Summary of the Risk Management Plan (RMP) for LEMTRADA®

LEMTRADA® (alemtuzumab)
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. This RMP summary is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le medicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of the product in Switzerland is the “Arzneimittelinformation/ Information sur le medicament” (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis(suisse)sa is fully responsible for the accuracy and correctness of the content of this published RMP summary.

1. THE MEDICINE AND WHAT IT IS USED FOR

According to Swiss label

Lemtrada is indicated as a disease-modifying monotherapy in adult patients with highly active relapsing-remitting multiple sclerosis (RRMS) despite prior treatment with a full and adequate cycle of at least one disease-modifying therapy.

According to EU SmPC

LEMTRADA is indicated as a single disease modifying therapy in adults with highly active relapsing remitting multiple sclerosis (RRMS) for the following patient groups:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

It contains alemtuzumab as the active substance and it is given by intravenous (IV) infusion.

Further information about the evaluation of LEMTRADA's benefits can be found in LEMTRADA'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/medicines/human/EPAR/lemtrada

2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of LEMTRADA, together with measures to minimize such risks and the proposed studies for learning more about LEMTRADA's risks, are outlined in the next sections.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and professional information addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that

the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of LEMTRADA, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

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 LEMTRADA is not yet available, it is listed under "missing information" outlined in the next section.

2.1. List of important risks and missing information

Important risks of LEMTRADA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered or 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 LEMTRADA. 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 (eg, on the long-term use of the medicine);

Table 1 - List of important risks and missing information

Important identified risks	Infusion-associated reactions Stroke (including haemorrhagic stroke)[a] Dissection of the cervicocephalic arteries [a] Myocardial infarction and myocardial ischaemia [a] Pulmonary alveolar haemorrhage [a] Thrombocytopenia [a] Thyroid disorders Immune thrombocytopenic purpura Nephropathies including anti-GBM disease Autoimmune hepatitis Serious infections Haemophagocytic lymphohistiocytosis Acquired Haemophilia A Thrombotic Thrombocytopenic Purpura Adult Onset Still's Disease (AOSD) Autoimmune Encephalitis (AIE) Acute acalculous cholecystitis (AAC)
Important potential risk	Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus, Guillain Barre syndrome) Malignancies Progressive multifocal leukoencephalopathy ***Specific to swiss market :*** *severe exacerbation by B-cell mediated MS during treatment with alemtuzumab*
Missing information	Pediatric use Use in patients aged >55 years (including use in elderly patients aged ≥65 years) Use in racial categories other than white

a This risk is temporally associated with LEMTRADA infusion.

GBM: Glomerular Basement Membrane

2.2. Summary of important risks

Table 2 – Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important identified risk: Infusion-associated reactions

Important identified risk: Infusion-associated reactions	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing
Risk factors and risk groups	Infusion-associated reactions are commonly reported with monoclonal antibody administration (1) and were observed in approximately 90% of patients treated with alemtuzumab in MS clinical trials. A higher than recommended dose and faster infusion rate also increase the risk of infusion-associated reactions. There is no identified pattern in terms of additive or synergistic factors. While Infusion-associated reactions have also been observed with use of alemtuzumab in B-CLL, reporting rates are different than those in MS patients, and AEs tend to be more severe in the B-CLL population. The recommended dosing regimens for B-CLL patients is 10-fold higher than for MS patients: B-CLL patients are dosed chronically for up to 3 months, compared to 2 annual courses for MS patients (5 days at month 0, 3 days at month 12). Alemtuzumab treatment is contraindicated in patients with hypersensitivity to alemtuzumab or its excipients.
Risk minimization measures	<u>Routine risk minimization measures:</u> • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding hypersensitivity to the active substance or excipients are included in SmPC section 4.3 and PL section 2. • Recommendations for premedication are included in SmPC sections 4.2 and 4.4 and in PL section 4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL section 2 • Recommendations to exercise caution until infusion associated reactions (eg, dizziness) are resolved are included in SmPC section 4.7. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. <u>Additional risk minimization measures:</u> None

Additional pharmacovigilance activities	<u>Additional Pharmacovigilance activities:</u> Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

AE: Adverse Event; B-CLL: B-cell Chronic Lymphocytic Leukemia; MS: Multiple Sclerosis; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 3 – Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important identified risk: Stroke (including haemorrhagic stroke)[a]

Important identified risk: Stroke (including haemorrhagic stroke)[a]	
Evidence for linking the risk to the medicine	Postmarketing There were no non-clinical findings suggestive of stroke in repeat-dose toxicity studies with alemtuzumab.
Risk factors and risk groups	The major risk factors for stroke include: • High Blood pressure • Diabetes • Smoking • Heart disease • Personal or family History of stroke or TIA • Brain aneurysms or AVMs • It is not clearly identified which patients are at risk of stroke with LEMTRADA use. However, significantly increased BP during infusion may be a risk factor for haemorrhagic stroke, and vital sign should be monitored prior to and during infusion as described in the SmPC. • The reported events followed no particular pattern in terms of risk groups. There was no dose related pattern. All 10 events of stroke temporally associated to LEMTRADA infusion occurred within 3 days of LEMTRADA administration. No pattern of additive or synergistic factors were observed.

Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding history of stroke is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with LEMTRADA infusion (pre-infusion, during infusion and post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Section 2 and 4, as well as information on the monitoring which will be done. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: • Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Risk of mortality study Final report: Q3 2024

a This risk is temporally associated with LEMTRADA infusion.
AVM: Arteriovenous Membrane; BP: Blood Pressure; DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics; TIA: Transient Ischaemic Attack.

Table 4 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any - Important identified risk: Dissection of the cervicocephalic arteries[a]

Important identified risk: Dissection of the cervicocephalic arteries[a]	
Evidence for linking the risk to the medicine	Postmarketing There were no non-clinical findings suggestive of vascular dissection in repeat-dose toxicity studies with alemtuzumab.
Risk factors and risk groups	Dissection of the cervicocephalic arteries are typically associated with "minor" cervical trauma, or torsion of the neck including variety of everyday activities. All of the reported events of arterial dissection appear to be in the extracranial compartment, adjacent to bony structures, which is where traumatic dissection typically occurs. Of the reported cases, there were 3 cases reported with regular chiropractic manipulations. There was no dose related pattern. Four out of 8 cases were reported with a TTO of 1-3 days from the last dose.
Risk minimization measures	Routine risk minimization measures: • Proposed label in SmPC sections 4.2, 4.3, 4.4 and 4.8. • Labeled in sections 2 and 4 of PL. • Contraindication regarding history of arterial dissection of the cervicocephalic arteries is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with LEMTRADA infusion. (pre-infusion, during infusion and postinfusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4, as well as information on the monitoring which will be done. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.
Risk minimization measures	Additional risk minimization measures: • Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Risk of mortality study Final report: Q3 2024

a This risk is temporally associated with LEMTRADA infusion.
DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics; TTO: Time to

Table 5 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any— Important identified risk: Myocardial infarction and myocardial ischaemia [a]

Important identified risk: Myocardial infarction and myocardial ischaemia [a]	
Evidence for linking the risk to the medicine	Postmarketing
Risk factors and risk groups	Risk factors that may cause myocardial infarction include: • Age (Men age 45 or older, women age 55 or older) • Tobacco • High blood pressure • High blood cholesterol or triglyceride levels • Obesity • Diabetes • Metabolic syndrome • Family history of heart attack • Lack of physical activity • Stress • Illicit drug use • A history of preeclampsia • No particular pattern in terms of risk groups was identified in the reported cases. There was no dose related pattern. All the cases of myocardial ischaemia were reported within 72 hours of last LEMTRADA infusion. No pattern of additive or synergistic factors were observed.

Risk minimization measures	<u>Routine risk minimization measures:</u> • Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Contraindication regarding history of angina pectoris or myocardial infarction is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with LEMTRADA infusion (pre-infusion, during infusion and postinfusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4, as well as information on the monitoring which will be done. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. <u>Additional risk minimization measures:</u> • Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	<u>Additional Pharmacovigilance activities:</u> PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

a This risk is temporally associated with LEMTRADA infusion.

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 6 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any—Important identified risk: Pulmonary alveolar haemorrhage[a]

Important identified risk: Pulmonary alveolar haemorrhage[a]	
Evidence for linking the risk to the medicine	Postmarketing
Risk factors and risk groups	Many disorders can cause pulmonary alveolar haemorrhage; they include (1): • Autoimmune disorders (eg, systemic vasculitides, Goodpasture syndrome, antiphospholipid antibody syndrome, connective tissue disorders); • Pulmonary infections (eg, hantavirus infection); • Toxic exposures (eg, trimellitic anhydride, isocyanates, crack cocaine, certain pesticides); • Drug reactions (eg, propylthiouracil, diphenylhydantoin, amiodarone; methotrexate, nitrofurantoin, bleomycin, montelukast, infliximab); • Cardiac disorders (eg, mitral stenosis); • Coagulation disorders caused by diseases or anticoagulant drugs; • Isolated pauci-immune pulmonary capillaritis; • Idiopathic pulmonary hemosiderosis; • Hematopoietic stem cell transplantation or solid organ transplantation. • The reported events of pulmonary alveolar haemorrhage followed no particular pattern in terms of risk groups. The reported risk window was between 1 day and 3 days from the last dose. No dose related, or pattern of additive or synergistic risk factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labelled in sections 4.2, 4.4 and 4.8 of SmPC. • Labelled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with LEMTRADA infusion (pre-infusion, during infusion and postinfusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4, as well as information on the monitoring which will be done. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available.Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available.Additional risk minimization measures:• Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.

Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

a This risk is temporally associated with LEMTRADA infusion.

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professiona; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 7 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any— Important identified risk: Thrombocytopenia[a]

Important identified risk: Thrombocytopenia[a]	
Evidence for linking the risk to the medicine	Clinical trials and postmarketing
Risk factors and risk groups	Non-immune thrombocytopenia can occur with a variety of conditions: • Infections (viral, HIV, bacterial infections or sepsis) • Chronic liver disorders • Hypersplenism • Congenital platelet disorders • Malignancies • Bone marrow disorders • Drugs (daptomycin, linezolid, valproic acid) • Over-the-counter remedies, supplements, foods, beverages or alcohol consumption. The reported events of non-immune immediate thrombocytopenia followed no particular pattern in terms of risk groups. There was no dose related pattern. Regarding the risk period, of the 28 cases with TTO ≤30 days, 9 occurred on the same day as the last alemtuzumab treatment and 7 were within 2 days after the last dose. No pattern of additive or synergistic factors were observed.
Risk minimization measures	<u>Routine risk minimization measures:</u> • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Instructions to reduce serious reactions temporally associated with LEMTRADA (pre-infusion, during infusion, post-infusion) are included in SmPC section 4.4. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4, as well as information on the monitoring which will be done. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. <u>Additional risk minimization measures:</u> Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis

Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

a This risk is temporally associated with LEMTRADA infusion.

HCP: Healthcare Professional; HIV: Human Immunodeficiency Virus; MS: Multiple Sclerosis; PL: Package Leaflet; Q: Quarter; SmPC Summary of Product Characteristics; TTO: Time to Onset.

Table 8 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any— Important identified risk: Thyroid disorders

Important identified risk: Thyroid disorders	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing
Risk factors and risk groups	In clinical trials, over all available follow up of the 1486 alemtuzumaba treated patients, 1466 had anti-TPO antibody testing at baseline. Patients with positive anti-TPO antibodies at baseline also had a higher incidence of abnormal TSH result wit simultaneous abnormal T3 or T4 compared to patients with negative antibodies. Of the 1466 patients with anti TPO testing at baseline, 91.4% tested negative and 8.6% tested positive. Of those who tested negative, 38.2% developed a thyroid AE. Of those who tested positive, 74.8% developed a thyroid AE. Thus, there is a higher risk of developing a thyroid AE in anti-TPO positive patients. However, of the patients with baseline anti TPO antibody testing who developed a thyroid AE, 86% had tested negative for anti-TPO antibodies which underlines the poor predictive value of the measure as a whole. Had anti-TPO positive status been an exclusion to alemtuzumab therapy, only a small number of patients (80 out of 1466, 5.4%) would have been spared a thyroid AE but, based on the lower efficacy observed in the control group, some of them would have experienced additional MS relapses and disability progression that were avoided with alemtuzumab treatment. Maternal transmission of anti-TSH receptor antibodies is associated with higher maternal titres of anti-TSH receptor antibodies in the third trimester. There was no dose related pattern. No pattern of additive or synergistic factors were observed.
Risk minimization measures	<u>Routine risk minimization measures:</u> • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.• Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations for thyroid function monitoring are included in SmPC section 4.4. • How to detect signs and symptoms of thyroid disorders and the need to seek for immediate medical attention is labelled in PL sections 2 and 4 as well as the summary of the tests to complete. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. <u>Additional risk minimization measures:</u> Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis

Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

a There were 1486 alemtuzumab-treated patients, out of which only 1485 had confirmed diagnosis of MS. One patient enrolled in study CAMMS223 and treated with alemtuzumab was subsequently found to have been mistakenly diagnosed with MS; in fact, the patient's symptoms were attributable instead to a familial, autosomal dominant disorder called CADASIL.

AE: Adverse Event; CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; HCP:Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics; TPO: Thyroid Peroxidase; TSH: Thyroid Stimulating Hormone.

Table 9 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any— Important identified risk: Immune thrombocytopenic purpura

Important identified risk: Immune thrombocytopenic purpura	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing
Risk factors and risk groups	None identified at present. As with other forms of Immune thrombocytopenic purpura, the data suggest that circulating anti platelet antibody and platelet-bound antibody assays are not predictive of alemtuzumab associated immune thrombocytopenic purpura. (2) There was no dose related pattern. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.• Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations to complete blood counts are included in SmPC section 4.4, as well as medical conduct to adopt if immune thrombocytopenic purpura onset is confirmed. • How to detect signs and symptoms of immune thrombocytopenic purpura and the need to seek for immediate medical attention is labelled in PL sections 2 and 4, as well as the summary of the tests to complete. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 10 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important identified risk: Nephropathies including anti-GBM disease

Important identified risk: Nephropathies including anti-GBM disease	
Evidence for linking the risk to the medicine	Clinical studies, medical literature, spontaneous reports received by Sanofi Genzyme and postmarketing.
Risk factors and risk groups	There is no indication that patients with pre-existing renal conditions are at greater risk of developing an event. There is no dosing related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations to complete serum creatinine levels and urinalysis blood counts are included in SmPC section 4.4, as well as medical conduct to adopt in case of clinically relevant changes in these results. • How to detect signs and symptoms of kidney disorders and the need to seek for immediate medical attention is labelled in PL sections 2 and 4, as well as the summary of the tests to complete.. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

GBM: Glomerular Basement Membrane; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics..

Table 11 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important identified risk: Autoimmune hepatitis

Important identified risk: Autoimmune hepatitis	
Evidence for linking the risk to the medicine	postmarketing.
Risk factors and risk groups	None identified. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • The need to perform liver function test before initial treatment and periodically thereafter are labelled in SmPC section 4.4. • How to detect signs and symptoms of liver disorders and the need to seek for immediate medical attention is labeled in PL sections 2 and 4. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis and/or posted on a website.
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 12 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any— Important identified risk: Serious infections

Important identified risk: Serious infections	
Evidence for linking the risk to the medicine	Clinical studies and postmarketing.
Risk factors and risk groups	Relapsing remitting MS patients who have been previously treated with immune suppressive agents are theoretically at increased risk for infection if subsequently treated with alemtuzumab, as concomitant use of alemtuzumab with any of these therapies could increase the risk of immunosuppression. In controlled clinical trials, the rate of infections and serious infections is greater in previously treated patients, regardless of treatment (ie, whether alemtuzumab-treated or interferon treated). Interim safety data from CAMMS223 suggested that MS patients treated with alemtuzumab were at an increased risk of developing HSV within 1 month of receiving alemtuzumab. (3) Additionally, patients with mobility restrictions may theoretically be at higher risk for infectious complications due to diminished mobility and functional capacity (eg, aspiration pneumonia, infected decubitus ulcers, presence of indwelling catheter, and dysphagia with aspiration). There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	<u>Routine risk minimization measures:</u> • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations regarding screening, prophylaxis and the conduct to adopt in patients with severe active infection are included in SmPC section 4.4. • Recommendations regarding screening, prophylaxis, treatment and the need to seek for immediate medical attention as well as the summary of tests to complete, for some infections are included PL sections 2 and 4. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. <u>Additional risk minimization measures:</u> Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis and/or posted on a website.

Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

HSV: Herpes Simplex Virus; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics..

Table 13 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important identified risk: Haemophagocytic lymphohistiocytosis

Important identified risk: Haemophagocytic lymphohistiocytosis	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups	None identified. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Recommendations provided to identify patients developing early manifestation of pathologic immune activation are labeled in SmPC section 4.4 as well as the need to consider diagnosis of haemophagocytic lymphohistiocytosis. • How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4.. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: • Communication Plan (DHPC). • Updated Educational materials (ie, HCP guide, HCP check-list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 14 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important identified risk: Acquired Haemophilia A

Important identified risk: Acquired Haemophilia A	
Evidence for linking the risk to the medicine	Clinical studies and Postmarketing
Risk factors and risk groups	Unknown. It is not known whether development of 1 treatment emergent antibody mediated autoimmune disorder predisposes to development of additional antibody mediated autoimmune diseases. Acquired haemophilia A is seen more frequently in the non-MS population with increasing age and may be drug-induced or arise in the setting of pregnancy, underlying autoimmune disease or malignancy. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Instructions for treatment initiation are included in SmPC section 4.2. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Recommendation provided to identify patients developing manifestation of acquired haemophilia A as well as the need to complete coagulopathy panel in case a patient presents such symptoms, are included in SmPC section 4.4. • Recommendations regarding signs and symptoms of acquired haemophila A and the need to seek for medical attention are included in PL sections 2 and 4. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Updated Educational materials (ie, HCP guide, HCP check-list, Patient guide, Patient alert card), planned to be distributed on a yearly basis
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

MS: Multiple Sclerosis; PL: Package Leaflet; PASS: Post-Authorization Safety Study; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 15 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important identified risk: Thrombotic thrombocytopenic purpura (TTP)

Important identified risk: Thrombotic thrombocytopenic purpura (TTP)	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups	None identified.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Instructions for treatment initiation are included in SmPC section 4.2. • Warning to conduct an urgent evaluation and prompt treatment as well as symptoms to identify TTP are included in SmPC section 4.4.. • Recommendations regarding signs and symptoms of TTP are included in PL sections 2 and 4. Section 2 of the PL also recommends getting medical help right away if TTP signs or symptoms occur... • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: • Updated Educational materials (ie, HCP guide, HCP check-list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 16 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important identified risk: Adult Onset Still's Disease (AOSD)

Important identified risk: Adult Onset Still's Disease (AOSD)	
Evidence for linking the risk to the medicine	Postmarketing.
Risk factors and risk groups	In the general population, AOSD is most often seen in young adults, with a higher prevalence in women.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Warning to conduct an urgent evaluation and treatment as well as symptoms to identify AOSD are included in SmPC section 4.4. The statement to "Consider interruption or discontinuation of treatment with LEMTRADA if an alternate etiology cannot be established" is also included in this section. • Potential symptoms of AOSD with multi-organ inflammation is described in PL sections 2 and 4. Section 2 of the PL also recommends getting medical help right away if AOSD symptoms occur. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: • Updated Educational materials (ie, HCP guide, HCP check-list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 17 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important identified risk: Autoimmune Encephalitis (AIE)

Important identified risk: Autoimmune Encephalitis (AIE)	
Evidence for linking the risk to the medicine	Postmarketing studies
Risk factors and risk groups	None identified.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: • Updated Educational materials (ie, HCP guide, HCP check-list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 18 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important identified risk: Acute acalculous cholecystitis

Important identified risk: Acute acalculous cholecystitis	
Evidence for linking the risk to the medicine	Clinical and Postmarketing
Risk factors and risk groups	None identified. There is no indication that patients with preexisting gallbladder conditions are at greatest risk of developing an event. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Conduct to adopt in case acalculous cholecystitis is suspected is included in SmPC section 4.4. • Recommendations regarding signs and symptoms of gall bladder inflammation and the need to seek for medical attention are included in PL sections 2 and 4. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: none
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

MS: Multiple Sclerosis; PL: Package Leaflet; PASS: Post-Authorization Safety Study; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 19 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important potential risk: Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus, Guillain Barre syndrome, Sarcoidosis)

Important potential risk: Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus, Guillain Barre syndrome, Sarcoidosis)	
Evidence for linking the risk to the medicine	Clinical studies and Postmarketing
Risk factors and risk groups	Not identified. It is not known whether development of 1 treatmentemergent antibody mediated autoimmune disorder predisposes to development of additional antibody mediated autoimmune diseases. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed..
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2. • Recommendations to complete blood count are included in SmPC section 4.4, as well as medical conduct to adopt if cytopenia is confirmed.. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

MS: Multiple Sclerosis; PL: Package Leaflet; PASS: Post-Authorization Safety Study; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 20 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important potential risk: Malignancies

Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	Clinical studies and Postmarketing
Risk factors and risk groups	Patients with a prior history of basal cell carcinoma are at increased risk for developing subsequent basal cell carcinoma. Women with HPV infections of the uterine cervix are at increased risk for cervical cancer. This risk may increase after immune suppression by alemtuzumab. There was no dose related pattern identified in the reported cases..
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • Labeled in sections 2 and 4 of PL. • Information regarding treatment initiation in patients with pre-existing and/or ongoing malignancy is labelled in SmPC section 4.4. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

HPV: Human Papilloma Virus; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics..

Table 21 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any– Important potential risk: Progressive multifocal leukoencephalopathy

Important potential risk: Progressive multifocal leukoencephalopathy	
Evidence for linking the risk to the medicine	Postmarketing
Risk factors and risk groups	Patients who are seropositive for JCV antibodies or are HIV positive are at increased risk for progressive multifocal leukoencephalopathy. Chronic lymphocytic leukemia and lymphoproliferative disorders are also associated with increased risk of progressive multifocal leukoencephalopathy. Prior exposure to immunosuppressive therapies also increases the risk for development of progressive multifocal leukoencephalopathy. There was no dose related pattern identified in the reported cases.
Risk minimization measures	Routine risk minimization measures: • Labeled in section 4.4 of SmPC. • Labeled in section 2 of PL. • Recommendations and exams to be completed in case of signs suggestive of PML are labeled in SmPC section 4.4. • Recommendations regarding signs and symptoms of PML and the need to seek for medical attention are included in PL sections 2 and 4. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: Updated Educational materials (ie, HCP guide, Patient guide, Patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

HCP: Healthcare Professional; HIV: Human Immunodeficiency Virus; JCV: John Cunningham Virus; MS: Multiple Sclerosis; PASS: PostAuthorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Addendum Table - Specific to Swiss Market utilization : Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any— Important potential risk:

severe exacerbation by B-cell mediated MS during treatment with alemtuzumab

In addition to the risks defined in the EU-RMP, the important potential risk for alemtuzumab, as proposed by Swissmedic and defined in the specific swiss addendum of RMP, is:

severe exacerbation by B-cell mediated MS during treatment with alemtuzumab	
Frequency with 95% CI	The frequency of confirmed exacerbation of B-cell mediated MS during treatment with alemtuzumab is not known (no confirmation on diagnosis).
Seriousness/outcomes	NA
Severity and nature of risk	Most of the reported cases are considered serious and led to hospitalization. There were some case reports assessed as non-serious events. As described in the literature, B-cell depleting therapy and retreatment with alemtuzumab may act as effective rescue options to manage the exarcebation of B-cell MS. To date, there are no reports of fatal B-cell mediated MS during treatment with alemtuzumab.
Background incidence/prevalence	NA
Risk groups or risk factors	There is no accepted method of identifying patients with the hypothetical entity of "B-cell mediated MS". In practice, the company will continue to surveil for cases that include some or all of the search terms employed in Sanofi's 15 May 2017 reply to Swissmedic on this topic. Nevertheless, there is no accepted scientific basis for a characterization of such cases as representing "B-cell mediated MS" in current medical literature. Given LEMTRADA's reputation as a high-efficacy therapy for RRMS adult patients with active disease, there is a likelihood that patients will be selected for LEMTRADA treatment precisely because they are considered to be at increased risk of severe MS exacerbation. Such patient selection mav ensure that incident cases will occur even if LEMTRADA does not in fact increase the risk of severe MS exacerbation, potentially resulting in a false "signal" of risk
Potential mechanism	The MAH considers that a risk of developing B-cell mediated MS in LEMTRADA (alemtuzumab) treated patients is not supported by current scientific evidence. Moreover, to the best of MAH's knowledge and based on the data presented there is no substantiated mechanism to illustrate such a risk: Although Haghikia et al. suggested that alemtuzumab might trigger B-cell-mediated secondary autoimmune disease, the hypothesis was not supported by investigations of B cells. In contrast, Schwenkenbecher et al. reported a similar case of a patient with severe disease exacerbation despite alemtuzumab therapy, while immunological CSF analyses showed predominantly T-cells and did not reveal a predominantly B-cell-driven pathology. Furthermore, the proportion of HLA-DR on peripheral blood T cells was slightly increased, indicating Tcell-driven disease activity.

Preventability	There is no known pattern for patients experiencing severe exacerbation of B-cell mediated MS during the treatment with alemtuzumab. No data on predictability or preventability can be provided.
Impact on individual patient	Case reports show that some of the patients that experienced a severe exacerbation of B-cell mediated MS were hospitalized and for some of the patients the events were assessed as medically significant.
Potential public health impact of safety concern	No patient experienced events have led to death or life threatening events.
Evidence source(s)	Literature: Haghikia A and al., Severe B-cell-mediated CNS disease secondary to alemtuzumab therapy, Lancet 2017 (16) 2, 104-106 Wehrum T, Beume LA, Stich O, et al. Activation of disease during therapy with alemtuzumab in 3 patients with multiple sclerosis. Neurology 2018;90:e601-e605. Wiendl H, Calabresi PA, Meuth SG. Defining response profiles after alemtuzumab: Rare paradoxical disease exacerbation. Neurology 2018;90:309-31 1 . Schwenkenbecher P, Deppe J, Hummert MW, et al. Management of MSrelapse during alemtuzumab therapy: ls it really B-cell-mediated? Mult Scler Relat Disord 2018;19:6-7. Akgûn K, Metz I, Kitzler H, et al. Rescue therapy with alemtuzumab in B cell/antibody-mediated multiple sclerosis. Ther Adv Neurol Disord 2018;11:1-4.
MedDRAterms	NA
Proposed routine and additional Pharmacovigilance activities	Routine Pharmacovigilance Further discussion of this important potential risk in the PSURs

Table 22 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any – Missing information: Pediatric use

Missing information: Pediatric use	
Risk minimization measures	Routine risk minimization measures: • Labeled in section 5.1 of SmPC. • Recommendations regarding use in paediatric population are included SmPC section 4.2 and PL section 2. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: Pediatric study EFC13429 Planned date for submission of final data: within 6 months of completion of the study (LPLV) in accordance with the Article 46 of paediatric regulation.

LPLV: Last Patient Last Visit; MS: Multiple Sclerosis; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 23 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any – Missing information: Use in patients aged >55 years (including use in elderly patients aged ≥65 years)

Missing information: **Use in patients aged >55 years (including use in elderly patients aged ≥65 years)**	
Risk minimization measures	Routine risk minimization measures: • Labeled in sections 4.2 and 5.2 of SmPC. • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None

Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Risk of mortality study Final report: Q3 2024

MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 24 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any – Missing information: Use in racial categories other than white

Missing information: Use in racial categories other than white	
Risk minimization measures	Routine risk minimization measures: LEMTRADA treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and MI, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Risk of mortality study Final report: Q3 2024

LPLV: Last Patient Last Visit; MS: Multiple Sclerosis; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

Table 25 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any – Missing information: Use in racial categories other than white

Missing information: Use in racial categories other than white	
Risk minimization measures	Routine risk minimization measures: • LEMTRADA treatment should only be initiated and supervised by a neurologist experienced in the treatment of patients with MS in a hospital with ready access to intensive care. Specialists and equipment required for the timely diagnosis and management of adverse reactions, especially myocardial ischaemia and myocardial infarction, cerebrovascular adverse reactions, autoimmune conditions, and infections, should be available. Resources for the management of cytokine release syndrome, hypersensitivity and/or anaphylactic reactions should be available. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional Pharmacovigilance activities: PASS OBS13434 Final report: 2031 Risk of mortality study Final report: Q3 2024

MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study: Q: Quarter..

2.3. Post-authorisation development plan

2.3.1 Studies which are conditions of the marketing authorisation

Table 26 - Studies which are conditions of the marketing authorization

A non-interventional post authorization safety study to investigate drug utilization and safety monitoring patterns for LEMTRADA (alemtuzumab): a cohort study
Purpose of the study: Subsequent to the Article 20 procedure, additional risk minimization measures were added to the EU-SmPC, inclusive of: a newly revised indication; newly added contraindications; and additional safety monitoring. The risk minimization measures are intended to minimize the risk of cardiovascular and cerebrovascular AEs and auto-immune adverse events such as autoimmune hepatitis, thyroiditis, cytopenias and nephropathies. The primary objectives of this study are to measure the proportion of newly prescribed LEMTRADA patients who o have the newly revised indication and; o do not have any of the revised contraindications at the time of prescribing. The secondary objective will focus on measuring adherence to the safety monitoring, prior to and during LEMTRADA infusion along with long-term safety monitoring.
A non-interventional post-authorization safety study to investigate the risk of mortality in patients prescribed LEMTRADA (alemtuzumab) relative to clinically similar MS patients using other disease modifying therapies: a cohort study
Purpose of the study: Existing data from trials and the post-marketing setting are not sufficient to understand fully whether there may be an increased risk of mortality (all-causes) associated with exposure to LEMTRADA. The primary objective is to examine whether MS patients treated with LEMTRADA have a higher risk of all-cause mortality than clinically similar MS patients treated with other DMT.

AE: Adverse Event; DMT: Disease Modifying Therapy; EU: European Union; MS: Multiple Sclerosis; SmPC: Summary of Product Characteristics.

2.3.2 Other studies in post-authorisation development plan

Table 27 - Other studies in post-authorization development plan

PASS OBS13434: A Prospective, Multicenter, Observational Cohort Study of Patients with Relapsing Forms of MS Treated with LEMTRADA (alemtuzumab) (cat. 3)
Purpose of the study: To better characterize the long-term safety profile of alemtuzumab in relapsing MS patients and to determine the incidence of adverse events of special interest. In addition, the following safety concerns: acute acalculous cholecystitis, thrombocytopenia and use in patients >55 years
Pediatric Study EFC13429: Open-label, rater-blinded, single-arm, before and after efficacy, safety and tolerability study of alemtuzumab in pediatric patients from 10 years to less than 18 years with RRMS with disease activity on prior disease modifying treatment (cat. 3)
Purpose of the study: To evaluate the efficacy, safety and tolerability of alemtuzumab (IV) before and after treatment in pediatric subjects with relapsing forms of MS, who have disease activity on prior therapy.

IV: Intravenous; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; RRMS: Relapsing Remitting Multiple Sclerosis.