EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data

Procedure number: EMEA/H/A-20/1483/C/3718/0028

Lemtrada

INN/active substance: alemtuzumab

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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1. Information on the procedure

During the assessment of the periodic safety update report (PSUSA) for Lemtrada (EMEA/H/C/PSUSA/00010055/201809), the following new emerging and serious safety concerns were highlighted in addition to the known safety profile of alemtuzumab, which raised major concerns to the Pharmacovigilance Risk Assessment Committee (PRAC):

- Fatal cases: Several fatal cases were identified during the PSUSA procedure, which indicate that the current recommendations for monitoring may be insufficient.

- Cardiovascular adverse events in close temporal association with Lemtrada infusions (e.g. cardiac ischaemia and myocardial infarction, ischaemic and haemorrhagic stroke, arterial dissection, pulmonary haemorrhage and embolism, vasculitis and thrombocytopenia), including a possible mechanistic relation to these adverse events.

- Immune-mediated diseases such as auto-immune hepatitis, hepatic injury, auto-immune-mediated central nervous system disease and Guillain-Barre Syndrome (GBS).

Limited information, including lack of detailed information on the individual cases, was available on these concerns during the PSUSA assessment, precluding a thorough evaluation.

On 10 April 2019 the European Commission (EC) therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data and requested the PRAC to assess the above safety concerns and their impact on the benefit-risk balance of Lemtrada and to issue a recommendation on whether the relevant marketing authorisation should be maintained, varied, suspended or revoked.

Provisional measures were introduced at the start of procedure to protect patients while the detailed evaluation was ongoing. As a provisional measure, it was recommended that *new treatment with Lemtrada should only be initiated in adult patients with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least two other disease modifying treatments, or in adult patients with highly active relapsing remitting multiple sclerosis where all other disease modifying treatments are contraindicated or otherwise unsuitable.*

2. Scientific discussion

2.1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system with unknown aetiology characterized by loss of motor and sensory function, which results from immune-mediated inflammation, demyelination, and axonal injury and loss. The global prevalence of MS is app. 2 million patients, an age-standardized rate of 28 per 100 000. Worldwide prevalence has increased over time. MS is the leading cause of non-traumatic disability in young adults, with a peak age of onset between 20 and 40 years.

Multiple sclerosis is more common in women than men by approximately 2 to 1. It tends to be more frequent in more developed countries; the highest prevalence rates are in North America (140 per 100 000) and Europe (108 per 100 000) and the lowest rates are in sub-Saharan Africa (2.1 per 100 000) and East Asia (2.2 per 100 000). There is an expected reduction in life expectancy of 7 to 10 years.

Multiple sclerosis can be classified into 4 clinical phenotypes: clinically isolated syndrome (CIS), relapsing remittent MS (RRMS), secondary progressive multiple sclerosis (SPMS), and primary progressive MS (PPMS). RRMS is the most common, characterized by different levels of disease activity

and severity, particularly in the early stages. Demyelination occurs during acute relapses lasting days to months, followed by partial or complete recovery during periods of remission where there is no disease activity. Approximately 55% of people with MS have RRMS. Higher percentages (85%) of patients have RRMS at diagnosis; however, 90% of people with RRMS progress to SPMS after 20 to 25 years.

Subpopulations of MS patients can be classified based on their history of relapse and accompanying MRI imaging features. There is no single definition of high-activity disease (HAD) or rapidly-evolving severe MS (RES) and the definitions of different authors vary (overview Fernandez O, 2017)[1]. The indication HAD RRMS has been used in the EU for several highly active disease-modifying therapies (DMTs). In addition RES RRMS has been defined in the EU regulatory context for other licensed DMTs; as 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

For patients with HAD, most designated MS centres /specialists currently adopt an approach of rapid and effective immunomodulation to prevent aggressive disease progression and severe disability accumulation. Early initiation of effective immunotherapy is considered important in this group of patients due to a narrow therapeutic window to prevent an irreversible accumulation of disability. Systematic reviews and meta-analyses have concluded that higher-efficacy therapies are most likely to reduce MS relapse rates in patients with HAD (Fernandez O, 2017).

2.1.1. Mode of Action

Alemtuzumab (Lemtrada) is a humanised monoclonal antibody (IgG1 kappa) which binds to CD52, a cell surface antigen present at high levels on T (CD3+) and B (CD19+) lymphocytes, and at lower levels on natural killer cells, monocytes and macrophages. There is little or no CD52 detected on neutrophils, plasma cells, or bone marrow stem cells. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis following cell surface binding to T and B lymphocytes, leading to rapid depletion of B- and T-lymphocytes.

Lymphocytes begin to repopulate after each depletion course, and the kinetics of repopulation are similar after the first and second courses. B cell recovery is usually complete within 6 months, whilst T lymphocyte counts slowly rise towards normal and may approach LLN by 12 months. Overall, approximately 80% of patients in clinical trials have total lymphocyte counts that reach the LLN within 12 months of each course.

The mechanism by which alemtuzumab exerts its therapeutic effects in MS is not fully elucidated. It is suggested that Lemtrada may have immunomodulatory effects through the depletion and repopulation of lymphocytes, including: alterations in the number, proportions, and properties of some lymphocyte subsets post-treatment, representation of regulatory T cell subsets, representation of memory T- and B-lymphocytes and transient effects on components of innate immunity (i.e., neutrophils, macrophages, NK cells).

Alemtuzumab has previously been authorised in the EU for treatment of B-cell chronic lymphocytic leukaemia (B-CLL), under the name MabCampath. In other regions of the world, alemtuzumab for B-cell chronic lymphocytic leukaemia (B-CLL) is still available under the name Campath.

[1] Fernandez O et al, 2017 Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? Mult Scler Relat Disord. 2017 Oct;17:75-83.

2.1.2. Cumulative estimated patient exposure from marketing experience, including sponsored, non-interventional studies

As of 31 March 2019, a cumulative total of approximately 25,292 patients were treated with Lemtrada (alemtuzumab) since marketing authorisation was granted in 2013. This represents an estimated 55,431 patient-years of exposure. Additionally, in the same period 1638 patients had received at least one treatment course with alemtuzumab in interventional clinical trials sponsored by Sanofi Genzyme. This represents a total cumulative exposure of 8635 patient-years. When clinical trial exposure is considered, the total cumulative number of patients is 26,930 and the cumulative exposure is 64,066 patient-years.

Approximately 50 % of patients are exposed in the EEA (13515 first course patients and 9868 continuing patients) and approximately 30 % in the USA.

2.2. Data on efficacy

The efficacy of alemtuzumab in RRMS patients is well established. No new efficacy data were made available during the current procedure to alter previous conclusions. A short summary of efficacy is given below. Further detail is available in the European Public Assessment report and the product information.

The Lemtrada clinical program comprises a completed Phase 2 study (CAMMS223), 2 completed confirmatory Phase 3 studies (CAMMS323 and CAMMS324, and an Extension Study (CAMMS03409) with follow-up data from the Phase 2 and 3 studies and for the treatment of consenting, eligible patients with additional courses of alemtuzumab. The Phase 2 and 3 studies were active-controlled, randomized, rater-blinded studies comparing the safety and efficacy of alemtuzumab to high-dose sc interferon beta-1a (IFNB-1a) in patients with RRMS. Studies CAMMS223 and CAMMS323 enrolled treatment-naïve patients, and Study CAMMS324 enrolled patients who had ≥1 relapse during prior MS treatment (for≥6 months) with interferon beta or glatiramer acetate.

Table 1 Key clinical and MRI endpoints from CAMMS03409

Clinical endpoints	CAMMS323	CAMMS324
Annualized relapse rate		
Range, individual years 3-6	0.12 – 0.19	0.16 – 0.24
Patients who are relapse free		
Range, individual years 3-6	83.2% - 88.3%	78.9% - 86.1%
Disability		
Confirmed disability worsening[a]		
Patients with 6-month CDW, cumulative years		
0-6	22.3%	29.7%
(95% CI)	(18.3%, 27.1%)	(25.4%, 34.5%)
Change from baseline in EDSS[b]		
Range, individual years 3-6	-0.08 – 0.09	-0.02 – 0.18
MRI endpoints		
Patients with new or enlarging T2 lesions, %		
Range, individual years 3-6	27.4% -33.2%	29.8% -33.0%
Patients with new gadolinium enhancing lesions, %		
Range, individual years 3-6	9.4% -13.3%	10.0% - 13.5%
Median annual % change in MRI-T2 lesion volume		
Range, individual years 3-6	-0.7% – 1.5%	-0.6% – 0.5%
Median annual % change in brain parenchymal fraction		
Range, individual years 3-6	-0.19% – -0.17%	-0.19% – -0.09%

a CDW was defined as an increase of at least 1 point on the expanded disability status scale (EDSS) from a baseline EDSS score ≥1.0 (1.5 point increase for patients with baseline EDSS of 0) that was sustained for 6 months.

b 2 Estimated using mixed model for repeated measures

CI: confidence interval; EDSS: Expanded Disability Status Scale

2.2.1. Long-term efficacy

Alemtuzumab's beneficial treatment effects are long term with evidence from the clinical program suggesting that these effects are maintained based on 3- and 5-year data from the supportive Phase 2 study CAMMS223 and 6-year data from the CAMMS03409 study with a two years additional follow-up in the TOPAZ study. Thus, many patients who receive alemtuzumab may not subsequently require further treatment in order to control their MS for an extended period. For those patients who do require additional courses, CAMMS03409 demonstrated efficacy of a third or fourth treatment course. In the CAMMS323 population, 41% of patients achieved confirmed disability improvement over 8 years, and 47% of patients from CAMMS324 achieved confirmed disability improvement over the same period. This data is supported by long-term retention rate in the TOPAZ study; 77% from CAMMS323 and 69 % from CAMMS324 who initiated treatment with alemtuzumab 12 mg stayed until the end of the Year 8 follow up (i.e., 8 years since initiation of treatment with alemtuzumab).

Maintained long-term efficacy of alemtuzumab was seen across age groups. The majority of participants in different age group had stable or improved EDSS scores versus baseline 8 years prior in the TOPAZ study (fig 1). Alemtuzumab had a positive effect on brain volume loss during the observation period of 8 years (fig. 2).

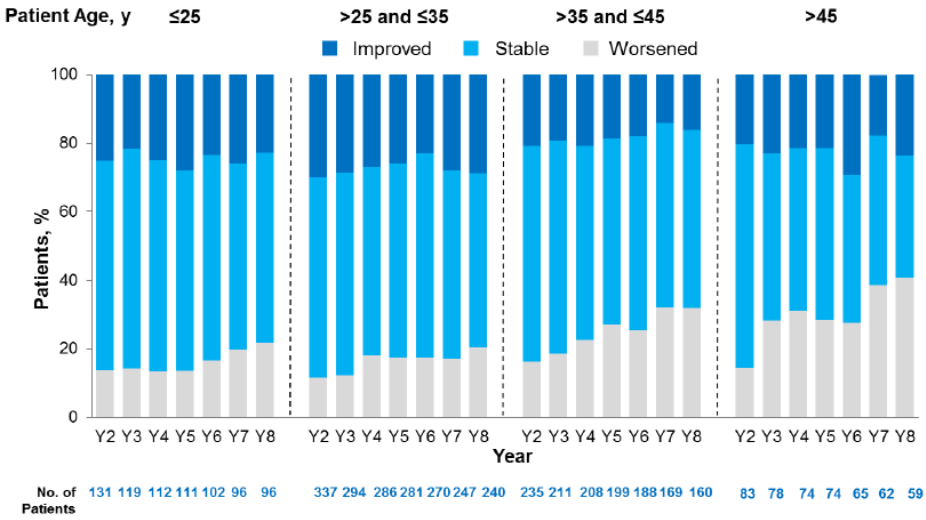

Figure 1 Participants with worsened, stable, or improved EDSS scores from the core study baseline by age in TOPAZ

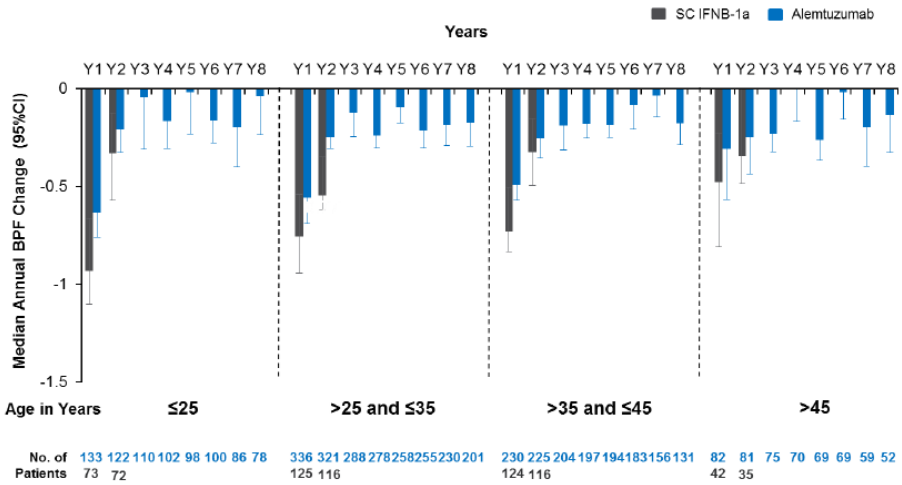

Figure 2 Change in brain volume loss over 8 years by age group at enrolment in TOPAZ

2.2.2. Benefits among patients with highly active disease

A substantial percentage of patients in the CAMMS323 and CAMMS324 study populations can be characterized as having highly active MS. At baseline in CAMMS323 and CAMMS324, 98% of the alemtuzumab treated patients had ≥1 relapse the previous year (in both studies), 50% to 60% had ≥2 relapses, and 45% to 46% had Gd+ MRI lesions at baseline. In this population with a high level of disease activity, the magnitude of alemtuzumab's treatment effects on diverse efficacy measures compared to those of INFB-1a was large in both relative and absolute terms, and clinically relevant.

Study CAMMS324 included a patient population that meets the first criterion for HAD defined above. The inclusion criteria included patients with 1 relapse in the previous year and at least 1 Gd-enhancing lesion or 9 or more T2 lesions, despite a full and adequate course of at least 1 DMT. In this study, alemtuzumab reduced the annualized relapse rate through 2 years of treatment by 49% compared with IFNB-1a ($p < 0.0001$) in patients. Further, confirmed disability worsening was reduced significantly in alemtuzumab patients compared with INFB 1a (hazard ratio 0.58 (0.38, 0.87), $p = 0.0084$).

Post-hoc analyses of data from the Phase 3 studies CAMMS324 and CAMMS323, of RRMS patients with 2 or more relapses in the prior year and at least 1 Gd-enhanced T1 lesion at baseline, were also presented. Data from other studies were not possible to take into account, due to differences in the MRI acquisition algorithms between the Phase 2 and Phase 3 studies. In this subgroup, the annualised relapse rate was 0.26 (95% CI: 0.20, 0.34) in the Lemtrada treated group (n = 205) and 0.51 (95% CI: 0.40, 0.64) in the IFNB-1a group (n = 102) (p<0.0001). As these results come from a post hoc analysis, they should be interpreted cautiously.

In CAMMS324 patients with rapidly evolving MS who had an inadequate response to prior therapy, alemtuzumab demonstrated durable efficacy on MRI outcomes, including brain volume loss, over 6 years. In CAMMS323 patients with HAD, long-term efficacy of alemtuzumab on MRI activity and brain atrophy in treatment-naive RRMS patients with HAD at core study baseline was demonstrated. These findings are consistent with clinical and radiologic outcomes for the overall CAMMS323 study population.

2.3. Data on safety

The main safety concerns to be assessed within this referral procedure are fatal cases, cardiovascular adverse events with particular focus on those occurring within 30 days of infusion, autoimmune diseases and hepatic injury, due to emerging safety data from the post marketing setting.

Overall, the cumulative reviews performed by the MAH have various limitations e.g. which PTs are used in database searches and in assessment of confounders. However, in most cases there is sufficient evidence to conclude a causal association with most of the serious adverse events.

2.3.1. Adverse reactions in close temporal relationship to infusion

2.3.1.1. Myocardial ischaemia and myocardial infarction

Analysis of data

Myocardial ischaemia occurs when blood flow to the heart is reduced, limiting the blood supply to the heart muscle and reducing transfer of oxygen and nutrients, leading to symptoms.

Two searches (myocardial infarction and myocardial ischemia) were performed in the MAH's safety database (from the International Birth Date [IBD] 12 September 2013 through 31 March 2019). Cases were assessed retrospectively against the World Health Organization's (WHO) definition for acute coronary syndrome.

- Myocardial ischaemia

The cumulative search retrieved 2 cases of cardiac ischaemia with time to onset (TTO) ≤ 30 days in a 24-year old female on day 1 of cycle 1 and in a 59 year old female about 1 week after cycle 2.

- Myocardial infarction

The cumulative search retrieved 32 cases with TTO ≤30 days. Of these 32 cases, 5 were excluded from further analysis for the other reasons (duplicate or non-MS indication). The remaining 27 cases with possible myocardial infarction and TTO ≤30 days were considered to have compatible chronology for a possible association with alemtuzumab. The age range of the concerned patients was 24 to 66 years; the mean age was 45 years. In 10 of 27 cases, the patient had one or more traditional risk factors for underlying coronary artery disease (e.g. diabetes, lipid disorder, smoking). In 18 of 27 cases (63 %) there were 1 or more immediate risk factors for myocardial infarction (e.g. increased blood pressure, tachycardia, bradycardia) (Tab.2). With respect to product use, for 25 of 27 cases, the alemtuzumab

dilution method and infusion rate are unknown. In 5 cases, the alemtuzumab cycle was prolonged (i.e. the infusions were not given on consecutive days). With respect to steroids and other pre-medications, 1 patient was pre-medicated with intravenous methylprednisolone at the recommended dose, 1 patient was pre-medicated with oral steroids, and 1 patient was not pre-medicated. For the remaining 24 cases, pre-medication with steroids was either not mentioned (n = 9) or poorly documented (n = 15).

Table 2 Pattern analysis of 27 cases of possible myocardial infarction with TTO ≤ 30 days

Parameters	Probable case or case with compatible chronology (n= 27)
Age	Range 24-66 years Mean: 45 years Median: 44 years
Sex	Female/male: 21/6
Time to onset	0 days: 14 1 day: 6 2 days: 1 5 days: 1 7 days: 1 8 days: 1 21 days: 1 32 days:1 Unknown: 1
One or more risk factors for underlying CAD	***10 cases***
One or more immediate risk factors for myocardial infarction	***18 cases***
Immediate risk factors for myocardial infarction	Hypertension event: 5 Blood pressure increased: 7 Blood pressure fluctuation: 1 Hypotension: 2 Bradycardia: 3 Heart rate decreased: 3 Sinus bradycardia: 2 Tachycardia: 3 Atrial flutter: 1 Heart rate increased: 3
Cycle of alemtuzumab therapy	Cycle 1: 21 Cycle 2: 4 Cycle unknown: 2

A tabulated summary of the 27 cases are shown in the table below (Tab. 3). It is important to note that the majority of cases occurred within 2 days after the last infusion. Two reports (thereof one fatality) which occurred on days 21 and 23 had other aetiologies (infections, ARDS).

Table 3 Reported events of interest, time to onset from first and last dose of alemtuzumab

Age & gender of patient	Reported event of interest	Cycle	TTO from last dose	TTO from first dose	Comment
50 y F	unstable angina	cycle 1	0 days	0 days	during infusion 1
44 y F	chest pain	cycle 1	0 days	0 days	2 hrs after starting infusion 1*
54 y F	myocardial infarct	cycle 1	0 days	1 day	on second day of infusion

47 y F	troponin increased	cycle 1	0 days	1 day	2nd infusion day (5 infusions over 12 days)
62 y F	ST elevation, RR ↑	cycle 1	0 days	3 days	2 infusions over 4 days?
43 y F	myocardial infarct	cycle 1	0 days	4 days	several hours after infusion 5
47y F	myocardial infarct	cycle 1	0 days	0 days	during infusion 1
40y F	troponin increased	cycle 1	0 days	1 day	several hours after 2nd infusion
65y M	troponin increased	cycle 1	0 days	2 days	several hours after infusion 3
36y F	ST elevation	cycle 1	0 days	3 days	at the end of 4th infusion
40y F	chest pain, myocardial necrosis	cycle 1	1 day	1 day	very limited information
24y F	acute coronary syndrome (Category A)	cycle 1	1 day	3 days	early morning, one day after infusion 3
30 y F	AMI, RR ↑	cycle 1	1 day	4 days	1 day after infusion 3?
48y F	myocardial infarct	cycle 1	1 day	5 days	1 day after infusion 5?
41y F	myocardial infarct (Category A)	cycle 1	1 day	5 days	1 day after completing 5 infusions?
32 y F	CPK-MB increased DD. pneumonitis	cycle 1	1 day	3 days	1 day after infusion 3
53y F	myocardial infarct, RR out of control	cycle 1	2 days	6 days	2 days after infusion 5[1]
62y F	troponin increased, SIRS, Sepsis, Pneumonia	cycle 1	21 days	25 days	5 infusions over 5 days, well tolerated
47y F	myocardial infarct, ARDS, sepsis MRSA, cardiac arrest,	cycle 1	23 days	27 days	23 days after infusion 5
66y F	chest pain	cycle 1	5 days	12 days	5 infusions over 8 days
33y F	myocardial infarct	cycle 1	7 days	14 days	5 infusions over 8 days
53y F	myocardial infarct resulting in RCA stent placement	cycle 1	8 days	12 days	8 days after infusion 5
40y F	myocardial necrosis marker increased	cycle 1(?)	unk	2 days	very limited information
27y M	ST elevation	cycle 2	0 days	0 days	during infusion 1
37y M	coronary artery occlusion, RR ↑, arrhythmia resulting in stent placement	cycle 2	0 days	0 days	1 hour after completing first infusion
51y F	chest pain	cycle 2	0 days	2 days	chest pain during 2nd and 3rd infusions
34y F	troponin increased	cycle 2	0 days	3 days	10 minutes after starting infusion 4

1 MI later not confirmed, MRSA: multi-drug resistent staph aureus, *Patient not pre-medicated

The searches for myocardial infarction and myocardial ischaemia identified 22 potential cases (1 potential case of myocardial ischaemia, and 21 potential cases of myocardial infarction) with TTO within 72 hours from the last infusion. According to the MAH two cases met Category A criteria for acute coronary syndrome (myocardial infarction). It is noted that the assessment of certainty of the diagnoses according to the WHO criteria for myocardial infarction by the MAH was very conservative, and that retrospective use of the case definition in particular for spontaneous reports may result in underestimation of related cases.

There was one fatal case of acute respiratory distress syndrome and sepsis which occurred 23 days after the last alemtuzumab infusion, respectively. In this case there was a report of myocardial infarction; however there was little or no evidence of a primary cardiac event caused by alemtuzumab.

It is concluded that the cumulative evidence is sufficient to consider acute coronary syndrome as an infusion-associated reaction. The majority of cases occurred within 48 hours after the last infusion.

Concerning pre-existing risk factors, the majority of patients had no medical history of a cardiac disease or other classical pre-existing risk factors for acute coronary syndrome, but according to the MAH 63% of patients developed infusion reactions such as increased blood pressure, tachycardia and bradycardia which might be a risk factor for acute coronary syndrome. Considering that up to 90% of patients treated in clinical studies with Lemtrada experienced infusion related reactions, this finding is considered to be expected. Due to a lack of discernible pattern it is difficult to identify in advance patients at risk for acute coronary syndrome.

Potential pathomechanism

A potential mechanism for infusion related reactions is that administration of alemtuzumab leads to an artificial induction of an inflammatory response mediated by release of pro-inflammatory cytokines such as IL-6, IL-1b, TNFα, IFNγ, IL-10, and potentially vasoactive compounds following peripheral lymphocyte cytolysis[2]. Administration of high-dose corticosteroids and antihistaminic agents provide some mediation of the expected signs and symptoms. Evidence supports potential enhancement of vasomotor tone within the coronary vasculature triggered by prolonged circulation of inflammatory cytokines. With a number myocardial ischaemic events reported, it appears there may be an idiosyncratic pre-disposition to appearance of symptoms. Notably, published data suggest that specific Fcγ receptor polymorphisms may predispose certain patients to increased cytokine release in response to alemtuzumab exposure[3, 4].

Risk minimisation

It is assumed that pre-existing cardiovascular disorders and risk factors such as known history of angina pectoris, myocardial infarction and patients with uncontrolled hypertension will increase the risk of acute coronary syndrome in case the patients develop cytokine release syndrome in close temporal association with the administration. As a consequence there is agreement that Lemtrada treatment should be avoided in these vulnerable patient groups.

However, it is noted that no pre-existing cardiovascular risk factor was identified for several patients who developed ACS (n=17/27).

Patients should also be carefully monitored before, during and after the infusion. Treatment should be stopped if any clinically significant abnormality occurs during the infusion.

[2] Thomas K, Eisele J, Rodriguez-Leal FA, Hainke U, Ziemssen T. Acute effects of alemtuzumab infusion in patients with active relapsing-remitting MS. Neurol Neuroimmunol Neuroinflamm. 2016 Apr 29;3(3):e228
[3] Alakhras NS, Qiu J, Rocha GV, Witcher DR, Koester A, You J, et al. FcγRIIIa-dependent IFN-γ release in whole blood assay is predictive of therapeutic IgG1 antibodies safety. MAbs. 2018 Aug/Sep;10(6):913-921
[4] Hussain K, Hargreaves CE, Rowley TF, Sopp JM, Latham KV, Bhatta P, et al. Impact of Human FcγR Gene Polymorphisms on IgG-Triggered Cytokine Release: Critical Importance of Cell Assay Format. Front Immunol. 2019 Mar 7;10:390

2.3.1.2. Cerebrovascular accident including arterial dissection

Data analysed

The search of the MAH's global pharmacovigilance database (from 12 September 2013 through 31 March 2019) retrieved 128 cases. One hundred three cases were excluded because they had a TTO >30 days, TTO unknown, or were duplicate cases and diagnoses outside of the events of interest (i.e., ischaemic stroke, haemorrhagic stroke, cervical arterial dissection). Twenty-five remaining cases of reported cerebrovascular accident which occurred within 30 days of an alemtuzumab infusion were included in the analysis. All 25 cases were serious, and one had a fatal outcome. There were 21 females and 4 males with an age range of 25 to 58 years (mean 42.5 years). Nine reports concerned patients below the age of 40 years. By country of incidence, 17 of 25 cases occurred in the United States. An overview of preferred terms of interest for the 25 cases is provided in the table below:

Table 4 Overview of preferred terms of interest in the analysis of cerebrovascular accident

	Event preferred term	Case count	Serious event count	Non-serious event count
Nervous system disorders	Basal ganglia haemorrhage	1	1	0
	Basal ganglia stroke	1	1	0
	Carotid artery dissection	2	2	0
	Central nervous system haemorrhage	1	1	0
	Cerebellar infarction	1	1	0
	Cerebral haemorrhage	3	3	0
	Cerebral infarction	2	2	0
	Cerebrovascular accident	8	8	0
	Haemorrhage intracranial	3	3	0
	Haemorrhagic stroke	2	2	0
	Intraventricular haemorrhage	1	1	0
	Ischaemic stroke	2	2	0
	Vertebral artery dissection	3	3	0
Vascular disorders	Arterial rupture	1	1	0
	Artery dissection	1	1	0

Cases with time to onset within 5 days from the last infusion

Multiple searches related to cerebrovascular disease identified 13 potential cases with time to onset within 5 days from the last infusion:

- Eight cases within 5 days from the last infusion were identified by the search criteria utilized as intracerebral haemorrhage. Six of the eight defined clinical cases are documented to have had been observed with increased blood pressure (BP) during the infusion period, one did

not comment on vital signs and one indicated BP stability. In review of the Azevedo article[5], 3 of 5 patients were discharged from the infusion centre with BP elevations. None of the cases reported clinically significant reductions in platelets.

- Four cases within 5 days from the last infusion were identified by the search criteria utilized as ischaemic stroke. One of the cases is unlikely clinically to represent an ischaemic stroke. One case has insufficient information to be classified. One of these 2 cases clinically confirmed to represent ischaemic strokes had documentation of an increase in BP, the other made no mention in the reporting. It is worth noting that the number of reported cerebral haemorrhages exceeded the number of reported cerebral infarctions, which is opposite the expected picture in the background population.
- One case within 5 days after the last infusion was identified by the search criteria utilized as arterial dissection. This patient was reported to have an increase in BP identified during the infusion period.

Cases with time to onset after 5 days from the last infusion until 30 days after the last infusion

Multiple searches related to cerebrovascular disease identified 12 potential cases with times to onset from >5 days until 30 days after the last infusion.

- Two cases had no confirmation of stroke. Four of the 12 potential cases were not able to be confirmed as cerebral ischaemic infarction, primary intracerebral haemorrhage, or arterial dissection by clinical assessment of the case descriptions. Based on clinical assessment of the case descriptions, 2 of the cases appear to be consistent with transient ischaemic attack or migraine equivalent. One of the cases based on clinical assessment of the case descriptions is noted to not be of ischaemic arterial origin but rather venous thrombosis in origin.
- Two cases within 5 to 30 days from the last infusion were identified by the search criteria utilized as ischaemic stroke, one patient with a history of stroke. Five cases within 5 to 30 days from the last infusion had cervical arterial dissection. Four patients recovered or had no ongoing neurological deficits over the course of time. One patient had some residual deficit. There were no fatalities in this patient population. No clear BP or heart rate changes that extended beyond the 5-day time period were identified in these cases.

Cervical dissections

The majority of the six identified cases of cervical arterial dissection in the peri-infusion period were of multiple vascular dissections. These dissections originate in the muscular middle layer of the vascular wall and only secondarily penetrate the intimal layer. The MAH is of the opinion that the relatively late appearance of cervical arterial dissections does not indicate an infusion related reaction and is conflicted by the probability of some inherent susceptibility such as chiropractic manipulation within individual patients with this occurrence. However the narratives of the respective reports lack any mentioning of a trauma. The possibility of vertebral artery dissection associated with chiropractic cervical manipulation has been discussed, and rates of 1 in 10 000 to 1 in 2 million have been reported in the literature[6]. Thus, it appears very unlikely that the artery dissections in patients treated with Lemtrada were all related to chiropractic dissection. Notably, several (young) patients with cervical

5 Azevedo CJ, Kutz C, Dix A, Boster A, Sanossian N, Kaplan J. Intracerebral haemorrhage during alemtuzumab administration. Lancet Neurol. 2019 Apr;18(4):329-331

6 Chen WL, Chern CH, Wu YL, Lee CH Vertebral artery dissection and cerebellar infarction following chiropractic manipulation. Emerg Med J 2006; 23

arterial dissections had experienced unusual multiple dissections. The MAH also argued that the latency of the events does not support a causal relationship. Considering that diagnoses may be delayed and the unusual pattern in young patients the causal relationship with alemtuzumab a casual association is considered at least possible.

Risk Minimization

Concerning haemorrhagic stroke, pre-identification of patients at high risk of haemorrhagic stroke is challenging because no biomarker / risk factor could be identified. Azevedo et al. reported that cerebral haemorrhage observed in the 4 of the 5 intracerebral haemorrhage cases demonstrated typical hypertensive haemorrhage, i.e. within basal ganglia that are supplied by the deep perforating arteries. There was one case each of frontal lobe haemorrhage and intraventricular haemorrhage. The authors reported that all 5 patients in the case series had increasing BP measurements at the infusion clinics prior to the day of the haemorrhage. Peak BP that was very close to or greater than 20% over the baseline BP. It was suggested that the potential combination of an endothelial dysfunction and sudden increase in BP causing haemorrhage in patients with pre-existing atherosclerotic changes might be a plausible explanation for the intracerebral haemorrhage. The relative increase of blood pressure as a potential biomarker for intracerebral bleedings was extensively discussed within the procedure. However it was noted that in the case series by Azevedo et al, not all patients had recorded systolic hypertension (two patients were normotonic). Also BP results after discharge from the infusion clinic are unknown and usually cerebral autoregulation maintains cerebral blood flow constant despite fluctuations in systemic BP. Although interesting, the hypothesis of Azevedo et al needs further confirmation. In addition, in the IVSS study[7], hypertension with systolic BP $\geq$160 mmHg was observed in 38.5% of participants, mainly after Day 3.

In conclusion, the increase of blood pressure $\geq$ 20 % of baseline was not considered a reliable biomarker for an increased risk of cerebral haemorrhage. The only risk minimization measure identified so far is to contraindicate vulnerable patients, i.e. patients with a history of stroke, history of arterial dissection of the cervicocephalic arteries or uncontrolled hypertension. Furthermore, patients should also be carefully monitored before, during and after the infusion. Treatment should be stopped if any clinically significant abnormality occurs during the infusion.

Regarding arterial dissection, considering the seriousness of the complication and the absence of reasonable alternative explanations, it is justified to contraindicate patients with a known history of arterial dissection of the cervicocephalic arteries.

2.3.1.3. Pulmonary haemorrhage

Data analysed

There were 7 cases of pulmonary haemorrhage retrieved. Six cases of pulmonary haemorrhage occurred on the day of the infusion in Cycle 1, and 1 case occurred few days after Cycle 3. There was a close temporal association with alemtuzumab in all the 7 cases. The review of cases did not find any fatal events, and all events recovered with treatment. At least in 2 cases, Goodpasture's syndrome was considered, but not confirmed/reported by the detection of anti-GBM antibodies. In five cases recovery was complete and respiratory symptoms, most frequently haemoptysis and cough, were transient. The outcome is unknown in 2 cases.

Pulmonary associated haemorrhage has been reported and is thought to represent pulmonary alveolar haemorrhage. Almost all instances were noteworthy for short latency following alemtuzumab infusion. The cumulative evidence is sufficient to suggest possible causal association

[7] Infusion vital sign study (OBS14379) - A prospective observational cohort study in adult patients with relapsing multiple sclerosis to assess patient safety during and after Lemtrada (alemtuzumab) infusions of the first treatment course

between alemtuzumab and pulmonary alveolar haemorrhage in close temporal relation to alemtuzumab infusion.

Pathomechanism

Although the mechanistic link between alemtuzumab and pulmonary alveolar haemorrhage has not been clearly elucidated, the short latency rules out an autoimmune mechanism. An alternative explanation could be pulmonary alveolar haemorrhage caused by cytokine release syndrome and associated capillary haemorrhage secondary to endothelial dysfunction.

Risk minimization

The predominant symptoms of dyspnoea and haemoptysis were distinct and enabled all patients to seek treatment. There was a lack of data regarding vital signs or laboratory parameters in the case reports, and as a result no potential early biomarkers to identify pulmonary arterial hypertension were found. However due to the distinct nature of symptoms, proper education would allow patients to seek medical care early. Pulmonary alveolar haemorrhage will be added to sections 4.2 and 4.4 of the product information as an event which may occur in close association with Lemtrada administration, and to section 4.8 as an adverse reaction of Lemtrada treatment (unknown frequency). Further, patients with known coagulopathy, and/ or being treated with anti-platelet or anti-coagulant therapy should be contraindicated.

2.3.1.4. Pulmonary embolism

A search of the MAH's pharmacovigilance database revealed 20 cases of pulmonary embolism within the timeframe of ≤30 days post-infusion of alemtuzumab. The search found that of these 20 cases, 12 events occurred in females, and 8 events occurred in males. The median age for the patients was 37 years.

The events are briefly described below:

- 13 cases occurred within cycle 1, 1 after cycle 2, cycle unknown in 6 cases
- 12 cases had TTO < 5 days or a few days
- 2 cases had unconfirmed pulmonary embolism
- 10 cases had confounders or were unlikely related due to various reasons – e.g. previous DVT history, superficial thrombophlebitis, hospitalization due to infection, obesity and immobility including being bed-ridden, concurrent Crohn's disease, long TTO from infusion, etc. unlikely associated with the infusion
- In 4 cases had insufficient information
- In 4 cases a causal association cannot be ruled out

Although the MAH argues that a higher risk for VTE is known for MS patients, it is noted that 12 cases (63%) out of 19 cases had TTO ≤5 days or a few days of infusion. This may be related to prolonged immobility during the infusion process. Based on the above described confounding factors the cumulative weighted evidence is at present insufficient to support a causal association between alemtuzumab and pulmonary embolism. This event should be closely monitored.

2.3.1.5. Thrombocytopenia

Data analysed

Immediate non-immune-mediated thrombocytopenia following alemtuzumab infusion has been reported in the literature. Reported cases range from asymptomatic to having signs of spontaneous bleeding. In the case series by Ranganathan[8], 3 of 22 patients developed mild self-limited bruising associated with a drop in platelet count from their baseline during the initial 5-day course of alemtuzumab. In the cases series by Yap and colleagues[9], 34 of 48 patients experienced a platelet count drop below the lower limit of normal (150,000/µL) during the first 5 days of any cycle of alemtuzumab therapy. Median time from first infusion to platelet drop below LLN (150 000/uL) was 2 days (range 1-6 days) with a normalisation of platelet count at median 7 days. All 48 patients had a normal baseline platelet count and no prior documented platelet disorder.

The cumulative search in the MAH's global pharmacovigilance database generated 71 cases with a TTO within 30 days after the last infusion including 3 fatal cases. All the fatal cases had important confounders. The MAH stated that due to lack of relevant information in the remaining 68 cases, it was not possible to assess the majority of the cases. However, important aspects were not analysed and might be missed. Also every concomitant medication (paracetamol, acyclovir) was regarded by the MAH as a confounder. Even pulmonary haemorrhage is considered as a confounder to decreased platelet count (and not a potential consequence of decreased platelet count). For example, the MAH stated that there was no indication that spontaneous intracranial haemorrhage or gastrointestinal bleeding was linked to critically low platelet count in their analyses and that it is unlikely that that immediate non-immune-mediated thrombocytopenia will cause spontaneous bleeding in the central nervous system. Notably, platelet counts were not reported in several cases of intracranial and pulmonary haemorrhages during /post infusion. Thus, thrombocytopenia cannot be definitely ruled out in these cases. Transient symptoms of thrombocytopenia such as petechia and ecchymosis are likely to be underreported. Because the procedure does also not address other bleeding events other than intracranial and pulmonary haemorrhages the statement of the MAH cannot be fully confirmed.

In summary thrombocytopenia in close temporal association with the administration of Lemtrada has been reported in clinical trials and literature within the first 5 days after infusion. However, uncertainties remain with regards to whether this is transient and mostly benign thrombocytopenia. This should continue to be monitored.

Risk Minimization

Platelet count needs to be monitored on Days 3 and 5 immediately post-infusion, for the first course of treatment as well as on Day 3 post-infusion in all subsequent courses. This recommendation is based on observations by Yap et al. Thirty-four (34) of 48 (71 %) patients in the cohort experienced thrombocytopenia with a median time from alemtuzumab infusion to thrombocytopenia of 2 days. Clinically significant thrombocytopenia needs to be followed until resolution. Referral to a haematologist for management should be considered. The product information will be updated accordingly.

2.3.2. Hepatic Injury

One hundred forty-eight cases of hepatic injury were retrieved from the MAH's database. Of these cases, 26 were Campath study cases, which were excluded from further analysis because they were

[8] Ranganathan et al. Immediate transient thrombocytopenia at the time of alemtuzumab infusion in multiple sclerosis. Multiple Sclerosis Journal 2018, Vol. 24(4) 540–542

[9] Yap SM, McNicholas N, Hutchinson M, McGuigan C. Immediate thrombocytopenia at time of alemtuzumab infusion for multiple sclerosis - Not always self-limiting, fully reversible or predictable. Mult Scler. 2018 Apr;24(4):552-553

obtained another disease setting. Twenty-seven (27) were autoimmune cases that are discussed as a part of the evaluation of autoimmune hepatitis cases, and the remaining 95 are analysed.

Of the 95 cases, 13 were non-serious and 82 were serious. Of the 82 serious cases, 7 were fatal and 10 were non-fatal suspected unexpected serious adverse reactions; 2 were reported with drug-induced liver injury, 51 cases (including 4 clinical trial cases) reported concomitant conditions/events/medications that may have precipitated autoimmune hepatitis, and the remaining 12 cases lacked past medical history/ concomitant medications and/or prior treatment information. A number of identified serious events retrieved from this search were indeed from non-MS patients who received alemtuzumab for other indications. Events seen in this group of patients included, but were not limited to reported hepatic failure, and hepatitis. All of these patients had strong confounders for liver injury such as medical history or concomitant medications.

The reported cases containing hepatic injury and hepatic failure as reported event terms in MS patients indicate that, in most cases, the hepatic injury and hepatic failure had other primary causes, e.g. infection, sepsis, or confounders such as concomitant medications. For example, among the fatal cases there was one case from the EU concerning a woman who died 11 days after the first cycle of alemtuzumab. DNA sequencing of the liver biopsy from the autopsy found cytomegalovirus.

The increased risk of infections (primarily during the lymphocyte depletion phase) and autoimmunity (during the lymphocyte repopulation phase) of alemtuzumab may as a secondary effect cause hepatic injury. In addition, cytokine release caused by alemtuzumab may be associated with massive but transient liver enzyme increase (labelled). The cumulative weighted evidence is at present considered insufficient to support a causal association between alemtuzumab and (permanent) hepatic injury (other than autoimmune hepatitis) as a primary effect.

2.3.3. Autoimmune Diseases

2.3.3.1. Autoimmune hepatitis

Data analysed

As of 31 March 2019, a total of 40 unique case reports autoimmune hepatitis (AIH) were retrieved from the MAH's database. Twelve of 40 cases did not meet the medical criteria of AIH. Fourteen cases had insufficient information. Five cases had concomitant conditions/events/medications that may have precipitated AIH. Nine cases had enough information and no known concomitant conditions/events/ medications. The nine cases of AIH in alemtuzumab-treated patients translate into a reporting rate of 16 cases per 100000 person-years. If patients with insufficient information are also included, these 28 cases translate into 50 cases per 100000 person-years. Although these estimations are associated with substantial uncertainty, this is higher than the rate reported in MS patients (17 to 23 per 100 000 person-years observed in the Optum HER database for MS patients). Given the established autoimmune potential of alemtuzumab, the weighted cumulative evidence is sufficient to support a causal association between alemtuzumab and AIH.

It is well known from clinical practice that common autoimmune disorders tend to coexist in the same subject and to cluster in families. Autoimmune thyroid diseases, comprising the two main entities Hashimoto's thyroiditis and Graves' disease, are the most common autoimmune diseases and are often observed together with other autoimmune diseases. The occurrence of two or more diseases in the

same patient is often referred to as polyautoimmunity. Without proving causality, the association between autoimmune thyroid diseases and other autoimmune diseases seems well substantiated[10].

Risk Minimization

Given that the evidence is sufficient to support a causal association between alemtuzumab and AIH, it is considered necessary to extend the monthly laboratory monitoring in the follow-up period of Lemtrada infusions to include also liver transaminases even though it is known that even frequent monitoring of transaminases may not avoid development of AIH and a serious course of hepatitis in all cases. The product information will be updated.

2.3.3.2. Autoimmune disorders

Pathomechanism

After alemtuzumab treatment, T- and B-cell reconstitution begins in the first month after treatment, with B-cells repopulating more rapidly than T-cells. Although the mechanism behind development of autoimmunity after alemtuzumab treatment is not well understood, the depletion and repopulation patterns of various lymphocyte subsets have been studied extensively. The development of secondary autoimmunity may depend not only on a recovery or altered ratios of particular immune cells or subsets of immune cells but also on a complex interaction between different subsets through altered clonal diversity as well as an imbalance between thymopoiesis versus homeostatic proliferation, which occurs in a subset of patients.

Time to onset of autoimmunity following Lemtrada infusions

Data from long term use of alemtuzumab in MS in cohorts of patients treated in the UK prior to marketing authorization and in extensions of the Phase 2 and 3 pivotal studies support that the current recommendation of monthly monitoring until 48 months after the last treatment course is proportionate for the detection of serious autoimmune events in the majority of patients, however, single cases of autoimmune disorders occurred after these period. Tuohy et al followed 87 patients treated with alemtuzumab in an investigator-led study in Cambridge, UK, from 1999 to 2012[11]. The median follow-up period was 7 years with a range of 33 to 144 months. Clinical autoimmune disease developed in 41 of 86 patients (48%, 1 patient was omitted from the total because of pre-existing thyroid disease). Autoimmunity was not associated with the number of alemtuzumab treatment courses administered ($p = 0.457$, Mann–Whitney U test). Thyroid autoimmunity developed in 35 of 86 (41%), of which 22/35 patients experienced hyperthyroidismus (Graves' disease). Three patients (3.5%) developed ITP, of which one patient developed Graves' disease 12 months after the first alemtuzumab infusion and ITP 43 months after the third cycle. Other autoimmune diseases seen were 1 case each of asymptomatic autoimmune neutropenia, autoimmune haemolytic anaemia, and Goodpasture syndrome requiring renal transplantation. Occurrence of autoimmune disease was most frequent during the first 3 years after first treatment, with the vast majority of autoimmune diseases occurring within 48 months after the last treatment, as seen in the figure below.

10 Bliddal S et al., Recent advances in understanding autoimmune thyroid disease: the tallest tree in the forest of polyautoimmunity. F1000Research 2017, 6(F1000 Faculty Rev):1776 Last updated: 28 SEP 2017

11 Tuohy O, Costelloe L, Hill-Cawthorne G, Bjornson I, Harding K, Robertson N, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. J Neurol Neurosurg Psychiatry. 2015 Feb;86(2):208-15

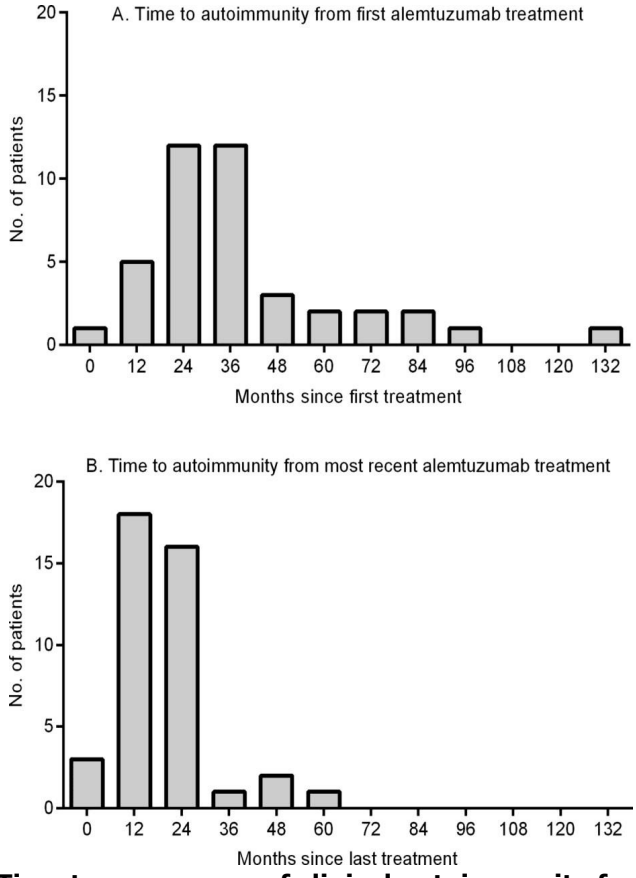

Figure 3 Time to occurrence of clinical autoimmunity from first and most recent alemtuzumab treatment (Tuohy et al (2015))

Willis et al[12] identified a cohort of 100 MS patients at 3 sites in the UK who had been treated with alemtuzumab since 2000 and followed them for 607 patient–years. Fifty-one autoimmune disease diagnoses were made in 47 patients. The thyroid gland was the most common site of autoimmunity, with 35% patients affected. Three patients developed ITP, and 13 other autoimmunity. Mean time to development of autoimmune disease was 995 days (median: 898; range: 30 to 3180 days) following the first treatment and a mean of 578 days (median: 394; range: 0 to 3180 days) after the most recent treatment. The risk of developing secondary autoimmunity was greatest in the 5 years following the first dose of alemtuzumab; 3 cases (all thyroid autoimmune disease) were observed after this time.

Review of long term safety data from the extension studies (CAMMS03409 and TOPAZ) of the 2 pivotal trials CAMMS323 and CAMMS324, indicated that the thyroid AE incidence peaked in Year 3 and declined subsequently through Year 8; cumulative incidence in Years 1 to 8 was 46.0% for thyroid AEs and 6.4% for serious thyroid AEs. The exclusion criteria of these studies should be taken into account when interpreting results (see section below).

Risk Minimisation

Cases of different autoimmune disorders continue to be reported with alemtuzumab in the literature. From the pivotal studies, it is known that autoimmune thyroidal disorders after Lemtrada treatment are very common while ITP and anti-GBM nephropathy are infrequent. This is also supported by

[12] Willis MD, Harding KE, Pickersgill TP, Wardle M, Pearson OR, Scolding NJ, et al. Alemtuzumab for multiple sclerosis: Long term follow-up in a multi-centre cohort. Mult Scler. 2016 Aug;22(9):1215-23.

literature data (42% of alemtuzumab treated patients with thyroid disorders[13]). Graves' disease comprises the most common cause of thyroid dysfunction[14, 15]. The frequency of all different non thyroidal autoimmune disorders after Lemtrada treatment is hard to estimate. In a study by Willis et al a cohort of 100 MS patients treated with Lemtrada and with a mean follow up of 6.1 years was identified. Prior to treatment all patients had normal thyroid function tests. In line with previous findings, after Lemtrada treatment 35% were affected by autoimmunity of the thyroid gland but also 13 other autoimmune disorders were diagnosed.

In the context of this procedure, reports describing poly-autoimmunity have been noted. For example, 9/11 cases with biopsy proven AIH had pre-existing or had developed autoimmune thyroid conditions prior to the development of AIH. These data indicate that autoimmune propensity and the potential for poly-autoimmunity are important factors to take into account for minimising the risk of autoimmune conditions associated with Lemtrada.

As there is no biomarker to identify patients at higher risk for serious autoimmune conditions following Lemtrada administration, the only possibility to minimize the risk is to avoid treatment in patients potentially vulnerable for (poly)autoimmunity, e.g. patients with pre-existing autoimmune disease (other than MS). In addition, patients who experience another autoimmune disease following Lemtrada administration should not be re-treated.

The MAH is of the opinion that contraindicating patients with another concomitant autoimmune disease, and those who develop additional autoimmune conditions following Lemtrada therapy will lead to the exclusion of a high percentage of patients including patients with fluctuating TSH levels which may result in incomplete treatment courses. The MAH performed a post hoc analyses of patients enrolled in the Lemtrada long-term extension studies (CAMMS03409 and LPS13649) with pre-existing, potentially autoimmune related thyroid conditions and an analysis of patients who developed a thyroid disorder after alemtuzumab and subsequently have been re-treated. Based on these data the MAH is of the opinion that there is no evidence of a higher frequency of a second additional autoimmunity.

Long term data from the extension studies (CAMMS03409 and TOPAZ) of the pivotal trials CAMMS323 and CAMMS 324 provide opportunity to assess long-term safety. However, the inclusion and exclusion criteria in these studies influence the final safety concerns, and the possibility to assess this aspect of co-morbid autoimmunity. In the CARE-MS I study (study 323) and in the CARE-MS II study (study 324) significant autoimmune diseases (including, but not limited to immune cytopenia, rheumatoid arthritis, systemic lupus erythematosus, other connective tissue disorders, vasculitis, inflammatory bowel disease and severe psoriasis) and patients with anti-thyroid stimulating hormone (TSH) receptor (TSHR) antibodies (above LLN) were excluded from the studies.. And in CAMMS 223 patients with a history of thyroid autoimmune disease and those with a history of significant autoimmune disease (e.g. inflammatory bowel disease, diabetes, lupus and severe asthma) were excluded. Exposure to certain immune-suppressive and immune-modulating agents was also an exclusion criterion.

The MAH also presented additional information from the ongoing, single-arm, prospective observational post authorisation safety study (PASS OBS 13432). At the data cut-off approximately 8% of enrolled patients had baseline co-morbid autoimmune events. There were 14.9 % of patients with baseline non-MS autoimmune comorbidity who developed at least one post-baseline autoimmune (AI) event and 14.1 % of patients without additional baseline autoimmune comorbidity developed at least one post-

[13] Pariani N, et al., Alemtuzumab-Induced Thyroid Dysfunction Exhibits Distinctive Clinical and Immunological Features. J Clin Endocrinol Metab. 2018 Aug;103(8):3010-3018

[14] Scappaticcio et al. Alemtuzumab-induced thyroid events in multiple sclerosis: a systematic review and meta-analysis. Journal of Endocrinological Investigation. August 2019

[15] Tuohy O, Costelloe L, Hill-Cawthorne G, Bjornson I, Harding K, Robertson N, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. J Neurol Neurosurg Psychiatry. 2015 Feb;86(2):208-15

baseline autoimmune event. No incidences were provided. Considering that the average duration of follow-up was 1.7 years at the data cut-off April 2019, a number of autoimmune events may still be expected to occur due to Lemtrada treatment (see Willis et al, Tuohy et al). This might also explain the lower percentage of secondary autoimmunity at the data-cut off compared to other studies. Thus, it can be concluded that the data presented by the MAH did not provide robust evidence that patients with pre-existing co-morbid autoimmunity are not at increased risk of developing further autoimmunity disorders post-treatment.

It is acknowledged that autoimmunity is multifactorial including genetic and environmental factors. It is also well known that common autoimmune disorders tend to coexist in the same subject and to cluster in families. Boelaert et al[16] performed a cross-sectional multicenter study of 3286 caucasian subjects (2791 with Graves' disease and 495 with Hashimoto´s thyroiditis). The frequency of another autoimmune disorder was approximately 10% in Graves' disease and 14% in Hashimoto´s thyroiditis index cases. These numbers indicate a heightened incidence of a second additional autoimmune disorder in patients with autoimmune thyroidal disease. From a safety perspective these numbers cannot be disregarded.

Despite warnings and precautions in section 4.4 of the SmPC an increased number of previously known as well as unknown autoimmune adverse reactions of Lemtrada continued to be reported. Many of these reports describe life- long diseases and some of them severe and even fatal. The mechanisms are not fully understood and no biomarkers have been identified. Thus, several of these serious adverse events of Lemtrada are unpredictable and largely unavoidable. Given the outstanding uncertainties regarding adequate risk minimization, exclusion of the most vulnerable patients is considered to be the only reasonable risk minimization measure at present. Thus, a contraindication in patients with other concomitant autoimmune diseases is necessary to decrease the risk of developing serious or even fatal autoimmune adverse reactions following Lemtrada treatment.

An analysis of data of TTO of autoimmune events from post marketing data and the long-term clinical program supports the notion that the currently recommended 48-month monitoring period (after the most recent alemtuzumab infusion) is adequate to monitor the majority of patients. However, patients and physicians should be made aware of the potential onset of autoimmune disorders after the 48 months period.

2.3.3.3. Vasculitis

Anti-GBM (glomerular basement membrane) vasculitis cases were excluded from the qualitative analysis as these represent an already known risk of Lemtrada.

A search of vasculitis cases in clinical studies found 4 cases of vasculitis (excluding the anti-GBM cases) including 1 fatal case in a patient also with intracerebral haemorrhage and confounding factors occurring more than 2 years after their fifth cycle of alemtuzumab.

The review of the MAH's pharmacovigilance database revealed 9 cases of vasculitis meeting the definition, occurring within the timeframe of ≤30 days post infusion of alemtuzumab. Of the 9 cases with TTO within 30 days, 2 cases occurred within 1 day, with the majority of cases occurring between 7 and 10 days. Six out of nine events occurred during first treatment course (cycle 1). Six of the 9 cases had no confirmed diagnosis of vasculitis. The 3 cases with a confirmatory diagnosis had leukocytoplastic vasculitis verified by a skin biopsy. The reported cases of vasculitis diagnosis are

[16] Boelaert K, et al., Prevalence and Relative Risk of Other Autoimmune Diseases in Subjects with Autoimmune Thyroid Disease. The American Journal of Medicine (2010) 123, 183.e1-183.e9.

confounded by concomitant mediations such as NSAIDs that are known to cause reactions including vasculitis pathology, and in cases where such medications are not reported, there is a possibility that those cases are still confounded. Use of NSAIDs and other analgesic/antipyretics after alemtuzumab infusion for symptomatic control of infusion-associated reactions is a common practice.

The weighted cumulative evidence is at present insufficient to suggest a causal association between alemtuzumab and events of vasculitis. This potential risk should be closely monitored and the MAH is expected to submit cumulative reviews and discuss vasculitis in the next PSURs.

2.3.3.4. Autoimmune-mediated CNS disease

Cases of severely exacerbated central nervous system (CNS) inflammation have been described in patients with MS under treatment with alemtuzumab[17,18,19]. The MAH reviewed 13 cases thereof six case reports of autoimmune-mediated CNS disease related to the use of alemtuzumab have been published. Five cases involved treatment of patients with RRMS, with one instance of neuromyelitis optica treatment with alemtuzumab. The authors suggest B-cell dependent autoimmunity related to different rates of B- and T cell repopulation. Although the case reports are a matter of concern, further evidence is needed to conclude whether CNS autoimmunity might be related to alemtuzumab or whether these cases reflect breakthrough disease. It is noted that it may be difficult in the clinical setting to differentiate symptoms of autoimmune-mediated disease from the MS natural history. Therefore, it is likely that CNS adverse events are under-reported.

In addition, isolated reports of other CNS complications in Lemtrada patients have been reviewed. Notably, there were two case reports of necrotizing encephalopathy (one case with concomitant autoimmune haemolytic anaemia with fatal outcome) and one case of autoimmune encephalitis.

Currently available information is insuficcient to draw a conclusion on causality at this stage, but CNS inflammation temporally related to Lemtrada should be monitored in periodic safety update reports (PSURs).

2.3.3.5. Other autoimmune reactions

A retrospective cohort study of MS patients compared to matched controls in the US Optum Database confirmed that MS patients have a 25% higher rate of being diagnosed with type 1 diabetes (IRR = 1.25, 95% CI = 1.08-1.44); a 2-fold higher rate of myositis diagnosis (IRR = 2.17, 95% CI = 2.02-2.33); and a 2-fold higher rate of sarcoidosis (IRR = 2.11, 95% CI = 1.69-2.62). The results for myasthenic syndrome, pneumonitis, and acquired haemophilia A were either not statistically significant or there were too few patients with an autoimmune outcome to draw any conclusion.

This needs however to be closely monitored. Therefore, a comprehensive signal evaluation report considering all available evidence for events of diabetes type 1, myasthenic syndrome, myositis, sarcoidosis and pneumonitis needs to be included with the next PSUR.

During the Article 20 procedure a new signal was identified and analysed. Cases of acquired haemophilia A (anti-factor VIII antibodies) have been reported in both clinical trial and post-marketing setting. Patients typically present with spontaneous subcutaneous hematomas and extensive bruising

[17] Haghikia A, Dentrou CA, Schneider R et al: Severe B-cell-mediated CNS disease secondary to alemtuzumab therapy. www.thelancet.com/neurology Vol 16 February 2017

[18] Rinaldi F, Federle L, Puthenparampil M, et al Evidence of B-cell dysregulation in severe CNS inflammation after alemtuzumab therapy. Neurol Neuroimmunol Neuroinflamm. 2018 Jan; 5(1): e420; Published online 2017 Dec 13. doi: 10.1212/NXI.0000000000000420

[19] Barton J, Hardy TA, Riminton S, et al. Tumefactive demyelination following treatment for relapsing multiple sclerosis with alemtuzumab. Neurology 2017;88:1004–1006

although haematuria, epistaxis, gastrointestinal or other types of bleeding may occur. The reported incidence in the general population is approximately 1.48/million/year. Up to 50% of cases of acquired haemophilia may be associated with a variety of clinical conditions. Treatment typically involves immunosuppression to eradicate the FVIII inhibitor, as well as haemostatic therapy to control bleeding. The reporting rate of acquired haemophilia A after treatment with Lemtrada is considered to be substantially higher compared to the background rate and suggests an increased risk which needs to be included in the product information.

Risk minimization

Information on acquired haemophilia needs to be included in the updated product information. In case of spontaneous subcutaneous haematomas and extensive bruising, haematuria, epistaxis, gastrointestinal or other types of bleeding a coagulopathy panel including aPTT must be obtained in all patients that present with such symptoms. HCPs should educate patients on the signs and symptoms of acquired haemophilia A and to seek immediate medical attention, if any of these symptoms are observed.

2.3.3.6. Guillain-Barre Syndrome (GBS)

A total of 13 cases of GBS were identified in the MAH's database. Two of these cases did not meet the medical criteria of GBS but were chronic inflammatory demyelinating polyneuropathy (CIDP). Of the 11 GBS cases in the database, 1 patient had apparently an MS relapse and was treated with steroids but neither plasmapheresis nor intravenous immunoglobulin.

The MAH calculated a reporting rate of 23.5 cases per 100 000 person-years and stated that this is not higher than GBS incidence rates of 37.7 per 100 000 patient years which have been observed in subjects diagnosed with MS. However, these figures are questionable, as the GBS reporting rate mentioned is much higher than the background incidence in the general population (1-2/100 000 patient years).

While a conclusion cannot presently be reached on a possible causal association, the potential risk of GBS should be re-discussed in the next PSUR, and an updated review should be provided. For the next PSUR, the MAH is asked to explore whether it is possible to calculate the background incidence of GBS in RRMS patients e.g. in the US Optum Database in order to perform an observed versus expected analysis.

2.3.4. Haemophagocytic lymphohistiocytosis (HLH)

Data analysed

HLH was identified as a serious risk of alemtuzumab and added to the product information in the last PSU. A EudraVigilance search until 20 August 2019 revealed a total of 11 case reports of HLH including two cases with fatal outcome. Two reports have been published[20]. One report is from the USA and 10 reports from the EEA. It was noted that one poorly documented case report may be a duplicate. Four patients developed additional other autoimmune diseases: 2 patients acquired haemophilia A, one patient Evans syndrome and one patient Still syndrome.

[20] Saarela M, Senthil K, Jones J et al. Hemophagocytic lymphohistiocytosis in 2 patients with multiple sclerosis treated with alemtuzumab. Neurology. 2018 May 1;90(18):849-851. doi: 10.1212/WNL.0000000000005420. Epub 2018 Mar 30

Risk Minimization

There are limited options to minimise the risk of this rare, life-threatening adverse event that occurs long after treatment. Information on HLH is already present in the product information and additional information should be provided in the educational materials for Lemtrada.

2.3.5. Fatalities

A search of the MAH database retrieved 246 cases. In the 246 cases (of which 169 cases were solicited and 77 cases were unsolicited), a total of 1890 events were reported. These 246 cases include, incidentally, a small number of cases outside of the adult multiple sclerosis (MS) indication (e.g. compassionate use cases for other indications, off-label use, and/or misdiagnosed MS) as well as some duplicate reports. The age distribution of patients with fatalities was 1 day (exposure during pregnancy) to 77 years, with an average age of 48.8 years. The highest number of fatalities occurred in the age group 36-50 years of age (n= 78 case reports), thus in a quite young patient population.

Mortality rate

According to the MAH, the mortality rate in clinical trials (CTs) with alemtuzumab was 0.17 per 100 patient-years. The estimated post-marketing mortality rate is currently 0.42 per 100 patient years. These data have considerable uncertainties, due to the nature of spontaneously reported data, as well as estimations f post marketing patient exposure. The distribution of reported fatalities differs between the regions (see table 5).

Table 5 Distribution of reported fatalities reported in association with Lemtrada by region

Regions	Cumulative no. of patients treated with alemtuzumab for MS	No. of fatality cases	Mortality reporting rate
EU	12777	51	0.4%
US	7441	164	2.2%
Rest of the world	5074	31	0.6%

Of the 169 solicited cases, 20 were from Europe, 23 from Rest of World, and 126 from the US. Of the 77 unsolicited cases, 32 were from Europe, 7 from Rest of World, and 38 from the US. The distribution of solicited and unsolicited case reports among regions shows a higher volume of solicited cases in the US. 77 % of USA and rest of world reports and 39 % of European reports are solicited reports. The number of unsolicited cases is more evenly distributed across regions (49% US, 42% EU, and 10% Rest of World); however, the highest number was in the US, although there are only approximately half as many Lemtrada-treated patients in the US (n= 7441 patients treated) as in the EU (12777 patients). Overall, these data support the notion that the increased frequency and variety of interactions with patients and HCPs in the US via patient support programs and REMS may be partly responsible for increased reports in the US. This may also be suggestive of underreporting in Europe.

Available data from the Lemtrada controlled clinical trials as well as real-world evidence studies were reviewed to determine differences in the patient populations. Baseline characteristics of patients in various studies, by region (US versus EU) indicate that US patients in the post-marketing settings are older and have a longer disease duration compared to the EU post-marketing setting. The

characteristics of the US Lemtrada patients may put them more at risk for serious adverse events, including fatalities, independent of any specific MS treatment.

Literature data also indicate potential differences in the mortality rate between regions and countries with a higher mortality rate in the USA (Kaufmann DW 2014) compared to some EU countries such as France[21] or Sweden[22]. These factors may contribute to the observed differences, however it is difficult to determine to what extent this might impact or skew observed reporting rates.

Fatal cases with time to onset within 30 days of last infusion

Of 246 fatal cases, information on time to onset was reported for 122 cases and was unknown for 124 cases. When the TTO from last infusion was reported, it ranged from 0 days to 6.5 years. In 15 cases with TTO from last infusion, there were 24 fatal events reported. Events reported more than once were cardiac arrest and sepsis, which were both reported twice. Seventeen cases nominally had TTO from last infusion reported within 30 days of last infusion (Table 6).

Table 6 Fatal events by System Organ Class with time to onset within 30 days of last infusion

Event SOC	Event PT	Last dose to onset	Total
BLOOD AND LYMPHATIC SYSTEM DISORDERS	PANCYTOPENIA	27 days 15 hrs	1
CARDIAC DISORDERS	ATRIAL FLUTTER	25 min	1
	CARDIAC ARREST	2 days	1
	CARDIAC ARREST	28 days	1
	MYOCARDIAL INFARCTION	27 days	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	FATIGUE	4. 2 days	1
	MULTIPLE ORGAN DYSFUNCTION	14 days	1
HEPATOBILIARY DISORDERS	HEPATIC FAILURE	14 days	1
INFECTIONS AND INFESTATIONS	BRONCHOPULMONARY ASPERGILLOSIS	14 days	1
	MENINGITIS LISTERIA	12 days	1
	PNEUMONIA	11 days	1
	pneumonia necrotising	14 days	1
	SEPSIS	13 days 15 hrs 19 min	1
	SEPSIS	13 days	1
	STREPTOCOCCAL BACTERAEMIA	13 days	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	FALL	3 days	1
NERVOUS SYSTEM DISORDERS	BRAIN INJURY	3 days	1
	CEREBRAL HAEMORRHAGE	4 days	1
	METABOLIC ENCEPHALOPATHY	27 days 15 hrs	1
	PARAESTHESIA	1 day	1
PSYCHIATRIC DISORDERS	COMPLETED SUICIDE	9 days 14 hrs 45 min	1
RENAL AND URINARY DISORDERS	ACUTE KIDNEY INJURY	13 days	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ACUTE RESPIRATORY DISTRESS	27 days	1

[21] Leray E, Vukusic S, Debouverie M et al. Excess Mortality in Patients with Multiple Sclerosis Starts at 20 Years from Clinical Onset: Data from a Large-Scale French Observational Study. PLoS One. 2015 Jul 6;10(7):e0132033. doi: 10.1371/journal.pone.0132033. eCollection 2015

[22] Langer-Gould A. Mortality rates in large US and Swedish rituximab-treated multiple sclerosis cohorts ECTRIMS 2018; 231830; 88. https://onlinelibrary.ectrims- congress.eu/ectrims/2018/ectrims-2018/231830/annette.langer-gould.mortality.rates.in.large.us.and.swedish.rituximab- treated.html?f=media=1*listing=3*browseby=8 (accessed 26 July 2019)

	RESPIRATORY FAILURE	4 days	1
Total			24

The analysis of these cases with fatal outcome and TTO ≤30 days showed that in several patients, causes for death were infections or sepsis due to immunosuppressive conditions in the immediate period after alemtuzumab treatment, which is a known risk for alemtuzumab. The young ages of patients with fatal adverse events as well as the short latency after alemtuzumab infusion are matters of concern.

Holmøy T et al[23] assessed 17 case reports from the EEA with fatal outcome (cut-off 11/2018) based on data from EudraVigilance. Four reviewers with clinical and research expertise in MS, neuroimmunology, infectious disease and clinical pharmacology reviewed information for 17 fatalities. In 10 of the cases, the fatal outcome was assessed as probably (n=9) or possibly (n=1) related to Lemtrada. It is worthwhile to note that 6/10 patients (60%) died within the first months after Lemtrada infusion.

The MAH was asked to evaluate whether the number of fatalities stratified by age and disease severity within different time periods might exceed the expected rate. This question could not be sufficiently answered. Considering the need to further understand incidence of mortality associated with Lemtrada treatment in the EU, better data sources than just spontaneously reported data are desirable. Therefore, a post-authorisation safety study needs to be set-up for this purpose (see section 5.1.1 of this report).

2.3.6. Opportunistic infections

Data analysed

Epstein-Barr virus (EBV) infections were uncovered when searching for hepatitis. A search in the MAH's global pharmacovigilance database with cut-off date of 31 March 2019 identified 4 cases of EBV hepatitis. One patient passed away due to multiorgan failure, including disseminated intravascular coagulation (DIC). Another case was a patient who developed EBV hepatitis and was treated in the intensive care unit with transplantation planned as high urgent rescue trial (but was not transplanted). A third case was a 27-year-old female patient who underwent liver transplantation. The last case was a woman who developed AIH noted as elevation of transaminases, jaundice, and pruritus. Immunological testing was positive for IgG, EBV antibody but also hepatitis B and E antibodies. EBV infections are not currently mentioned in the product information but a causal relationship between alemtuzumab treatment and EBV reactivation is plausible.

Risk minimization

Information regarding EBV reactivation needs to be included in the product information. A cumulative review of cases of EBV hepatitis should be presented in the next PSUR.

2.4. Conclusion on Safety

As number of serious, life-threatening and disabling risks associated with Lemtrada have been assessed. Myocardial ischaemia, myocardial infarction and cerebrovascular events including arterial dissection and haemorrhagic stroke, pulmonary haemorrhage and transient thrombocytopenia have been identified as risks in close temporal association with the infusion of alemtuzumab. These events may at least partly be related to cytokine release.

[23] Holmoy et al. Adverse events with fatal outcome associated with alemtuzumab treatment in multiple sclerosis. BMC Res Notes. 2019 Aug 12;12(1):497. doi: 10.1186/s13104-019-4507-6.

Following the review, it has been confirmed that Lemtrada causes secondary autoimmune disease including auto-immune hepatitis, thyroiditis, ITP, acquired haemophilia A, nephropathies, cytopenias and serious immunological reactions such as HLH. Cases of poly-autoimmunity associated with Lemtrada have also been identified.

During the procedure, also other adverse reactions were identified which are also considered related to Lemtrada such as EBV re-activation.

One general characteristic of alemtuzumab which impacts on its safety profile and on risk management is the very long treatment effect, and therefore the infrequent administration regimen. Thus, due to the long-term effect of alemtuzumab, treatment discontinuation has limited value from a risk management perspective.

No surrogate or biomarker for patients at risk for serious cytokine release or autoimmunity was identified. Therefore many of the newly-identified risks associated to Lemtrada are unpredictable and largely unavoidable. In such circumstances it is necessary to restrict use of the alemtuzumab to patients who can benefit the most from treatment and who may be ready to accept the serious risks associated with treatment. This includes not just a restricted therapeutic indication but also contraindications in subpopulations anticipated, due to risk factors, to be at higher risk of developing the serious adverse reactions.

3. Expert consultation

During the review, PRAC sought the advice of the Scientific Advisory Group Neurology and their feedback is described below.

Question 1

Based on available evidence, and taking your clinical experience into account, can a subgroup of patients with highly active multiple sclerosis be defined who could benefit from alemtuzumab treatment and for whom there are few other treatment options or an unmet medical need? What is you view on extrapolation of efficacy data obtained in earlier lines of treatment, to a later line treatment?

The SAG experts discussed the potential indication wording[24] that would be acceptable and will reflect the demonstrated benefits, but take into account the real-life use and the known safety issues with the product. They advocated caution, mentioning that by defining recommendations for the use of alemtuzumab after "two other DMTs for highly active MS", the regulatory bodies may over-promote the use of other disease-modifying treatments in MS, with well-known long-term risks. Recommending the use of other DMTs on the basis of incomplete data confirming that this would indeed lead to an improved safety, was not considered as an acceptable way forward by the SAG experts. They mentioned that indicating alemtuzumab in a "last line" position without sufficient data to support this recommendation may be dangerous, as in that case it may be used in a more vulnerable population, where the safety profile of the drug could result in an even worse outcome: patients may still experience all the risks, while not having all the benefits of the treatment.

The SAG experts agreed unanimously that the proposed indication wording is problematic and will not be acceptable. An alternative solution would be to not mention "two other DMTs for highly active MS" in the indication and to instead focus on factors for "poor prognosis", while strengthening at the same time the risk mitigation measures. Efforts are needed for defining risk minimization measures, and

[24] In the context of the Scientific Advisory Group discussion, the proposed wording for the therapeutic indication was: *adult patients with highly active relapsing remitting multiple sclerosis despite a full and adequate course of treatment with at least two other disease modifying treatments for highly active MS, or in adult patients with highly active relapsing remitting multiple sclerosis where all other disease modifying treatments are contraindicated or otherwise unsuitable.*

especially in establishing specialized centres, where the drug should be applied, as this has shown to reduce the risks.

Using the currently approved indication for Tysabri as an example (https://www.ema.europa.eu/en/documents/product-information/tysabri-epar-product-information_en.pdf), the experts stated that the failure of only "one DMT" in patients with "highly active MS" should be sufficient to allow for alemtuzumab to be used. The experts considered it necessary to reinforce the fact that patients and specialists will have to discuss and assess all the available options, before using alemtuzumab. The indication should be reflecting the real-life use and permit that the drug is used even as a "first-line" treatment in patients that will be eligible. Losing time before patients have access to this therapy will result in delaying the best treatment window for a lot of them and reduce their chance in getting an optimal disease-modifying effect.

The position expressed by the patient representatives was that with the proposed indication wording, for MS patients of young age and low EDSS it would be impossible to get alemtuzumab before they have failed all other DMTs, while in the meantime patients will progress irrevocably in their disease. Hence, the representative supported that the patients should have the ability to receive the treatment earlier, and not delay due to a prescribed need to fail all other DMTs, which "last-line" indication would imply.

In conclusion, SAG experts agreed that the indication wording should clearly state that alemtuzumab should be used in "Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or in Patients with rapidly evolving severe relapsing remitting multiple sclerosis" (as per the accepted definition).

In addition, instead of trying to define a sub-group of MS patients in whom the drug should be used, a better approach will be to try to impose the gathering of data on risk factors, in order to define the patient population in which the treatment should be contraindicated.

Even though extrapolation of efficacy of alemtuzumab from MS patients in early stages of their disease to the ones in a more advanced stage is difficult, based on the available data, the position of the SAG experts was that it should still be possible.

Question 2

Based on available evidence, could the experts identify any factors that may help predict at-risk patients for both acute serious infusion related events, as well as autoimmune events?

The SAG experts considered that, based on the available data, there is no way to define appropriate predictive factors for the majority of the serious adverse effects.

The issue of the observed cases of HLH (hemophagocytic lymphohistiocytosis) was highlighted by the SAG experts and it was recommended that it be further explored through additional studies. It was also highlighted that specific studies should be designed by the MAH in order to better understand the effect of the cytokine release related side effects on the efficacy of prevention measures (such as corticosteroid therapy administered before the treatment initiation).

Question 3

Please discuss the effectiveness of the proposed risk minimisation measures in clinical practice.

The SAG experts could provide no clear answer on RMM effectiveness, because there are no data. They highlighted that it should be recommended that more information is gathered on the efficacy of corticosteroid use before treatment. There is a strong recommendation that the patients should be treated, monitored and followed-up in highly specialized centres.

Regarding a proposal to keep patients hospitalised for up to 5 days after the end of the infusion, it was agreed that there are no data suggesting that this will be beneficial, at the same time it is considered impractical. The patient representative reinforced that it is not feasible to expect patients to stay in hospital 5 days after infusion.

Again, the SAG stressed the necessity for the MAH to promote studies assessing the efficacy of the risk minimisation measures.

4. Benefit-risk balance

The efficacy of alemtuzumab in RRMS patients across multiple parameters of the disease is well established and maintained over long term follow up. This level of efficacy is present across a wide range of patient populations, as evidenced by the consistency of findings across various subgroups of participants in alemtuzumab clinical studies.

As part of the current review, a number of serious, life-threatening and disabling risks associated with Lemtrada have been assessed. Acute coronary syndrome and cerebrovascular events including arterial dissection and haemorrhagic stroke, pulmonary haemorrhage and transient thrombocytopenia have been identified as risks in close temporal association with the infusion of alemtuzumab. These risks are considered to be related to cytokine release syndrome, which has been described in the literature for alemtuzumab[25,26].

Following the review, it has been reconfirmed that Lemtrada causes secondary autoimmune disease including auto-immune hepatitis, thyroiditis, ITP, acquired haemophilia A, nephropathies, cytopenias and serious immunological reactions such as HLH. Cases of poly-autoimmunity associated with Lemtrada have also been identified.

During the procedure, also other new adverse reactions were identified which are also considered related to Lemtrada such as EBV re-activation.

One general characteristic of alemtuzumab which impacts on its safety profile and on risk management is the very long treatment effect, and thereby the infrequent administration regimen. Thus, due to the long-term effect of alemtuzumab, treatment discontinuation has limited value from a risk management perspective.

No surrogate or biomarker for patients at risk for serious cytokine release or autoimmunity was identified. Therefore many of the newly-identified risks associated to Lemtrada are unpredictable and largely unavoidable. In such circumstances it is necessary to restrict use of the alemtuzumab to patients who can benefit the most from treatment and who may be ready to accept the serious risks associated with treatment. This includes not just a restricted therapeutic indication but also contraindications in subpopulations anticipated, due to risk factors, to be at higher risk of developing the serious adverse reactions.

[25] Wing MG et al. Mechanism of first-dose cytokine-release syndrome by CAMPATH 1-H: involvement of CD16 (FcgammaRIII) and CD11a/CD18 (LFA-1) on NK cells. J Clin Invest 1996;98(12):2819-2826

[26] Thomas K, Eisele J, Rodriguez-Leal FA, Hainke U, Ziemssen T. Acute effects of alemtuzumab infusion in patients with active relapsing-remitting MS. Neurol Neuroimmunol Neuroinflamm. 2016 Apr 29;3(3):e228

In this context, and taking also into account the advice of the SAG, PRAC concluded that Lemtrada should be 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 MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

With this conclusion, PRAC acknowledges that early initiation of high-efficacy DMTs in patients with highly active (aggressive) or rapidly evolving RRMS is increasingly viewed as a strategy to prevent or postpone irreversible damage that occurs early in the disease course[27]. Recent studies of RRMS with long-term follow-up have shown that disease-modifying therapies (DMTs) reduce the proportion of patients who progress to SPMS compared to the proportion of untreated patients who progress.

Furthermore, when selecting the most appropriate and effective treatment for the patient, the safety profile and the possibility to manage risks effectively should also be taken into consideration. Vulnerable patient groups such as patients with severe active infections until complete resolution, uncontrolled hypertension, a history of arterial dissection of the cervicocephalic arteries, of stroke, angina pectoris or myocardial infarction and patients with known coagulopathy, on anti-platelet or anti-coagulant therapy, should be contraindicated. Patients with other concomitant autoimmune diseases (besides MS) should also be contraindicated to minimise the risk of development of additional autoimmune disorders.

In order to ensure adequate monitoring of patients before, during and after the infusion of alemtuzumab, rapid diagnosis and prompt and adequate treatment of the above-mentioned risks, the infusion of alemtuzumab should take place in a hospital with availability of experts and adequate equipment to manage the risks. The MAH proposed to include also specialised infusion centres with ready access to intensive care. Specialists from other medical disciplines (e.g. cardiologists) and equipment for timely diagnosis and management of adverse reactions however requires, in the view of PRAC, a hospital setting. The PRAC considered a recommendation for a longer follow-up period in hospital (for up to 5 days after the last infusion) to allow for prompt identification and management of serious adverse reactions that may occur. However it was ultimately considered that this long hospitalisation may not be feasible and that, as highlighted by the SAG, there is limited data to indicate it will have a substantial impact in the management of post-infusion adverse reactions.

New infusion instructions are also proposed to allow early identification and management of serious adverse reactions temporally associated with infusion. In addition to close monitoring of cardiovascular function before, during and after the infusion, this also includes new recommendations for platelet count measurement during the infusion cycle and for post-infusion monthly liver transaminase testing.

Currently, safety follow-up of patients is recommended from initiation of the first treatment course and until 48 months after the last treatment course. However, in individual cases autoimmune conditions may occur or be diagnosed later so healthcare professionals should be aware of this possibility.

Cases of pulmonary embolism, vasculitis, CNS autoimmune disease and GBS have been reported. The current evidence is insufficient to conclude on a causal relationship with Lemtrada. There are uncertainties about a potential causal relationship with a number of other autoimmune adverse events

[27] Fernandez O et al, 2017 Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? Mult Scler Relat Disord. 2017 Oct;17:75-83.

reported in temporal association with Lemtrada, and these will have to continue to be closely monitored in the future.

In future PSURs, the MAH is expected to submit cumulative reviews and discuss the following safety concerns: vasculitis, CNS inflammation, GBS, diabetes type 1, myasthenic syndrome, myositis, sarcoidosis, GBS, pneumonitis and EBV hepatitis.

A matter of concern is the post-marketing reporting rate of fatalities, including those with short latency after alemtuzumab infusion. The relative young age of patients who died within a short period (30 days) from Lemtrada treatment is also noted. A post authorisation safety study is needed to address these concerns.

A study is also needed to assess the effectiveness of the risk minimisation measures adopted during this review. Considering the serious and unpredictable nature of the newly-identified adverse reactions, it is important to understand whether the newly implemented measures are adhered to in clinical practice.

The MAH for Lemtrada will also disseminate a DHPC to inform healthcare professionals of the outcome of this review, and the educational material for both healthcare professionals and patients will be updated.

In view of the above, PRAC concluded that the benefit-risk balance of Lemtrada remains favourable subject to changes to the product information, the educational materials and additional pharmacovigilance activities described above. As a consequence, PRAC recommended the variation to the terms of the marketing authorisation for Lemtrada.

5. Risk management

5.1. Pharmacovigilance activities

5.1.1. Non- interventional studies

In order to further address concerns about mortality, mortality rates will be analysed using data from existing EU Registries. This analysis will likely include the external comparison cohort study (ECCS) that is complementary to the ongoing Lemtrada PASS (OBS13434) study. The ECCS includes at present data from registries from two EU Member States and participation of other countries continues to be investigated. In an effort to increase the currently relatively low sample size, it may be possible to utilize data from the alemtuzumab PASS (OBS13434) which intends to include up to 3000 patients treated with Lemtrada.

A study is also needed to assess the effectiveness of the risk minimisation measures adopted during this review. Considering the serious and unpredictable nature of the newly-identified adverse reactions, it is important to understand whether these new measures will be adhered to in clinical practice. This drug utilisation study may be performed using data from EU MS registries.

PRAC recommended the following conditions to the marketing authorisation of Lemtrada:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to investigate the incidence of mortality in patients treated with Lemtrada compared to a relevant patient population, the MAH shall submit the results of a post-authorisation safety study comparing Lemtrada to an adequate control.	Q3 2024

Non-interventional post-authorisation safety study (PASS): In order to assess compliance with the therapeutic indication and effectiveness of measures to minimise the risk of cardiovascular and cerebrovascular adverse events in close temporal association with Lemtrada infusion and immune-mediated adverse reactions, the MAH shall submit the results of a drug utilisation study.	Q3 2024

Submission of the study protocols to PRAC in accordance with Article 107n(1) of Directive 2001/83/EC should occur by July 2020.

In addition, the MAH shall submit an updated version of the Risk Management Plan incorporating all amendments and additional activities defined in this procedure, for assessment within 1 month from the Commission Decision.

5.2. Risk minimisation measures

5.2.1. Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information are necessary in order to minimise the risks associated with the use of Lemtrada. These changes include amendments to sections 4.1, 4.2, 4.3, 4.4, 4.8 and 5.1 of the SmPC.

The indication was restricted to treatment of 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 MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

In addition, the PRAC considered that Lemtrada use should be contraindicated in patients with:

- Severe active infection until complete resolution.
- Uncontrolled hypertension.
- History of arterial dissection of the cervicocephalic arteries.
- History of stroke.
- History of angina pectoris or myocardial infarction.
- Known coagulopathy, on anti-platelet or anti-coagulant therapy.
- Other concomitant autoimmune diseases (besides MS)

Further warnings and precautions of use relating to the risk(s) associated with the use of Lemtrada were also included and other important information harmonised.

The Package Leaflet was amended accordingly.

5.2.2. Direct Healthcare Professional Communication/Communication plan

The PRAC agreed on the wording of a Direct Healthcare Professional Communication including information on:

- The revised therapeutic indication of Lemtrada
- The additional contraindications
- The need for Lemtrada to only be administered in hospital setting with ready access to intensive case
- The need for patients to be monitored for autoimmune disorders for at least 48 months after the last infusion and be advised that these disorders may also occur later than 48 months after the last infusion
- Revised infusion instructions intended to reduce serious reactions temporally associated with Lemtrada infusion.

5.2.3. Educational materials

The educational materials for Lemtrada will be revised and updated in accordance with the outcome of this procedure. Key messages for the Healthcare professionals' guide, prescriber checklist, patient guide and patient alert card have been updated in annex II of the product information.

6. Conditions to the marketing authorisations

The PRAC recommended the following conditions to the marketing authorisation of Lemtrada:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to investigate the incidence of mortality in patients treated with Lemtrada compared to a relevant patient population, the MAH shall submit the results of a post-authorisation safety study comparing Lemtrada to an adequate control.	Q3 2024
Non-interventional post-authorisation safety study (PASS): In order to assess compliance with the therapeutic indication and effectiveness of measures to minimise the risk of cardiovascular and cerebrovascular adverse events in close temporal association with Lemtrada infusion and immune-mediated adverse reactions, the MAH shall submit the results of a drug utilisation study.	Q3 2024

In addition, in accordance with Article 23 of Regulation (EC) No 726/2004, Lemtrada will be included in the list of products for additional monitoring. The relevant information as well as the pictogram (black triangle) will be added in the product information.

7. Grounds for Recommendation

Whereas,

- PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Lemtrada.

- PRAC reviewed data currently available from post-marketing setting and from clinical trials on fatal cases, cardiovascular adverse events in close temporal association with Lemtrada infusions and immune-mediated diseases, including data provided in writing and at an oral explanation. PRAC also considered the views expressed by the neurology scientific advisory group.
- PRAC concluded that myocardial ischaemia, myocardial infarction, haemorrhagic stroke, dissection of the cervicocephalic arteries, pulmonary alveolar haemorrhage and thrombocytopenia may occur in close temporal association with the infusion of Lemtrada. PRAC also concluded that alemtuzumab is associated with immune-mediated diseases such as autoimmune hepatitis, haemophilia A and haemophagocytic lymphohistiocytosis (HLH), which can happen with a delay of months to years after the latest treatment. PRAC noted that these risks, which are serious and which can in some cases have a fatal outcome, are largely unpredictable.
- As a consequence, PRAC recommended that treatment with Lemtrada should be restricted to patients with highly active relapsing remitting multiple sclerosis 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, 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 MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.
- Lemtrada should also be contraindicated in patients with:
    - severe active infections until complete resolution,
    - uncontrolled hypertension,
    - history of arterial dissection of the cervicocephalic arteries,
    - history of stroke,
    - history of angina pectoris or myocardial infarction,
    - coagulopathy, on antiplatelet or anti-coagulant therapy
    - concomitant autoimmune diseases other than multiple sclerosis.
- Furthermore, PRAC recommended that Lemtrada should only be administered in a hospital setting with ready access to intensive care.
- PRAC also made additional recommendations for monitoring of patients before, during and after infusion to ensure timely diagnosis and management of adverse reactions.
- The PRAC considered that given the serious and unpredictable nature of the risks, and that effective risk minimisation is key to support a positive benefit-risk balance, a drug utilisation study is necessary to assess effectiveness of risk minimisation measures.
- PRAC also considered that the data currently available on mortality incidence is limited and therefore the MAH shall investigate the incidence of mortality in patients treated with Lemtrada compared with a relevant patient population.

In view of the above, PRAC concluded that the benefit-risk balance of Lemtrada remains favourable subject to changes to the product information, the educational materials and additional pharmacovigilance activities described above.

As a consequence, PRAC recommended the variation to the terms of the marketing authorisation for Lemtrada.

Appendix 1

Divergent position

Article 20 of Regulation (EC) No 726/2004

Procedure No: EMEA/H/A-20/1483/C/3718/0028

Lemtrada (INN/active substance: alemtuzumab)

Divergent statement

The undersigned PRAC members disagree with the recommendation of PRAC for the following Lemtrada indication:

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 MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.*

This recommendation is based on reported cases of pulmonary embolism, vasculitis, CNS autoimmune disease, GBS, myocardial ischemia, myocardial infarction, cervicocephalic arterial dissection, cerebral haemorrhage, as well as a number of other autoimmune adverse events reported in temporal association with Lemtrada. A matter of concern is the higher than expected post-marketing reporting rate of fatalities compared to clinical trials including those with short latency after alemtuzumab infusion, and the relative young age of patients who died within a short time (30 days) after Lemtrada treatment without any known risk factor.

Due to several remaining uncertainties on the risks associated with Lemtrada use, the undersigned PRAC members consider that a more restrictive indication is needed, in line with the provisional measures introduced following the start of Procedure under Article 20 of Regulation (EC) No 726/2004, initiated on 10 April 2019. The new risks assessed during the referral are considered unpredictable in the majority of patients treated with Lemtrada. In the opinion of the undersigned PRAC members it is of special concern that no risk minimization measures (RMM) have been identified that can prevent, modify or reduce the occurrence of the severe risks associated with Lemtrada treatment. Although contraindications are introduced to prevent the prescription to the most vulnerable patients and recommendations to implement additional clinical and laboratory monitoring will be made as a conclusion of the referral , it is still not known whether the proposed risk minimization measures could significantly reduce or prevent the newly identified risks and protect patients. In the opinion of the undersigned PRAC members the only reasonable RMM would be to limit the number of patients exposed to Lemtrada. Therefore, Lemtrada indication should be restricted to: "adult patients with highly active relapsing remitting multiple sclerosis (RRMS), despite a full and adequate course of treatment with at least two other disease modifying treatments (DMTs), or in patients with highly active RRMS where any other DMT is contraindicated or otherwise unsuitable".

The undersigned PRAC members have considered as well that currently there are available more therapeutic alternatives for the treatment of highly active RRMS than those available when alemtuzumab was authorised, and their position takes also into account the fact that contrarily to other DMTs which could be interrupted if adverse reactions occur, Lemtrada has a particular administration schedule (once a year) that makes this measure not possible to apply.

Once more information is gathered through the studies imposed to the MAH as category 1 studies, and less uncertainties remain, Lemtrada indication could be reconsidered. Meanwhile, in view of the serious and life-threatening risks associated with alemtuzumab, indication should be kept as stated in the provisional measures taken by the European Commission in April 2019.

PRAC Members expressing a divergent opinion:

Eva A. Segovia	31 October 2019
Ghania Chamouni	31 October 2019
David Olsen	31 October 2019
Jean Michel Dogné	31 October 2019