



## Summary of the Risk Management Plan (RMP) for LEMTRADA<sup>®</sup>

LEMTRADA<sup>®</sup> (alemtuzumab)

Marketing Authorisation Holder : sanofi-aventis (suisse) sa

RMP version 8.1

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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 médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of the product in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see [www.swissmedicinfo.ch](http://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**

|                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <b>Important identified risks</b> | Infusion-associated reactions<br>Stroke (including haemorrhagic stroke) <sup>a</sup><br>Dissection of the cervicocephalic arteries <sup>a</sup><br>Myocardial infarction and myocardial ischaemia <sup>a</sup><br>Pulmonary alveolar haemorrhage <sup>a</sup><br>Thrombocytopenia <sup>a</sup><br>Thyroid disorders<br>Immune thrombocytopenic purpura<br>Nephropathies including anti-GBM disease<br>Autoimmune hepatitis<br>Serious infections<br>Haemophagocytic lymphohistiocytosis<br>Acute acalculous cholecystitis<br>Acquired Haemophilia A<br>Thrombotic Thrombocytopenic Purpura |
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| <b>Important potential risk</b> | <p>Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus, Guillain Barre syndrome)</p> <p>Malignancies</p> <p>Progressive multifocal leukoencephalopathy</p> <p><b>Specific to swiss market :</b><br/><i>severe exacerbation by B-cell mediated MS during treatment with alemtuzumab</i></p>                                                                   |
| <b>Missing information</b>      | <p>Impact on fertility</p> <p>Use during pregnancy</p> <p>Use during lactation</p> <p>Pediatric use</p> <p>Use in patients aged &gt;55 years (including use in elderly patients aged ≥65 years)</p> <p>Impact on response to vaccination and value of pre-treatment vaccination</p> <p>Use in patients with renal impairment</p> <p>Use in patients with hepatic impairment</p> <p>Use in racial categories other than white</p> |

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**

| <b>Important identified risk: Infusion-associated reactions</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <b>Evidence for linking the risk to the medicine</b>            | <p>Clinical studies and postmarketing</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Risk factors and risk groups</b>                             | <p>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.</p> <p>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).</p> <p>Alemtuzumab treatment is contraindicated in patients with hypersensitivity to alemtuzumab or its excipients.</p> |

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| <p><b>Risk minimization measures</b></p>              | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding hypersensitivity to the active substance or excipients are included in SmPC section 4.3 and PL section 2.</li> <li>• Recommendations for premedication are included in SmPC sections 4.2 and 4.4 and in PL section 4.</li> <li>• How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL section 2</li> <li>• Recommendations to exercise caution until infusion associated reactions (eg, dizziness) are resolved are included in SmPC section 4.7.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |
| <p><b>Additional pharmacovigilance activities</b></p> | <p><u>Additional Pharmacovigilance activities:</u></p> <p>Drug Utilization Study<br/>Final report: Q3 2024</p> <p>Risk of mortality study<br/>Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

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)<sup>a</sup>**

| <b>Important identified risk: Stroke (including haemorrhagic stroke)<sup>a</sup></b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| <b>Evidence for linking the risk to the medicine</b>                                 | <p>Postmarketing</p> <p>There were no non-clinical findings suggestive of stroke in repeat-dose toxicity studies with alemtuzumab.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Risk factors and risk groups</b>                                                  | <p>The major risk factors for stroke include:</p> <ul style="list-style-type: none"> <li>• High Blood pressure</li> <li>• Diabetes</li> <li>• Smoking</li> <li>• Heart disease</li> <li>• Personal or family History of stroke or TIA</li> <li>• Brain aneurysms or AVMs</li> </ul> <p>• 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.</p> <p>• 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.</p> |

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| <p><b>Risk minimization measures</b></p>              | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labelled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding history of stroke is included in SmPC section 4.3 and PL section 2.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• Instructions to reduce serious reactions temporally associated with LEMTRADA infusion (pre-infusion, during infusion and post-infusion) are included in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Communication Plan (DHPC).</li> <li>• Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.</li> </ul> |
| <p><b>Additional pharmacovigilance activities</b></p> | <p>Additional Pharmacovigilance activities:</p> <p>PASS OBS13434</p> <p>Final report: 2031</p> <p>Drug Utilization Study</p> <p>Risk of mortality study</p> <p>Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

<sup>a</sup> 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<sup>a</sup>**

| <b>Important identified risk: Dissection of the cervicocephalic arteries<sup>a</sup></b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| <b>Evidence for linking the risk to the medicine</b>                                     | Postmarketing<br>There were no non-clinical findings suggestive of vascular dissection in repeat-dose toxicity studies with alemtuzumab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Risk factors and risk groups</b>                                                      | 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 8 cases, there were 3 cases reported with regular chiropractic manipulations.<br><br>There was no dose related pattern. Four out of 8 cases were reported with a TTO of 1-3 days from the last dose.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Risk minimization measures</b>                                                        | <u>Routine risk minimization measures:</u> <ul style="list-style-type: none"> <li>• Proposed label in SmPC sections 4.2, 4.3, 4.4 and 4.8.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding history of arterial dissection of the cervicocephalic arteries is included in SmPC section 4.3 and PL section 2.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• Instructions to reduce serious reactions temporally associated with LEMTRADA infusion. (pre-infusion, during infusion and postinfusion) are included in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> |
| <b>Risk minimization measures</b>                                                        | <u>Additional risk minimization measures:</u> <ul style="list-style-type: none"> <li>• Communication Plan (DHPC).</li> <li>• Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Additional pharmacovigilance activities</b>                                           | <u>Additional Pharmacovigilance activities:</u><br>PASS OBS13434<br>Final report: 2031<br>Drug Utilization Study<br>Final report: Q3 2024<br>Risk of mortality study<br>Final report: Q3 2024                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

<sup>a</sup> 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 Onset.



**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 <sup>a</sup>**

| <b>Important identified risk: Myocardial infarction and myocardial ischaemia <sup>a</sup></b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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| <b>Evidence for linking the risk to the medicine</b>                                          | Postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Risk factors and risk groups</b>                                                           | <p>Risk factors that may cause myocardial infarction include:</p> <ul style="list-style-type: none"> <li>• Age (Men age 45 or older, women age 55 or older)</li> <li>• Tobacco</li> <li>• High blood pressure</li> <li>• High blood cholesterol or triglyceride levels</li> <li>• Obesity</li> <li>• Diabetes</li> <li>• Metabolic syndrome</li> <li>• Family history of heart attack</li> <li>• Lack of physical activity</li> <li>• Stress</li> <li>• Illicit drug use</li> <li>• A history of preeclampsia</li> </ul> <p>• 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.</p> |

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| <p><b>Risk minimization measures</b></p>              | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labelled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labelled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding history of angina pectoris or myocardial infarction is included in SmPC section 4.3 and PL section 2.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• Instructions to reduce serious reactions temporally associated with LEMTRADA infusion (pre-infusion, during infusion and postinfusion) are included in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Communication Plan (DHPC).</li> <li>• Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.</li> </ul> |
| <p><b>Additional pharmacovigilance activities</b></p> | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434<br/>           Final report: 2031<br/>           Drug Utilization Study<br/>           Final report: Q3 2024<br/>           Risk of mortality study<br/>           Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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<sup>a</sup>**

| <b>Important identified risk: Pulmonary alveolar haemorrhage<sup>a</sup></b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| <b>Evidence for linking the risk to the medicine</b>                         | Postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Risk factors and risk groups</b>                                          | <p>Many disorders can cause pulmonary alveolar haemorrhage; they include (1):</p> <ul style="list-style-type: none"> <li>• Autoimmune disorders (eg, systemic vasculitides, Goodpasture syndrome, antiphospholipid antibody syndrome, connective tissue disorders);</li> <li>• Pulmonary infections (eg, hantavirus infection);</li> <li>• Toxic exposures (eg, trimellitic anhydride, isocyanates, crack cocaine, certain pesticides);</li> <li>• Drug reactions (eg, propylthiouracil, diphenylhydantoin, amiodarone; methotrexate, nitrofurantoin, bleomycin, montelukast, infliximab);</li> <li>• Cardiac disorders (eg, mitral stenosis);</li> <li>• Coagulation disorders caused by diseases or anticoagulant drugs;</li> <li>• Isolated pauci-immune pulmonary capillaritis;</li> <li>• Idiopathic pulmonary hemosiderosis;</li> <li>• Hematopoietic stem cell transplantation or solid organ transplantation.</li> </ul> <p>• 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.</p>                                                                                                                                                                                                                                                                                                                                        |
| <b>Risk minimization measures</b>                                            | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labelled in sections 4.2, 4.4 and 4.8 of SmPC.</li> <li>• Labelled in sections 2 and 4 of PL.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• Instructions to reduce serious reactions temporally associated with LEMTRADA infusion (pre-infusion, during infusion and postinfusion) are included in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Communication Plan (DHPC).</li> <li>• Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.</li> </ul> |

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| <b>Additional pharmacovigilance activities</b> | <u>Additional Pharmacovigilance activities:</u><br>PASS OBS13434<br>Final report: 2031<br>Drug Utilization Study<br>Final report: Q3 2024<br>Risk of mortality study<br>Final report: Q3 2024 |
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a This risk is temporally associated with LEMTRADA infusion.

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; 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<sup>a</sup>**

| <b>Important identified risk: Thrombocytopenia<sup>a</sup></b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| <b>Evidence for linking the risk to the medicine</b>           | Clinical trials and postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Risk factors and risk groups</b>                            | <p>Non-immune thrombocytopenia can occur with a variety of conditions:</p> <ul style="list-style-type: none"> <li>• Infections (viral, HIV, bacterial infections or sepsis)</li> <li>• Chronic liver disorders</li> <li>• Hypersplenism</li> <li>• Congenital platelet disorders</li> <li>• Malignancies</li> <li>• Bone marrow disorders</li> <li>• Drugs (daptomycin, linezolid, valproic acid)</li> <li>• Over-the-counter remedies, supplements, foods, beverages or alcohol consumption.</li> <li>• 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.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Risk minimization measures</b>                              | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• Instructions to reduce serious reactions temporally associated with LEMTRADA (pre-infusion, during infusion, post-infusion) are included in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis</p> |

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| <b>Additional pharmacovigilance activities</b> | <u>Additional Pharmacovigilance activities:</u><br>PASS OBS13434<br>Final report: 2031<br>Drug Utilization Study<br>Final report: Q3 2024<br>Risk of mortality study |
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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**

| <b>Important identified risk: Thyroid disorders</b>  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| <b>Evidence for linking the risk to the medicine</b> | Clinical studies and postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Risk factors and risk groups</b>                  | <p>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 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.</p> <p>Maternal transmission of anti-TSH receptor antibodies is associated with higher maternal titres of anti-TSH receptor antibodies in the third trimester.</p> <p>There was no dose related pattern. No pattern of additive or synergistic factors were observed.</p> |
| <b>Risk minimization measures</b>                    | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• 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.</li> <li>• Recommendations for thyroid function monitoring are included in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis</p>      |

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| <b>Additional pharmacovigilance activities</b> | <u>Additional Pharmacovigilance activities:</u><br>PASS OBS13434<br>Final report: 2031<br>Drug Utilization Study<br>Risk of mortality study<br>Final report: Q3 2024 |
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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**

| <b>Important identified risk: Immune thrombocytopenic purpura</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| <b>Evidence for linking the risk to the medicine</b>              | Clinical studies and postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Risk factors and risk groups</b>                               | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Risk minimization measures</b>                                 | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis</p> |
| <b>Additional pharmacovigilance activities</b>                    | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434<br/>           Final report: 2031<br/>           Drug Utilization Study<br/>           Risk of mortality study<br/>           Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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**

| <b>Important identified risk: Nephropathies including anti-GBM disease</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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| <b>Evidence for linking the risk to the medicine</b>                       | Clinical studies, medical literature, spontaneous reports received by Sanofi Genzyme and postmarketing.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Risk factors and risk groups</b>                                        | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Risk minimization measures</b>                                          | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• 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.</li> <li>• 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..</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>Updated Educational materials (ie, HCP guide, HCP check list, Patient guide, Patient alert card), planned to be distributed on a yearly basis</p> |
| <b>Additional pharmacovigilance activities</b>                             | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434<br/>           Final report: 2031<br/>           Drug Utilization Study<br/>           Risk of mortality study<br/>           Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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**

| <b>Important identified risk: Autoimmune hepatitis</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| <b>Evidence for linking the risk to the medicine</b>   | postmarketing.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Risk factors and risk groups</b>                    | None identified. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Risk minimization measures</b>                      | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• The need to perform liver function test before initial treatment and periodically thereafter are labelled in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>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.</p> |
| <b>Additional pharmacovigilance activities</b>         | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434<br/>           Final report: 2031<br/>           Drug Utilization Study<br/>           Risk of mortality study<br/>           Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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**

| <b>Important identified risk: Serious infections</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <b>Evidence for linking the risk to the medicine</b> | Clinical studies and postmarketing.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Risk factors and risk groups</b>                  | <p>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.</p> <p>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).</p> <p>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)</p> <p>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).</p> <p>There was no dose related pattern identified in the reported cases.</p> <p>No pattern of additive or synergistic factors were observed.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Risk minimization measures</b>                    | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• Recommendations regarding screening, prophylaxis and the conduct to adopt in patients with severe active infection are included in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>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.</p> |



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| <b>Additional pharmacovigilance activities</b> | <u>Additional Pharmacovigilance activities:</u><br>PASS OBS13434<br>Final report: 2031<br>Drug Utilization Study<br>Risk of mortality study<br>Final report: Q3 2024 |
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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**

| <b>Important identified risk: Haemophagocytic lymphohistiocytosis</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <b>Evidence for linking the risk to the medicine</b>                  | Postmarketing.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Risk factors and risk groups</b>                                   | None identified. There was no dose related pattern identified in the reported cases. No pattern of additive or synergistic factors were observed.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Risk minimization measures</b>                                     | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• 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.</li> <li>• How to detect signs and symptoms, the need to seek for immediate medical attention is labeled in PL Sections 2 and 4..</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Communication Plan (DHPC).</li> <li>• Updated Educational materials (ie, HCP guide, HCP check-list, Patient guide, Patient alert card), planned to be distributed on a yearly basis.</li> </ul> |
| <b>Additional pharmacovigilance activities</b>                        | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434<br/>           Final report: 2031<br/>           Drug Utilization Study<br/>           Risk of mortality study<br/>           Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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: Acute acalculous cholecystitis**

| <b>Important identified risk: Acute acalculous cholecystitis</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| <b>Evidence for linking the risk to the medicine</b>             | Clinical and Postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Risk factors and risk groups</b>                              | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Risk minimization measures</b>                                | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Conduct to adopt in case acalculous cholecystitis is suspected is included in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u><br/>none</p> |
| <b>Additional pharmacovigilance activities</b>                   | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434<br/>Final report: 2031<br/>Drug Utilization Study<br/>Risk of mortality study<br/>Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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: Acquired Haemophilia A**

| <b>Important identified risk: Acquired Haemophilia A</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| <b>Evidence for linking the risk to the medicine</b>     | Clinical studies and Postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Risk factors and risk groups</b>                      | <p>Unknown. It is not known whether development of 1 treatment emergent antibody mediated autoimmune disorder predisposes to development of additional antibody mediated autoimmune diseases.</p> <p>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.</p> <p>There was no dose related pattern identified in the reported cases.</p> <p>No pattern of additive or synergistic factors were observed.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Risk minimization measures</b>                        | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.</li> <li>• 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.</li> <li>• Recommendations regarding signs and symptoms of acquired haemophilia A and the need to seek for medical attention are included in PL sections 2 and 4.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>Updated Educational materials (ie, HCP guide, HCP check-list, Patient guide, Patient alert card), planned to be distributed on a yearly basis</p> |
| <b>Additional pharmacovigilance activities</b>           | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434</p> <p>Final report: 2031</p> <p>Drug Utilization Study</p> <p>Risk of mortality study</p> <p>Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

MS: Multiple Sclerosis; PL: Package Leaflet; PASS: Post-Authorization Safety Study; 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: Thrombotic thrombocytopenic purpura (TTP)**

| <b>Important identified risk: Thrombotic thrombocytopenic purpura (TTP)</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| <b>Evidence for linking the risk to the medicine</b>                        | Postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Risk factors and risk groups</b>                                         | None identified                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Risk minimization measures</b>                                           | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.</li> <li>• Instructions for treatment initiation are included in SmPC section 4.2.</li> <li>• Warning to conduct an urgent evaluation and prompt treatment as well as symptoms to identify TTP are included in SmPC section 4.4.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>Updated Educational materials (ie, HCP guide, Patient guide, Patient alert card), planned to be distributed on a yearly basis</p> |
| <b>Additional pharmacovigilance activities</b>                              | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434<br/>           Final report: 2031<br/>           Drug Utilization Study<br/>           Risk of mortality study<br/>           Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

**Table 17 - 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)**

|                                                                                                                                                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Important potential risk: Other autoimmune disorders (ie, cytopenias, including severe neutropenia, myasthenic syndrome, type 1 diabetes mellitus, Guillain Barre syndrome)</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Evidence for linking the risk to the medicine</b>                                                                                                                               | Clinical studies and Postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Risk factors and risk groups</b>                                                                                                                                                | Not identified. It is not known whether development of 1 treatmentemergent antibody mediated autoimmune disorder predisposes to development of additional antibody mediated autoimmune diseases.<br><br>There was no dose related pattern identified in the reported cases.<br><br>No pattern of additive or synergistic factors were observed..                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Risk minimization measures</b>                                                                                                                                                  | <u>Routine risk minimization measures:</u> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Contraindication regarding other concomitant autoimmune diseases (beside MS) is included in SmPC section 4.3 and PL section 2.</li> <li>• Recommendations to complete blood count are included in SmPC section 4.4, as well as medical conduct to adopt if cytopenia is confirmed..</li> <li>• 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.</li> </ul><br><u>Additional risk minimization measures:</u><br>None |
| <b>Additional pharmacovigilance activities</b>                                                                                                                                     | <u>Additional Pharmacovigilance activities:</u><br>PASS OBS13434<br>Final report: 2031<br>Drug Utilization Study<br>Risk of mortality study<br>Final report: Q3 2024                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

MS: Multiple Sclerosis; PL: Package Leaflet; PASS: Post-Authorization Safety Study; 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 potential risk: Malignancies**

| <b>Important potential risk: Malignancies</b>        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Evidence for linking the risk to the medicine</b> | Clinical studies and Postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Risk factors and risk groups</b>                  | <p>Patients with a prior history of basal cell carcinoma are at increased risk for developing subsequent basal cell carcinoma.</p> <p>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..</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Risk minimization measures</b>                    | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2, 4.3, 4.4 and 4.8 of SmPC.</li> <li>• Labeled in sections 2 and 4 of PL.</li> <li>• Information regarding treatment initiation in patients with pre-existing and/or ongoing malignancy is labelled in SmPC section 4.4.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |
| <b>Additional pharmacovigilance activities</b>       | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434</p> <p>Final report: 2031</p> <p>Drug Utilization Study</p> <p>Risk of mortality study</p> <p>Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

HPV: Human Papilloma Virus; MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; PL: Package Leaflet; 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: Progressive multifocal leukoencephalopathy**

| <b>Important potential risk: Progressive multifocal leukoencephalopathy</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Evidence for linking the risk to the medicine</b>                        | Postmarketing                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Risk factors and risk groups</b>                                         | 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.                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Risk minimization measures</b>                                           | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in section 4.4 of SmPC..</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>Updated Educational materials (ie, HCP guide, Patient guide, Patient alert card), planned to be distributed on a yearly basis.</p> |
| <b>Additional pharmacovigilance activities</b>                              | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434</p> <p>Final report: 2031</p> <p>Drug Utilization Study</p> <p>Risk of mortality study</p> <p>Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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:

| <b>severe exacerbation by B-cell mediated MS during treatment with alemtuzumab</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Frequency with 95% CI</b>                                                       | The frequency of confirmed exacerbation of B-cell mediated MS during treatment with alemtuzumab is not known (no confirmation on diagnosis).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Seriousness/outcomes</b>                                                        | NA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Severity and nature of risk</b>                                                 | <p>Most of the reported cases are considered serious and led to hospitalization. There were some case reports assessed as non-serious events.</p> <p>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.</p> <p>To date, there are no reports of fatal B-cell mediated MS during treatment with alemtuzumab.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Background incidence/prevalence</b>                                             | NA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Risk groups or risk factors</b>                                                 | <p>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.</p> <p>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 may 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</p> |
| <b>Potential mechanism</b>                                                         | <p>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.</p>                                                |

|                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Preventability</b>                                               | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Impact on individual patient</b>                                 | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Potential public health impact of safety concern</b>             | No patient experienced events have led to death or life threatening events.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Evidence source(s)</b>                                           | Literature:<br>Haghikia A and al., Severe B-cell-mediated CNS disease secondary to alemtuzumab therapy, Lancet 2017 (16) 2, 104-106<br>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.<br>Wiendl H, Calabresi PA, Meuth SG. Defining response profiles after alemtuzumab: Rare paradoxical disease exacerbation. Neurology 2018;90:309-311 .<br>Schwenkenbecher P, Deppe J, Hummert MW, et al. Management of MSrelapse during alemtuzumab therapy: Is it really B-cell-mediated? Mult Scler Relat Disord 2018;19:6-7.<br>Akgün 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. |
| <b>MedDRA terms</b>                                                 | NA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Proposed routine and additional Pharmacovigilance activities</b> | Routine Pharmacovigilance<br>Further discussion of this important potential risk in the PSURs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

**Table 20 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any— Missing information: Impact on fertility**

| <b>Missing information: Impact on fertility</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Risk minimization measures</b>               | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in section 4.6 and 5.3 of SmPC.</li> <li>• Labeled in section 2 of PL.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |

MS: Multiple Sclerosis; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

**Table 21 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any – Missing information: Use during pregnancy**

| <b>Missing information: Use during pregnancy</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Risk minimization measures</b>                | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.4, 4.6 and 5.3 of SmPC.</li> <li>• Labeled in section 2 of PL.</li> <li>• Recommendations for contraception and actions to take in case of concomitant thyroid disorder are included in SmPC sections 4.4 and 4.6.</li> <li>• Recommendation regarding pregnancy, including in case of concomitant thyroid disorders are included PL section 2.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |
| <b>Additional pharmacovigilance activities</b>   | <p><u>Additional Pharmacovigilance activities:</u></p> <p>Pregnancy registry OBS13436 to monitor the outcomes</p> <p>Planned date for submission of final data: Q4 2021</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

MS: Multiple Sclerosis; PL: Package Leaflet; 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: Use during lactation**

| <b>Missing information: Use during lactation</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Risk minimization measures</b>                | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in section 4.6 and 5.3 of SmPC.</li> <li>• Labeled in section 2 of PL.</li> <li>• Recommendations regarding breast feeding are included in SmPC section 4.6 and PL section 2</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |

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: Pediatric use**

| <b>Missing information: Pediatric use</b>      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Risk minimization measures</b>              | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in section 5.1 of SmPC.</li> <li>• Recommendations regarding use in paediatric population are included SmPC section 4.2 and PL section 2.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |
| <b>Additional pharmacovigilance activities</b> | <p><u>Additional Pharmacovigilance activities:</u></p> <p>Pediatric study EFC13429</p> <p>Planned date for submission of final data.: As detailed in the modification to the pediatric investigation plan decision (2016). Changes agreed with the pediatric committee will supersede this outline.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

MS: Multiple Sclerosis; PL: Package Leaflet; 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 patients aged >55 years (including use in elderly patients aged ≥65 years)**

| <b>Missing information: Use in patients aged &gt;55 years (including use in elderly patients aged ≥65 years)</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Risk minimization measures</b>                                                                                | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in sections 4.2 and 5.2 of SmPC.</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |
| <b>Additional pharmacovigilance activities</b>                                                                   | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434</p> <p>Final report: 2031</p> <p>Risk of mortality study</p> <p>Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

MS: Multiple Sclerosis; PASS: Post-Authorization Safety Study; 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: Impact on response to vaccination and value of pre-treatment vaccination**

| <b>Missing information: Impact on response to vaccination and value of pre-treatment vaccination</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Risk minimization measures</b>                                                                    | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Recommendations regarding vaccination are included in SmPC section 4.4 and PL section 2..</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |

MS: Multiple Sclerosis; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

**Table 26 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any – Missing information: Use in patients with renal impairment**

| <b>Missing information: Use in patients with renal impairment</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Risk minimization measures</b>                                 | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in section 4.2 of SmPC..</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |

MS: Multiple Sclerosis; SmPC: Summary of Product Characteristics.

**Table 27 - Important risks and missing information with corresponding risk minimization activities and additional pharmacovigilance activities if any – Missing information: Use in patients with hepatic impairment**

| <b>Missing information: Use in patients with hepatic impairment</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Risk minimization measures</b>                                   | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• Labeled in section 4.2 of SmPC..</li> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |

MS: Multiple Sclerosis; SmPC: Summary of Product Characteristics.

**Table 28 - 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**

| <b>Missing information: Use in racial categories other than white</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Risk minimization measures</b>                                     | <p><u>Routine risk minimization measures:</u></p> <ul style="list-style-type: none"> <li>• 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.</li> </ul> <p><u>Additional risk minimization measures:</u></p> <p>None</p> |
| <b>Additional pharmacovigilance activities</b>                        | <p><u>Additional Pharmacovigilance activities:</u></p> <p>PASS OBS13434<br/>           Final report: 2031<br/>           Risk of mortality study<br/>           Final report: Q3 2024</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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 29 - Studies which are conditions of the marketing authorization**

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**A non-interventional post authorization safety study to investigate drug utilization and safety monitoring patterns for LEMTRADA (alemtuzumab): a cohort study**

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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.

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**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**

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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.

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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 30 - Other studies in post-authorization development plan**

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**PASS OBS13434: A Prospective, Multicenter, Observational Cohort Study of Patients with Relapsing Forms of MS Treated with LEMTRADA (alemtuzumab) (cat. 3)**

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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

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**Pregnancy Registry OBS13436: International LEMTRADA pregnancy exposure cohort in MS (cat 3)**

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Purpose of the study:

To monitor reports of use and/or adverse events in pregnancy, and pregnancy outcomes

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**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)**

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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.

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