CA (n=7). Overall, there were no apparent trends in adverse pregnancy outcomes. The 1 major CA (PT: PPD) was identified from a literature source PPD. A female patient of unknown age was exposed to Mavenclad 66 days before her last menstrual period. The authors reported that no clinical intervention was required. As no medical history, prior or concomitant medications, Mavenclad dosing information, or event details were provided; the causality was not assessable by the Company.
Risk factors and risk groups	Unknown

Important Potential Risk: Teratogenicity / Adverse Pregnancy Outcomes	
Preventability	Contraception: All efforts should be made in order to prevent pregnancies in patients treated with cladribine or in females whose partners are treated with cladribine to avoid potential adverse pregnancy outcomes as defined in Part V.1 under teratogenicity/adverse pregnancy outcomes. At the beginning of each treatment year, counseling of patients regarding the potential risk for the fetus and the need for effective contraception is recommended. In women of childbearing potential, pregnancy must be excluded before the initiation of cladribine in Year 1 and Year 2 and prevented by use of effective contraception during cladribine treatment and for at least 6 months after the last dose. Women who become pregnant under therapy with oral cladribine should discontinue treatment. Male patients must take precautions to prevent pregnancy of their partner, during cladribine treatment and for at least 6 months after the last dose. Additional risk minimization measures are described in Part V, V.2.
Impact on the risk-benefit balance of the product	Cladribine interferes with DNA synthesis and use during pregnancy may result in teratogenicity and adverse pregnancy outcomes. Cladribine has been shown to be effective at treating adult patients with relapsing multiple sclerosis, through reducing relapse rates and delaying disease progression, especially in patients with highly active disease. Overall the clinical benefit of cladribine for treating a debilitating condition is considered to outweigh the risk of teratogenicity/adverse pregnancy outcomes that can be managed in clinical practice through use of effective contraception during treatment and for at least 6 months after last dose by women of childbearing potential and male patients to prevent pregnancy of their female partner. The risk of teratogenicity/adverse pregnancy outcomes will be further characterized in the CLEAR study (pregnancy PASS), but this is unlikely to impact the risk-benefit balance of cladribine
Public health impact	None identified

Important Potential Risk: Seizures	
Potential mechanism:	Not known; with high doses of parenteral cladribine neurotoxicity was observed but no seizures.
Evidence source and strength of evidence	Individual case safety reports from post marketing 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
Characterization of the risk	Clinical trial data include only single cases of seizures with no imbalance between the placebo and the cladribine treatment group. *Postapproval Data* Frequency As of 07 Jul 2023, cumulatively, 133 ICSRs of seizures in ~78,613 patients were reported (crude incidence: 0.002). Cumulatively, the 133 ICSRs included 138 seizure AEs from postapproval sources, of which 126 AEs were serious. The outcome reported for these events was resolved or resolved with sequelae for 26 AEs, resolving and not resolved for 15 AEs (each), and not reported/unknown for 81 AEs. One ICSR reported a fatal event of Seizure. This ICSR reported limited information about patient's medical history, concomitant medications, latency and clinical course of event for a establishing a causal association. None of the AEs related to seizures were suspected to be related to Mavenclad by the Company.
Risk factors and risk groups	Not known

Important Potential Risk: Seizures	
Preventability	Not known.
Impact on the risk-benefit balance of the product	Taking into account the small number of seizures in ~78,613 patients exposed to Mavenclad, the impact on the risk-benefit balance is currently considered as low
Public health impact	None identified

SVII.3.2 Presentation of the Missing Information

Missing Information: Sequential Use of Other Immunosuppressive or Immunomodulatory Agents After Cladribine Treatment	
Evidence source and strength of evidence	The long-term safety of cladribine was studied in the observational PREMIERE registry. However, safety data in patients receiving sequential treatment with other immunosuppressive or immunomodulatory agents after treatment with oral cladribine are limited. Cumulatively, 13 cases with immunosuppressive/immunomodulatory agents administered after Mavenclad treatment, which are indicated as cosuspect drugs, were identified from postapproval sources. The cosuspect drugs included apremilast, fingolimod, ozanimod, azathioprine, methotrexate, natalizumab, ofatumumab, tacrolimus, and teriflunomide. Overall, 34 AEs (23 nonserious and 11 serious) were reported, with Lymphopenia (n=4), Lymphocyte count decreased and Multiple sclerosis relapse (n=2, each) being the most common PTs. Of the 11 serious AEs, 7 were not suspected (unlikely) to be related to Mavenclad by the Company, 1 AE was not assessable and 3 were likely to be related to Mavenclad (AEs=cellulitis, lower respiratory tract infection and white blood cell count decreased). In 71 cases, it was not specified whether the use of the cosuspect immunomodulatory/immunosuppressive agent was subsequent to Mavenclad treatment or not.
Anticipated risk/ consequence of the missing information	The safety of cladribine in this population is unknown but a potential additive effect on the immune system may occur when immunosuppressive or immunomodulatory agents are used after treatment with cladribine. Further collection of data relating to patients receiving sequential treatment with other immunosuppressive or immunomodulatory agents after treatment with oral cladribine will be through collection and evaluation of spontaneous reports in the postapproval setting (routine pharmacovigilance). As a further pharmacovigilance measure, sequential use of immunosuppressive or immunomodulatory agents will be quantified by an additional secondary objective, corresponding outcome, and analysis in the ongoing CLARION study (long-term PASS). The objective will assess the impact of the first subsequent use of immunomodulatory/immunosuppressive agents on the incidence of AESIs in patients with highly active RRMS after oral cladribine treatment.

Missing Information: Impact of Exposure to Prior Immunomodulatory/Immunosuppressive Agents on Subsequent Risks Following Cladribine Exposure	
Evidence source and strength of evidence	From the clinical program of cladribine in MS, there is limited experience from participants who have been previously treated with other immunomodulatory/ immunosuppressive agents. Cumulatively, 40 cases with immunomodulatory/immunosuppressive agents administered prior to Mavenclad treatment, which are indicated as cosuspect/concomitant drugs, were identified from postapproval sources. These cases described prior use of alemtuzumab, teriflunomide, fingolimod, dimethyl fumarate, interferon beta-1a, daclizumab, ciclosporin, natalizumab, ocrelizumab, infliximab and glatiramer acetate. Overall, 114 AEs (82 nonserious and 32 serious) were reported, with MS relapse and lymphopenia being the most common AE (5 AEs, each). 2 of the SAEs were suspected (likely) to be related to Mavenclad (PTs: Cellulitis and Dermatitis allergic). In 8 additional cases, it was not specified whether the use of the immunomodulatory/ immunosuppressive agent was prior to Mavenclad treatment.
Anticipated risk/ consequence of the missing information	There is limited experience on the safety of cladribine in this but a potential additive effect on the immune system may occur when immunosuppressive or immunomodulatory agents are used prior to treatment with cladribine. In addition to routine pharmacovigilance, the impact of exposure to prior immunomodulatory/immunosuppressive agents on subsequent risks following cladribine exposure will be characterized and further quantified in the ongoing CLARION study (long-term PASS) (Part III).

Missing information: Long-term safety data in particular for malignancy risk	
Evidence source:	The long-term safety of cladribine was studied in the observational PREMIERE registry. However, long-term safety data in particular for malignancy risk are limited.
Population in need of further characterization:	In addition to routine pharmacovigilance, long-term safety data in particular for malignancy risk will be collected in patients treated with cladribine and further quantified in the ongoing CLARION (long-term PASS) (Part III).

Part II: Module SVIII – Summary of the Safety Concerns

Table 14 Summary of Safety Concerns

Summary of safety concerns	
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

Part III: Pharmacovigilance Plan (Including Post-Authorisation Safety Studies)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for:

- ***Important identified risk: Liver injury***
- ***Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)***

Implementation of targeted questionnaires for following up of spontaneous reports of liver injury (to be used for all serious cases and for cases with ALT ≥ 5x ULN or ALP ≥ 2x ULN), and PML including suspicion of PML (Annex 4).

III.2 Additional Pharmacovigilance Activities

CLARION (Long-term PASS) - Summary

CCI **Long-term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine**

Study short name and title:

CLARION (Long-term PASS)

Rationale and study objectives:

This study aims at evaluating the safety profile, in terms of incidence of adverse events of special interest, in patients with highly active relapsing-remitting multiple sclerosis (R[R]MS) newly started on oral cladribine or fingolimod. The study will also assess the impact of prior and subsequent use of immunomodulatory/immunosuppressive agents on the incidence of adverse events of special interest.

Study design:

Multi-country, multi-center, long-term, based on a mix of primary data collection and secondary data, non-interventional PASS comparing patients with highly active R(R)MS newly initiating oral cladribine (cladribine cohort) to R(R)MS patients newly initiating fingolimod (comparator cohort).

Study population:

Patients with highly active R(R)MS newly started on oral cladribine or fingolimod according to local labels.

Milestones:

- Protocol Version 1.0 approval (by PRAC) on 31 May 2018, Version 2.0 approved on 27 July 2018 Version 3.0 approved on 18 February 2019 CCI
- Start of data collection - The start of data collection for the first country based on secondary use of data were in October 2017 and for primary use of data (Germany) on the 25 September 2018. End of data collection will be 15 years after start of data collection (Q3 2033).
- Final report -1 year at the latest after the end of data collection (Q3 2034).

CLEAR (Pregnancy PASS) - Summary

CCI **Pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study**

Study short name and title:

CLEAR (Pregnancy PASS)

Rationale and study objectives:

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

Study design:

Multi-country, cohort database study

Study population:

Female MS patients treated with oral cladribine before or during pregnancy and female partners of male MS patients treated with cladribine who father the pregnancy

Milestones:

- Protocol approval (by PRAC) on 26 July 2018 CCI [redacted]
- Start of data extraction for feasibility assessment counts to check sample size in each included database: 14 December 2020.
- Date for which the analytical data set is completely available: Q4 2027. Once the study has included 134 live births from pregnant women with MS exposed to oral cladribine and 268 live births from pregnant women with MS unexposed to any DMD for all databases combined or 5 years after the first feasibility check in each of the databases if the targeted sample size cannot be reached, whichever occurs first.

Final report of study results: submission to the European Medicines Agency (EMA) within one year of the last data analysis (anticipated in Q4 2028 at the latest), independently of the fact that the target sample size (134 live births in the cohort of pregnant women with MS exposed to oral cladribine and 268 in the cohort of pregnant women with MS unexposed to any DMD) for all databases combined will have been reached or not.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 15 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (key to benefit-risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances (key to benefit-risk)				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
CLARION (long-term PASS) Ongoing	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	• Severe (Grade ≥3) lymphopenia • Herpes zoster • Tuberculosis • Severe infections • Progressive Multifocal Leukoencephalopathy (PML)	Protocol approval	31 May 2018
			Start of data collection	start dates for the first countries in which data sources are based on secondary use

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	cladribine or fingolimod. The study will also assess the impact of prior and subsequent use of immunomodulatory/immunosuppressive agents on the incidence of adverse events of special interest	• Opportunistic infections (other than tuberculosis and PML) • Malignancies • Seizures • Impact of exposure to prior immunomodulatory/ immunosuppressive agents on subsequent risks following cladribine exposure • Long-term safety data in particular for malignancy risk • Sequential use of other immunosuppressive or immunomodulatory agents after cladribine treatment		of data: October 2017; and in Germany where the study is based on primary use of data: 25 September 2018
			Interim results reports	Planned after 3, 6, 9, and 12 years after start of data collection (i. e. submitted on 30 September 2021, anticipated in Q3 2024, Q3 2027, and Q3 2030, respectively)
			Study progress updates presenting the course of enrolment along with safety data from the pharmacovigilance database	Submitted with each PSUR/PBRER
			Final study report	Planned 1 year at the latest after end of data collection (Q3 2034; taking into account the duration of enrolment and of follow-up).
Pregnancy PASS (CLEAR) Ongoing	A multi-country, cohort database study to investigate whether the exposure to oral cladribine before or during pregnancy, in women with MS treated with oral cladribine or in pregnancies fathered by MS patients treated with cladribine, is associated with adverse pregnancy or infant outcomes	• Teratogenicity/ adverse pregnancy and infant outcomes	Protocol approval	26 Jul 2018
			Biannual feasibility checks will be performed to assess the number of pregnant women captured in each of the selected databases	Bi-annually during the first two years after launch and then annually
			Start of data collection (anticipated date	14 December 2020. The first data analysis will be

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			of the first data analysis)	performed when at least one of the participating data sources has reached at least 25 pregnant women with MS exposed to oral cladribine and 50 pregnant women with MS unexposed to any DMD.
			Study progress updates presenting the course of enrolment along with safety data from the pharmacovigilance database	To be submitted with each PSUR/PBRER
			End of data collection (date of the last data analysis)	Q4 2027. Once the study has included 134 live births from pregnant women with MS exposed to oral cladribine and 268 live births from pregnant women with MS unexposed to any DMD for all databases combined or 5 years after the first feasibility check in each of the databases if the targeted sample size cannot be reached, whichever occurs first
			Final study report	Planned at the latest one year after the date of the last data analysis (anticipated in Q4 2028)

Part IV: Plans for Post-Authorisation Efficacy Studies

No planned or ongoing post-authorization efficacy studies are conditions of the marketing authorization for cladribine.

Part V: Risk Minimization Plan (Including Evaluation of the Effectiveness of Risk Minimization Activities)

V.1 Routine Risk Minimization Measures

Table 16 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Severe (Grade ≥3) lymphopenia	Routine risk communication: • *Lymphopenia is described as an adverse reaction (EU SmPC section 4.8; Package leaflet (PL) section 4)* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Herpes zoster	Routine risk communication: • *Herpes zoster is described as an adverse reaction (EU SmPC section 4.8; PL section 4)* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Tuberculosis	Routine risk communication: • *Tuberculosis is described as an adverse reaction (EU SmPC section 4.8; PL section 4)*

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: • *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)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Liver injury	Routine risk communication: • *Liver injury is described as an adverse drug reaction (EU SmPC section 4.8, PL section 4)* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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)* Other routine risk minimization measures: • *Legal status: subject to restricted medical prescription*
Severe infections	Routine risk communication: • *None* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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)*

Safety concern	Routine risk minimization activities
	• *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)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Progressive Multifocal Leukoencephalopathy (PML)	Routine risk communication: • *None* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Opportunistic infections (other than tuberculosis and PML)	Routine risk communication: • *None* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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)* • *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)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Malignancies	Routine risk communication:

Safety concern	Routine risk minimization activities
	• *Observation of malignancy events is described (EU SmPC section 4.4, 4.8; PL section 2)* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Teratogenicity/adverse pregnancy outcomes	Routine risk communication: • *Embryolethal and teratogenic effects as well as chromosomal damage observed in animals are described (EU SmPC section 4.6, 5.3; PL section 2)* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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 (EU SmPC section 4.4, 4.6; PL section 2)* • *At the beginning of each treatment year, counseling of patients regarding the potential risk to the fetus and the need for effective contraception is recommended (EU SmPC section 4.4, 4.6)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Seizures	Routine risk communication: • *None* Routine risk minimization activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimization measures: • *Legal status: subject to restricted medical prescription*
Sequential use of other immunosuppressive or immunomodulatory agents after cladribine treatment	Routine risk communication: • *None* Routine risk minimization activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimization activities
	• *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)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Impact of exposure to prior immunomodulatory/immunosuppressive agents on subsequent risks following cladribine exposure	Routine risk communication: • *None* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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 immunosuppressive/immunomodulatory agent* *(EU SmPC section 4.4; PL section 2)* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*
Long-term safety data in particular for malignancy risk	Routine risk communication: • *None* Routine risk minimization activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimization measures beyond the Product Information: • *Legal status: subject to restricted medical prescription*

V.2 Additional Risk Minimization Measures

Additional risk minimization: Mavenclad Prescriber Guide

Objectives:

The Prescriber Guide provides guidance on the risk management of cladribine to ensure that prescribers, and their patients, are adequately informed on the treatment regimen, requirements for blood cell count testing/monitoring, liver parameter testing, screening for latent infections, monitoring of early signs and symptoms of infections and liver injury, management of infections and liver injury, precautions regarding pregnancy prevention (Annex 6).

The Prescriber Guide addresses the following safety concerns:

Important identified risks

- Severe (Grade ≥3) lymphopenia, to ensure compliance to hematological testing and treatment requirements;
- Herpes zoster, to ensure awareness of signs and symptoms suggestive for this infection;
- Tuberculosis, to raise awareness about this risk;
- Liver injury, to ensure awareness of this risk and compliance to testing of liver parameters.

Important potential risks

- Progressive multifocal leukoencephalopathy (PML), opportunistic infections (other than PML and tuberculosis) and severe infections, to ensure awareness of signs and symptoms suggestive of these risks;
- Malignancies, to raise awareness on this risk because:
  - Patients with current active malignancies must not receive Mavenclad treatment;
  - Patients should be advised to follow standard cancer screening;
- Teratogenicity/adverse pregnancy outcomes, to ensure that female patients of childbearing potential / partners of male patients receiving Mavenclad:
  - Receive counseling before starting the treatment (consisting of two treatment courses administered at the beginning of two consecutive years) both in year 1 and 2;
- Use effective contraception during treatment and for at least 6 months after the last dose

Rationale for the additional risk minimization activity

The efficacy and safety of cladribine for the treatment of adult patients with highly active relapsing multiple sclerosis has been demonstrated in clinical trials. In clinical practice educating the prescriber about the important risks and precautions for use of cladribine is important for achieving the best patient outcome. This is especially relevant given the dosing schedule of cladribine, with a dosing interval of 1 year between start of treatment courses, as this could impair prescriber knowledge and retention of the key guidance and warnings for use. The Prescriber Guide is an important reference tool for prescribers providing guidance, in addition to the SmPC, on the risk management of cladribine in clinical practice.

Target audience and planned distribution path:

The target audience is all prescribers who are expected to prescribe Mavenclad.

Prior to launch of Mavenclad in each Member State the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the program, are agreed with each National Competent Authority (NCA).

Plans to evaluate the effectiveness of the interventions and criteria for success:

Respective ICSRs will be reviewed to evaluate whether or not risk minimization measures as listed in the product labeling and educational material were adhered to.

Reporting rate of the respective risk, severity and complications / pregnancy outcomes will be periodically reviewed and comparison between periods will be reported in PBRERs.

Incidence of the respective risk (i.e. AEs of special interest) and of the important potential risk of seizures in the long-term PASS will be periodically reviewed and reported; for teratogenicity/adverse pregnancy outcomes the proportion of outcomes of cladribine exposed pregnancies in the pregnancy PASS will be periodically reviewed and reported.

Criteria for success are generally a stable reporting rate/incidence rate of the respective risk between review periods, which is consistent with the incidence rate of the respective risk as observed in clinical trials; in case of tuberculosis or PML: no cases or a low number; in case of malignancies: reporting rates consistent with background rates of a specific malignancy type in patients with MS); in case of adverse pregnancy outcome/teratogenicity: low exposure to oral cladribine and low proportion of adverse pregnancy outcomes/teratogenicity received in each periodic review and as collected in the Pregnancy PASS.

Additional risk minimization: Mavenclad Patient Guide

Objectives:

The Patient Guide provides an introduction to Mavenclad treatment, its side effects, the important potential risks and information on pregnancy prevention.

The Patient Guide addresses the following safety concerns:

Important identified risks

- Severe (Grade ≥3) lymphopenia, to explain about the risk of lymphopenia and its impact on infections
- Herpes zoster, to ensure awareness of signs and symptoms of this infection
- Tuberculosis, to ensure awareness of signs and symptoms of this infection
- Liver injury, to ensure awareness of signs and symptoms suggestive of this risk and risk minimization measures

Important potential risks

- Progressive multifocal leukoencephalopathy (PML), opportunistic infections (other than PML and tuberculosis) and severe infections, to ensure awareness of signs and symptoms suggestive of these risks;
- Malignancies, to explain what is known about the risk of cancer with cladribine and how the risk will be minimized through patient selection and cancer screening;
- Teratogenicity/adverse pregnancy outcomes, to explain what is known about the risk of birth defects/miscarriage and to highlight the need for effective contraception.

Rationale for the additional risk minimization activity

The efficacy and safety of cladribine for the treatment of adult patients with highly active relapsing multiple sclerosis has been demonstrated in clinical trials. In clinical practice educating the patient about the important risks and precautions for use of cladribine is important for maintaining the safety of the patient. The patient's understanding of the risks is fundamental for identifying and reporting early signs and symptoms of the important risks to their healthcare professional to ensure timely treatment. This is especially relevant given the dosing schedule of cladribine that involves a dosing interval of 1 year between start of treatment courses, as the long time lag could impair patient knowledge and retention of the key guidance and warnings for use. The Patient Guide is an important reference tool for patients for providing guidance, in addition to the PL, on the safety and use of cladribine.

Target audience and planned distribution path

The target audience is all patients who are expected to use Mavenclad.

Prior to launch of Mavenclad in each Member State the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the program, are agreed with each NCA.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Respective ICSRs will be reviewed to evaluate whether or not risk minimization measures as listed in the product labeling and educational material were adhered to.

Reporting rate of the respective risk, severity and complications / pregnancy outcome will be periodically reviewed and comparison between periods will be reported in PBRERs.

Incidence of the respective risk (i.e. AEs of special interest) and of the important potential risk of seizures in the long-term PASS will be periodically reviewed and reported; for teratogenicity/adverse pregnancy outcomes the proportion of outcomes of cladribine exposed pregnancies in the pregnancy PASS will be periodically reviewed and reported.

Criteria for success are generally a stable reporting rate/incidence rate of the respective risk between review periods, which is consistent with the incidence rate of the respective risk as observed in clinical trials; in case of tuberculosis or PML: no cases or a low number; in case of malignancies: reporting rates consistent with background rates of a specific malignancy type in patients with MS); in case of adverse pregnancy outcome/teratogenicity: low exposure to oral cladribine and low proportion of adverse pregnancy outcomes/teratogenicity received in each periodic review and as collected in the Pregnancy PASS.

Removal of additional risk minimization activities

Not applicable.

V.3 Summary of Risk Minimization Measures

Table 17 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Severe (Grade ≥3) lymphopenia	Routine risk minimization measures: • *Lymphopenia is described as an adverse reaction (EU SmPC section 4.8; 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 ACL ≥ 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 minimization measures: • *Prescriber Guide* • *Patient Guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activity: • *CLARION (long-term PASS)*
Herpes zoster	Routine risk minimization 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* Additional risk minimization measures: • *Prescriber Guide* • *Patient Guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activity: • *CLARION (long-term PASS))*

Safety concern	Risk minimization measures	Pharmacovigilance activities
Tuberculosis	Routine risk minimization 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 minimization measures: • *Prescriber Guide* • *Patient Guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activity: • *CLARION (long-term PASS))*
Liver injury	Routine risk communication: • *Liver injury is described as an adverse drug reaction (EU SmPC section 4.8, PL section 4)* Routine risk minimization activities recommending specific clinical measures to address the risk: • *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)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Liver injury questionnaire* Additional pharmacovigilance activity: *None*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: • *Prescriber Guide* • *Patient Guide*	
Severe infections	Routine risk minimization 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 minimization measures: • *Prescriber Guide* • *Patient Guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activity: • *CLARION (long-term PASS))*
Progressive Multifocal Leukoencephalopathy (PML)	Routine risk minimization 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)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *PML follow-up form* Additional pharmacovigilance activity: • *CLARION (long-term PASS)*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• *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 minimization measures: • *Prescriber Guide* • *Patient Guide*	
Opportunistic infections (other than tuberculosis and PML)	Routine risk minimization 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)* • *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 minimization measures: • *Prescriber Guide* • *Patient Guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activity: • *CLARION (long-term PASS)*
Malignancies	Routine risk minimization 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)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activity: • *CLARION (long-term PASS)*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• *Legal status: subject to restricted medical prescription* Additional risk minimization measures: • *Prescriber Guide* • *Patient Guide*	
Teratogenicity/adverse pregnancy outcomes	Routine risk minimization 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.. (EU SmPC section 4.4, 4.6; PL section 2)* • *At the beginning of each treatment year, counseling 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 minimization measures: • *Prescriber Guide* • *Patient Guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activity: • *CLEAR (pregnancy PASS)*
Seizures	Routine risk minimization measures: • *Legal status: subject to restricted medical prescription* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *CLARION (long-term PASS*)
Sequential use of other immunosuppressive or immunomodulatory agents after cladribine treatment	Routine risk minimization 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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *CLARION (long-term PASS):*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: • *None*	The impact of the subsequent use of immunomodulatory / immunosuppressive agents on the incidence of AESIs in patients with highly active R(R)MS after oral cladribine treatment will be assessed
Impact of exposure to prior immunomodulatory/ immunosuppressive agents on subsequent risks following cladribine exposure	Routine risk minimization 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 immunosuppressive/ immunomodulatory agent (EU SmPC section 4.4; PL section 2)* • *Legal status: subject to restricted medical prescription* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *CLARION (long-term PASS)*
Long-term safety data in particular for malignancy risk	Routine risk minimization measures: • *Legal status: subject to restricted medical prescription* Additional risk minimization measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activity: • *CLARION (long-term PASS)*

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 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 authorized 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 minimize 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Mavenclad, these measures are supplemented with *additional risk minimization* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, 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 minimize 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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 minimization measures	Routine risk minimization 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)*

Important identified risk: Severe (Grade ≥3) lymphopenia	
	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 minimization 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-authorization 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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 minimization measures	Routine risk minimization 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* Additional risk minimization 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-authorization 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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 patients).

Important identified risk: Tuberculosis	
	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 minimization measures	Routine risk minimization 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 minimization 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-authorization development plan.

Important identified risk: Liver injury	
Evidence for linking the risk to the medicine	Several individual case safety reports from postapproval 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.
Risk minimization measures	Routine risk minimization 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*

Important identified risk: Liver injury	
	Additional risk minimization measures: *Prescriber Guide* *Patient Guide* *Direct Healthcare Professional Communication (Of note, this was submitted previously in last approved EU RMP v1.7 package and distributed in the MAH territory as applicable).*
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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 minimization measures	Routine risk minimization 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 minimization 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-authorization 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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 minimization measures	Routine risk minimization 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 minimization 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-authorization 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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 minimization measures	Routine risk minimization 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 minimization 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-authorization 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 2 and Phase 3 studies that evaluated oral, intravenous and subcutaneous cladribine in different treatment regimens (1,976 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 minimization measures	Routine risk minimization 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 minimization 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-authorization 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 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 participants 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 minimization measures	Routine risk minimization 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 (EU SmPC section 4.4, 4.6; PL section 2)* *At the beginning of each treatment year, counseling 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 minimization 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-authorization development plan.

Important potential risk: Seizures	
Evidence for linking the risk to the medicine	Individual case safety reports from postapproval 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 minimization measures	Routine risk minimization measures: *Legal status: subject to restricted medical prescription*

Important potential risk: Seizures	
Additional pharmacovigilance activities	Additional pharmacovigilance activity: *CLARION Study (Long-term PASS)* See section II.C of this summary for an overview of the post-authorization development plan.

Missing information: Sequential use of other immunosuppressive or immunomodulatory agents after cladribine treatment	
Risk minimization measures	Routine risk minimization 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 minimization 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-authorization development plan.

Missing information: Impact of exposure to prior immunomodulatory/immunosuppressive agents on subsequent risks following cladribine exposure	
Risk minimization measures	Routine risk minimization 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 minimization 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-authorization development plan.

Missing information: Long-term safety data in particular for malignancy risk	
Risk minimization measures	Routine risk minimization measures *Legal status: subject to restricted medical prescription* Additional risk minimization measures *None*

Missing information: Long-term safety data in particular for malignancy risk	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *CLARION Study (Long-term PASS)* See section II.C of this summary for an overview of the post-authorization 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 authorization 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.

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

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[1]Targeted questionnaire

Progressive multifocal leukoencephalopathy (PML)

(Skip all questions below for which the information has already been provided at the AE Report Form or by other mean)

Patient	Initials:	Birth date:_____(dd - mmm - yyyy)

Has the diagnosis of PML been confirmed?	☐ **Yes** ☐ **No** (diagnosis ruled out) ☐ **Work-up ongoing**	**Details** (Please provide reasons for assessment)
Clinical presentation		**Details** (Please provide details including dates (dd/mm/yyyy) and course)
Signs and symptoms (such as cognitive and/or behavioural abnormalities, clumsiness, motor weakness, hemiparesis, gait abnormality, incoordination, speech or language disorders, visual deficits, sensory deficits, headache, seizures)	☐ **Yes** ☐ **No** ☐ **[2]Uk**	

[1] This form has to be used as addition to the Adverse Event Report Form collecting in addition to the above: event onset; severity, serious criteria, outcome of the event, exposure to suspected medicinal product and patient demographics.
[2] =unknown

Diagnostics		Details (Please provide results of investigations including date (dd/mm/yyyy) and reference ranges as applicable)
Neurological examination	☐ **Yes** ☐ **No** ☐ **Uk**	Date: Findings:
Brain imaging *If yes,* *please indicate whether the results are compatible with PML diagnosis*.	☐ **Yes** ☐ **No** ☐ **Uk**	Type of imaging: Date: Findings:
Serum JC virus antibody test	☐ **Yes** ☐ **No** ☐ **Uk**	Date: Findings:

Lumbar puncture	□ **Yes** □ **No** □ **Uk**	Date: Cell count: Glucose: Protein: Cytology: Other: JC virus DNA (PCR): positive □ negative □ indeterminate □ Other infectious agent:
JC virus DNA test in peripheral blood	□ **Yes** □ **No** □ **Uk**	Date: Findings:

Brain biopsy *If yes, please indicate whether the results are compatible with PML diagnosis.*	□ **Yes** □ **No** □ **Uk**	Date: Findings: Tissue PCR for JC virus: Positive □ negative □ indeterminate □ not done □ Immunohistochemistry: Positive □ negative □ indeterminate □ not done □ Electron microscopy: Positive □ negative □ indeterminate□ not done □
CD4 cell count, **CD8 cell count** *Was a test performed at the time of diagnosis or within 6 months before diagnosis*?	□ **Yes** □ **No** □ **Uk**	Date: Findings:
Other investigations (e.g. complete blood cell counts)	□ **Yes** □ **No** □ **Uk**	Date: Findings:

Differential Diagnosis		**Details** (Please specify in detail what elements resembled or not the typical lesions of PML)
Is there evidence for a diagnosis other than PML (such as MS progression, stroke, brain tumor, CNS vasculitis, other forms of encephalopathy) ?	☐ **Yes** ☐ **No** ☐ **Uk**	
PML treatment		**Details** (Please specify treatment, date if applicable or ongoing, duration and effectiveness)
How was PML treated? (plasma exchange, immunoadsorption, other)		
Relevant Medical History		**Details** (Please indicate onset date, course of disease and end date if applicable or ongoing)
Multiple Sclerosis *Please specify including subject's condition according to expanded disability status scale (EDSS) score*		
History of malignancy *If yes, please specify*	☐ **Yes** ☐ **No** ☐ **Uk**	
History of autoimmune disease, *If yes, please specify*	☐ **Yes** ☐ **No** ☐ **Uk**	

Immune Deficiency *If yes, please specify*	☐ **Yes** ☐ **No** ☐ **Uk**	
Other *If yes, please specify*	☐ **Yes** ☐ **No** ☐ **Uk**	
Relevant family history		**Details** (Please specify type of disease and concerned relative)
Is there a family history of a relevant disease such as autoimmune disease, immune deficiency?	☐ **Yes** ☐ **No** ☐ **Uk**	

Previous and concomitant medication(s)
Details

Please list previous disease modifying drugs (DMDs)

Drug Trade Name	Lot No.	Dose	Frequency	Route	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)

Please list other drugs administered to the patient within the previous 2 years (especially immunosuppressive drugs other than DMDs)

Drug Trade Name	Lot No.	Dose	Fre-quency	Route	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	On-going	Indication
							☐	
							☐	
							☐	

Reporter's name: _____

Signature:_____Date:_____

*Targeted questionnaire

Liver injury

(Skip all questions below for which the information has already been provided at the AE Report Form or by other means)

Patient Initials: Birth date:_____(dd - mmm - yyyy)

Clinical presentation / investigations		Details (If yes, please provide details, dates, findings, outcome)
Signs and symptoms reported (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice, dark urine)	☐ **Yes** ☐ **No** ☐ **[1]Unk**	
Liver and coagulation parameters available *(*such as ALT; AST, AP, Total Bilirubin, INR, aPTT)?	☐ **Yes** ☐ **No** ☐ **Unk**	
Other laboratory results available *(e.g. anti smooth muscle antibodies, viral serology)?*	☐ **Yes** ☐ **No** ☐ **Unk**	
Liver biopsy / histology performed?	☐ **Yes** ☐ **No** ☐ **Unk**	
Hepatic imaging performed (such as ultrasound, CT, MRI)?	☐ **Yes** ☐ **No** ☐ **Unk**	
Any other investigations performed?	☐ **Yes** ☐ **No** ☐ **Unk**	
Treatment measures reported	☐ **Yes** ☐ **No** ☐ **Unk**	
Clinical course and status of the patient reported	☐ **Yes** ☐ **No** ☐ **Unk**	

Relevant medical history / risk factors		Details (If yes, please provide details, dates, findings, therapy, outcome)

*This form has to be used as addition to the Adverse Event Report Form collecting in addition to the above: event onset; severity, serious criteria, outcome of the event, exposure to suspected medicinal product and patient demographics. ‘
The questionnaire has used for all serious cases of liver injury and for cases with ALT ≥ 5x ULN or ALP ≥ 2x ULN.
[1] =unknown

*Targeted questionnaire

Liver injury

(Skip all questions below for which the information has already been provided at the AE Report Form or by other means)

Patient Initials: Birth date:_____(dd - mmm - yyyy)

Liver parameters/laboratory parameters prior to start of Mavenclad treatment available? (such as ALT; AST, AP, Total Bilirubin)	☐ **Yes** ☐ **No** ☐ **Unk**	
Previous episodes of liver value elevation on other drugs known? Causative agent?	☐ **Yes** ☐ **No** ☐ **Unk**	
History of liver impairment/ liver disease Child-Pugh score?	☐ **Yes** ☐ **No** ☐ **Unk**	
History of alcoholic liver disease	☐ **Yes** ☐ **No** ☐ **Unk**	
History of acute hepatitis Viral serology?	☐ **Yes** ☐ **No** ☐ **Unk**	
History of chronic hepatitis Viral serology?	☐ **Yes** ☐ **No** ☐ **Unk**	
History of autoimmune hepatitis	☐ **Yes** ☐ **No** ☐ **Unk**	
History of cholelithiasis or cholecystitis	☐ **Yes** ☐ **No** ☐ **Unk**	
Alcohol use Which drinks - frequency	☐ **Yes** ☐ **No** ☐ **Unk**	
Other relevant medical history/ family history/ other risk factors If yes, specify	☐ **Yes** ☐ **No** ☐ **Unk**	

Previous and concomitant medication(s)		

*Targeted questionnaire

Liver injury

(Skip all questions below for which the information has already been provided at the AE Report Form or by other means)

Patient Initials: Birth date:_____(dd - mmm - yyyy)

Previous disease modifying drugs (DMDs)	☐ **Yes** ☐ **No** ☐ **Unk**	*If yes, please provide details in the lists below.*
Immunosuppressive drugs other than DMDs *(e.g. glucocorticoids, methotrexate, azathioprine, mercaptopurine, cyclosporine, tacrolimus, sirolimus*)	☐ **Yes** ☐ **No** ☐ **Unk**	
Other relevant co-medication within the previous 2 years, especially use of potentially hepatoxic agents such as isoniazid	☐ **Yes** ☐ **No** ☐ **Unk**	

Please list previous disease modifying drugs (DMDs)

Drug Trade Name	Lot No.	Dose	Frequency	Route	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)

Please list immunosuppressive drugs other than DMDs

Drug Trade Name	Lot No.	Dose	Fre-quency	Route	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	On-going	Indication
							☐	
							☐	
							☐	

Please list other relevant co-medication and herbal/dietary supplements within the previous 2 years

Drug Trade Name	Lot No.	Dose	Fre-quency	Route	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	On-going	Indication
							☐	

*Targeted questionnaire

Liver injury

(Skip all questions below for which the information has already been provided at the AE Report Form or by other means)

Patient Initials: Birth date:_____(dd - mmm - yyyy)

							☐	
							☐	

Reporter's name: _____

Signature:_____Date:_____

Annex 6 Details of Proposed Additional Risk Minimization Activities

Prior to the launch of Mavenclad in each Member State the Marketing Authorization Holder (MAH) must agree about the content and format of the educational program, including communication media, distribution modalities, and any other aspects of the program, with the National Competent Authority.

The educational program is aimed at increasing awareness and providing information concerning the signs and symptoms of important risks of cladribine, and how to manage them. This applies to the important identified risks: severe lymphopenia, herpes zoster, tuberculosis (TB) and liver injury and to the important potential risks: severe infections, Progressive multifocal leukoencephalopathy (PML), opportunistic infections other than TB and PML malignancies, and teratogenicity/adverse pregnancy outcomes. Emphasis is put on pregnancy prevention with specific information for female and male patients.

The MAH shall ensure that in each Member State where Mavenclad is marketed, all healthcare professionals who are expected to prescribe and all patients/carers who are expected to use Mavenclad have access to/are provided with the following **educational package**:

- Prescribers Guide
- Patient Guide

The **healthcare professional educational material** should contain:

- Summary of Product Characteristics
- Prescriber Guide

The **Prescriber Guide** shall contain the following key messages:

- Purpose of the prescriber guide: to provide information on the most important risks and activities required to minimize these risks
- Purpose of the patient guide: to be used in the discussion with the patient to support the early identification of signs and symptoms of potential adverse reactions and timely treatment
- Detailed description of the treatment regimen of Mavenclad
- Details on how to minimize the risks of lymphopenia, liver injury, severe infections, PML, and malignancies through appropriate monitoring and management (e.g. lymphocyte count monitoring, testing of liver parameters, appropriate anti-infective treatment in case of infections)
- Emphasis on the potential risk of teratogenicity/adverse pregnancy outcome and respective risk minimization measures: contraindication to treat pregnant women, counselling of patients before initiation of Mavenclad including advice on the need of effective contraception in female patients of child bearing potential and male patients during Mavenclad treatment with guidance on effective contraceptive methods.
- Request to report suspected adverse reactions and pregnancies

The **patient educational material** should contain:

- Package leaflet
- Patient Guide

The **Patient Guide** shall contain the following key messages:

- Introduction to Mavenclad (indication and administration).
- Description of the main side effects and potentials risks (lymphopenia, herpes zoster, tuberculosis, liver injury, severe infections, malignancy, and Progressive multifocal leukoencephalopathy (PML)) and measures to manage the risks; reminder of the importance of notifying the treating physician if certain symptoms occur or worsen.
- Emphasis on the potential risk of harm to the unborn baby and the importance of pregnancy prevention during treatment with Mavenclad by use of effective contraception methods for both, female patients of childbearing potential and male patients. Emphasis that cladribine is prohibited in pregnant women.
- Request to report suspected adverse reactions and pregnancies.