Summary of risk management plan for LEMTRADA (Alemtuzumab)

This is a summary of the Risk Management Plan (RMP) for LEMTRADA. The RMP details important risks of LEMTRADA how these risks can be minimized, and how more information will be obtained about LEMTRADA's risks and uncertainties (missing information).

LEMTRADA's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how LEMTRADA should be used.

This summary of the RMP for LEMTRADA 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 LEMTRADA's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

LEMTRADA is indicated as a single disease modifying therapy (DMT) in adults with highly active relapsing remitting multiple sclerosis (RRMS) (see SmPC for the full indication) for the following patient group:

- Patients with highly active disease despite a full and adequate course of treatment with at least one 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

II. 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 package leaflet and SmPC 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.

II.A 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 (IARs)
	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 risks	Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, T1DM, GBS, sarcoidosis)
	Malignancies
	Progressive multifocal leukoencephalopathy
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.

AAC: Acute acalculous cholecystitis; AIE: Autoimmune Encephalitis; AOSD: Adult Onset Still's Disease; GBM: Glomerular Basement Membrane; GBS: Guillain-Barre Syndrome; IAR: Infusion-Associated Reaction; T1DM: Type 1 Diabetes Mellitus.

II.B 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 (IARs)

Important identified risk: Infusion-associated reactions (IARs)	
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 [a] 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 IAR. 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	**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.

Important identified risk: Infusion-associated reactions (IARs)	
	• 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 IARs (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 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	Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

a Schwarz MI. Diffuse Alveolar Hemorrhage. Merck Manual Professional Version. 2018.

AE: Adverse Event; B-CLL: B-cell Chronic Lymphocytic Leukemia; IAR: Infusion-Associated Reaction; MI: Myocardial Infarction; 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 BP • 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. The majority of stroke cases temporally associated to LEMTRADA infusion occurred within 3 days of LEMTRADA administration. No pattern of additive or synergistic factors were observed.

Important identified risk: Stroke (including haemorrhagic stroke)[a]	
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 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: 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	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.

AVM: Arteriovenous Membrane; BP: Blood Pressure; HCP: Healthcare Professional; MI: Myocardial Infarction; 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.

Important identified risk: Dissection of the cervicocephalic arteries[a]	
Risk minimization measures	Routine risk minimization measures: • Proposed label in sections 4.2, 4.3, 4.4 and 4.8 of SmPC. • 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 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 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: 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	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; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics.

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

Important identified risk: Myocardial infarction (MI) 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 BP • High blood cholesterol or triglyceride levels • Obesity • Diabetes • Metabolic syndrome • Family history of heart attack

Important identified risk: Myocardial infarction (MI) and myocardial ischaemia[a]	
	• 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. Most 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	Routine risk minimization measures: • 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 MI 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 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 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: 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	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.

BP: Blood Pressure; HCP: Healthcare Professional; MI: Myocardial Infarction; 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 (PAH)[a]

Important identified risk: Pulmonary alveolar haemorrhage (PAH)[a]	
Evidence for linking the risk to the medicine	Postmarketing

Important identified risk: Pulmonary alveolar haemorrhage (PAH)[a]	
Risk factors and risk groups	Many disorders can cause PAH; they include: (**Error! Reference source not found.**) • 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 PAH 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 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 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: 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	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; MI: Myocardial Infarction; PASS: Post-Authorization Safety Study; PAH: Pulmonary Alveolar Haemorrhage; 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. 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. • 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 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: 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	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; MI: Myocardial Infarction; 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[a] alemtuzumab 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 with 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	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 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 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: Educational materials (ie, HCP guide, HCP checklist, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study

Important identified risk: Thyroid disorders	
	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; MI: Myocardial Infarction; 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 (ITP)

Important identified risk: Immune thrombocytopenic purpura (ITP)	
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 ITP, the data suggest that circulating anti-platelet antibody and platelet-bound antibody assays are not predictive of alemtuzumab associated ITP. [a] 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 ITP 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 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: Educational materials (ie, HCP guide, HCP check-list, patient guide, patient alert card) planned to be distributed on a yearly basis.

Important identified risk: Immune thrombocytopenic purpura (ITP)	
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

a Cuker A, Coles AJ, Sullivan H, Fox E, Goldberg M, Oyuela P, et al. A distinctive form of immune thrombocytopenia in a phase 2 study of alemtuzumab for the treatment of relapsing-remitting multiple sclerosis. Blood. 2011 Dec 8;118(24):6299-305.

HCP: Healthcare Professional; ITP: Immune Thrombocytopenic Purpura; MI: Myocardial Infarction; 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 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: Educational materials (ie, HCP guide, HCP check-list, patient guide, patient alert card) planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Drug Utilization Study

Important identified risk: Nephropathies including anti-GBM disease	
	Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

GBM: Glomerular Basement Membrane; HCP: Healthcare Professional; MI: Myocardial Infarction; 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 (AIH)

Important identified risk: Autoimmune Hepatitis (AIH)	
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 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: 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	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

AIH: Autoimmune Hepatitis; HCP: Healthcare Professional; MI: Myocardial Infarction; 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. [a] 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	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 severe active infection until complete resolution is included in SmPC section 4.3 and PL section 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 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: Educational materials (ie, HCP guide, HCP check list, patient guide, patient alert card) planned to be distributed on a yearly basis.

Important identified risk: Serious infections	
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

a CAMMS223 Trial Investigators, Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, et al. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med. 2008 Oct 23;359(17):1786-801.

HSV: Herpes Simplex Virus; HCP: Healthcare Professional; MI: Myocardial Infarction; 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 (HLH)

Important identified risk: Haemophagocytic Lymphohistiocytosis (HLH)	
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	<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 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 HLH. • 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 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. <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	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study

Important identified risk: Haemophagocytic Lymphohistiocytosis (HLH)	
	Final report: Q3 2024

HCP: Healthcare Professional; HLH: Haemophagocytic Lymphohistiocytosis; MI: Myocardial Infarction; 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 (AHA)

Important identified risk: Acquired Haemophilia A (AHA)	
Evidence for linking the risk to the medicine	Clinical 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 AHA 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 AHA 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 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: Updated Educational materials (ie, HCP guide, HCP check-list, patient guide, patient alert card), planned to be distributed on a yearly basis.

Important identified risk: Acquired Haemophilia A (AHA)	
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

AHA: Acquired Haemophilia A; HCP: Healthcare Professional; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; 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 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: Updated Educational materials (ie, HCP guide, patient guide, patient alert card), planned to be distributed on a yearly basis.

Important identified risk: Thrombotic thrombocytopenic purpura (TTP)	
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics; TTP: Thrombotic Thrombocytopenic Purpura.

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

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. [a]
Risk minimization measures	Routine risk minimization measures: • Labeled in section 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 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: Updated Educational materials (ie, HCP guide, patient guide, patient alert card) planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031

a Ruscitti P, Cipriani P, Masedu F, Iacono D, Ciccia F, Liakouli V, et al. Adult-onset Still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. BMC Med. 2016 Dec 1;14(1):194.

AOSD: Adult Onset Still's Disease; HCP: Healthcare Professional; MS: Multiple Sclerosis; MI: Myocardial Infarction; PASS: Post-Authorization Safety Study; PL: Package Leaflet; 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: • Proposed label in sections 4.4 and 4.8 of SmPC. • Proposed label 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 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: Updated Educational materials (ie, HCP guide, patient guide, patient alert card), planned to be distributed on a yearly basis.
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024

AIE: Autoimmune Encephalitis; CI: Confidence Interval; HCP: Healthcare Professional; MS: Multiple Sclerosis; SmPC: Summary of Product Characteristics; PL: Package Leaflet.

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

Important identified risk: Acute acalculous cholecystitis (AAC)	
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 pre-existing 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 4.4 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.

Important identified risk: Acute acalculous cholecystitis (AAC)	
	• 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 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 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

AAC: Acute Acalculous Cholecystitis; MI: Myocardial Infarction; 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, T1DM, GBS, Sarcoidosis)

Important potential risk: Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, T1DM, GBS, 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 treatment-emergent 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 4.3, 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 is 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 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

Important potential risk: Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, T1DM, GBS, Sarcoidosis)	
Additional pharmacovigilance activities	PASS OBS13434 Final report: 2031 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

GBS: Guillain-Barre Syndrome; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; Q: Quarter; SmPC: Summary of Product Characteristics; T1DM: Type 1 Diabetes Mellitus.

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 4.4 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 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 Drug Utilization Study Final report: Q3 2024 Risk of mortality study Final report: Q3 2024

HPV: Human Papilloma Virus; MI: Myocardial Infarction; 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 (PML)

Important potential risk: Progressive Multifocal Leukoencephalopathy (PML)	
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 PML. Chronic lymphocytic leukemia and lymphoproliferative disorders are also associated with increased risk of PML. Prior exposure to immunosuppressive therapies also increases the risk for development of PML. 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 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: Updated Educational materials (ie, HCP guide, HCP checklist, patient guide, patient alert card), planned to be distributed on a yearly basis.
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; MI: Myocardial Infarction; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; PML: Progressive Multifocal Leukoencephalopathy; Q: Quarter; SmPC: Summary of Product Characteristics.

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 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	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; MI: Myocardial Infarction; MS: Multiple Sclerosis; PL: Package Leaflet; 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 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

MI: Myocardial Infarction; 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

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

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

Table 25 - Studies which are conditions of the marketing authorization

A non-interventional PASS to investigate drug utilization and safety monitoring patterns for LEMTRADA (alemtuzumab)
Purpose of the study: LEMTRADA was subject to an EMA Article 20 referral (EMEA/H/A-31/1483/C/3718/0028) initiated in 2019, following findings of serious safety concerns from post-marketing data. During the procedure, new and cumulative safety data were assessed. Subsequently, changes to the EU-SmPC label were implemented. The indication has been revised and additional safety information has been included under “Contraindications” and “Special warnings and precautions for use” sections of the EU-SmPC. The primary objectives of this study are to measure the proportion of prescribed LEMTRADA patients who • have the newly revised indication and; • 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 PASS to investigate the risk of mortality in MS patients treated with alemtuzumab (LEMTRADA) relative to comparable MS patients using other DMTs

Purpose of the study:

Following an EMA Article 20 referral (EMEA/H/A-31/1483/C/3718/0028) in 2019, an investigation into the risk of mortality in MS patients treated with LEMTRADA compared to a relevant MS patient population is required for years during which LEMTRADA has been in use.

Research objective/question: To ascertain whether MS patients treated with LEMTRADA have a higher risk of all-cause mortality than comparable MS patients treated with other HE-DMT.

AE: Adverse Event; DMT: Disease Modifying Therapy; EU: European Union; EMA: European Medicines Agency; HE-DMT: Highly Efficacious-Disease Modifying Therapy; MS: Multiple Sclerosis; SmPC: Summary of Product Characteristics.

II.C.2 Other studies in post-authorization development plan

Table 26 - 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: 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.