RISK MANAGEMENT PLAN
For
Teriflunomide
Version 2.1

RMP Version to be Assessed as Part of this Application:

RMP Version Number	2.1
Data Lock Point for this RMP	31-Jul-2024
Date of Final Sign Off	07-Apr-2026
Rationale for Submitting an Updated RMP	RMP updated in line with the reference product Aubagio® (teriflunomide) RMP version 9.1, dated 28-Mar-2024 (MAH Sanofi), published by EMA on 12-Jun-2024 and the CHMP Type IB WS variation assessment report for Procedure No. EMA/VR/0000320266, Worksharing applicant (WSA): Viatris Limited for teriflunomide
Summary of Significant Changes in this RMP	The following significant changes were made in the current RMP: • Harmonising the RMPs of all teriflunomide marketing authorisations procedures for which the MAH has an approved RMP. • Updates in Part II modules SVII and SVIII to align the safety concerns with the reference product Aubagio® (teriflunomide) RMP version 9.1, dated 28-Mar-2024 (MAH Sanofi), published by EMA on 12-Jun-2024.

Other RMP Versions Under Evaluation:

RMP Version Number	2.0	
Submitted On	Not applicable	
Procedure Number	EMEA/H/C/005962	
	IS/H/0482/001/DC	

Details of the Current RMP:

Version Number	EMEA/H/C/005962	1.3
	IS/H/0482/001/DC	1.2
Approved with Procedure	EMEA/H/C/005962 IS/H/0482/001/DC	
Date of Approval (Opinion Date)	EMEA/H/C/005962	09-Nov-2022
	IS/H/0482/001/DC	23-Nov-2022

EEA QPPV name: Andrea Oliva, PhD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification System
CP	Centralized Procedure
DCP	Decentralized Procedure
DHO-DH	Dihydroorotate Dehydrogenase
DLP	Data Lock Point
EEA	European Economic Area
EMA/ EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EUROCAT	European Surveillance of Congenital Anomalies
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
ICSR	Individual Case Safety Report
MAH	Marketing Authorization Holder
MS	Multiple Sclerosis
PL	Package leaflet
PML	Progressive Multifocal Leukoencephalopathy
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
RMM	Risk Minimization Measures
SmPC	Summary of Product Characteristics
TFU	Targeted Follow-Up
WHO	World Health Organization
WOCP	Women Of Child-Bearing Potential

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Teriflunomide
Pharmacotherapeutic Group(s) (ATC Code)	Immunosuppressants, Selective immunosuppressants ATC code: L04AK02
Marketing Authorisation Holder (MAH)	EMEA/H/C/005962 – Mylan Pharmaceuticals Ltd IS/H/0482/001/DC – Viatris Ltd
Medicinal Products to Which this RMP Refers	02
Invented Name(s) in the European Economic Area (EEA)	EMEA/H/C/005962 – Teriflunomide Mylan 14 mg film-coated tablets IS/H/0482/001/DC – Tergio
Marketing Authorisation Procedure	EMEA/H/C/005962 IS/H/0482/001/DC
Brief Description of the Product	Chemical class: Teriflunomide belongs to the pharmacotherapeutic group of Immunosuppressants, Selective immunosuppressants. Summary of mode of action: Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), which functionally connects with the respiratory chain. As a consequence of the inhibition, teriflunomide generally reduces the proliferation of rapidly dividing cells that depend on *de novo* synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of T-lymphocytes. Important information about its composition: Not applicable
Hyperlink to the Product Information:	PI available in section 1.3.1 of the dossier

<table>
<tr><td>Indication(s) in the EEA</td><td>Current:

<table><tr><td>EMEA/H/C/005962</td><td>Teriflunomide is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS).</td></tr><tr><td>IS/H/0482/001/DC</td><td>Teriflunomide is indicated for the treatment of adult patients and paediatric patients aged 10 years and older (body weight > 40 kg) with relapsing remitting multiple sclerosis (MS).</td></tr></table>
Proposed:
Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:

<table><tr><td>EMEA/H/C/005962
and IS/H/0482/001/DC</td><td>Adults
In adults, the recommended dose of teriflunomide is 14 mg once daily.

Paediatric population (10 years and older)
In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:
- Paediatric patients with body weight > 40 kg: 14 mg once daily.
- Paediatric patients with body weight ≤ 40 kg: 7 mg once daily.

Paediatric patients who reach a stable body weight above 40 kg should be switched to 14 mg once daily.

Teriflunomide is only available as 14 mg film-coated tablets. Thus, it is not possible to administer Teriflunomide to patients that require less than a full 14 mg dose. If an alternate dose is required, other teriflunomide products offering such an option should be used.</td></tr></table></td></tr>
</table>

	Proposed: Not applicable
Pharmaceutical Form(s) and Strengths	Current: Teriflunomide 14 mg film-coated tablets Proposed: Not applicable
Is the Product Subject to Additional Monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

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

Not applicable.

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

Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Not applicable.

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

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

Not applicable.

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

Not applicable.

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

Not applicable.

Part II: Module SV - Post-authorisation Experience

Not applicable.

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

Not applicable.

Part II: Module SVII - Identified and Potential Risks

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

Viatris has an approved RMPs for teriflunomide generic medicine version 1.3 for centralized procedure (CP) EMEA/H/C/005962 and version 1.2 for decentralized procedure (DCP) IS/H/0482, with the following safety concerns:

Table 2: SVII- Summary of safety concerns

	CP EMEA/H/C/005962 RMP version 1.3 (approved on 09-Nov-2022) and DCP IS/H/0482 version 1.2 (approved on 23-Nov-2022)
Important Identified Risks	• Hepatic effects

	CP EMEA/H/C/005962 RMP version 1.3 (approved on 09-Nov-2022) and DCP IS/H/0482 version 1.2 (approved on 23-Nov-2022)
	• Hypertension • Hematologic effects • Infections • Acute Pancreatitis
Important Potential Risks	• Teratogenicity • Serious opportunistic infections, including PML
Missing Information	• Long-term safety in paediatric patients

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

Not applicable.

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

Not applicable.

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

The risk "Long-term safety in paediatric patients" previously classified as missing information is removed from the list of safety concerns in line with the list of safety concerns of reference product Aubagio® (teriflunomide) RMP version 9.1 dated 28-Mar-2024 published on EMA website on 12-Jun-2024.

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

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

Not applicable as this RMP for teriflunomide follows the same safety concerns as the safety concerns of the reference substance Aubagio® (teriflunomide) RMP version 9.1 dated 28-Mar-2024 published on EMA website on 12-Jun-2024.

SVII.3.2. Presentation of the Missing Information

Not applicable as this RMP for teriflunomide follows the same safety concerns as the safety concerns of the reference substance Aubagio® (teriflunomide) RMP version 9.1 dated 28-Mar-2024 published on EMA website on 12-Jun-2024.

Part II: Module SVIII - Summary of the Safety Concerns

Table 3: SVIII- Summary of safety concerns

Important Identified Risks	• Hepatic effects • Hypertension • Hematologic effects • Infections • Acute Pancreatitis
Important Potential Risks	• Teratogenicity

	• Serious opportunistic infections, including PML
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

The Pharmacovigilance System Master File contains details of the system and processes that the MAH has in place to identify and characterize the risks recognised in the safety specification.

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the risks:

- Hepatic effects (Drug induced liver injury form)
- Acute Pancreatitis (Pancreatic disorder form)
- Teratogenicity (Pregnancy reporting form)
- Serious opportunistic infections, including PML (PML form)

The forms are provided in Annex 4 of the RMP.

The MAH will ensure continuous collection and follow-up on cases of pregnancy with exposure to teriflunomide (either during pregnancy or in the relevant time interval before conception, given the product's very long half-life), including reports of (pregnancy) exposure without outcome data or with a normal outcome. Use of targeted questionnaires for follow-up.

Regular submission of cumulative structured analyses of all collected pregnancy cases within periodic safety update reports (PSURs), taking the following into account in order to improve the overall product comparability:

- Overall patient exposure data for the respective product expressed as patient-years based on World Health Organization (WHO) defined daily dose of 14 mg.
- Separate analysis of prospectively and retrospectively reported pregnancy cases; provision of details about time point of exposure to teriflunomide (before/during pregnancy, taking into account the long half-life and information on accelerated elimination procedure)
- Use of European Surveillance of Congenital Anomalies (EUROCAT) definitions of major congenital malformations, spontaneous abortions, stillbirths etc.

III.2 Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product (Aubagio®, Sanofi-Aventis Groupe).

V.1 Routine Risk Minimisation Measures

Table 4: Part V.1- Description of routine risk minimisation measures by safety concern

Safety Concern	Routine Risk Minimisation Activities
Important Identified Risks	
Hepatic effects	Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.2, 4.3, and 4.4 PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine
Hypertension	Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine
Hematologic Effects	Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.3 and 4.4 PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine
Infections	Routine risk communication: SmPC sections 4.4 and 4.8

Safety Concern	Routine Risk Minimisation Activities
	PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.3 and 4.4 PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine
Acute Pancreatitis	Routine risk communication: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine
Important Potential Risks	
Teratogenicity	Routine risk communication: SmPC section 4.3 PL section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.6 PL section 2 Other risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine
Serious opportunistic infections, including PML	Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.3 and 4.4 PL sections 2 and 4 Other risk minimisation measures beyond the Product Information: Medicine's legal status: Prescription only medicine

V.2 Additional Risk Minimisation Measures

This medicine has additional risk minimisation measures/aRMM tools for the following risks:

- Hepatic effects
- Hypertension
- Hematologic effects
- Infections
- Teratogenicity
- Serious opportunistic infections, including PML

The additional risk minimisation measures/aRMM tools consist of: Healthcare professional (HCP) guide and patient card.

Objectives of Additional Risk Minimisation Activities/aRMM tools:

To address the risks of hepatic effects, hypertension, hematologic effects, infections, teratogenicity, and serious opportunistic infections, including PML, the MAH proposes HCP guide to educate HCPs about specific risks, their early symptoms and the best course of action to be taken when these appear, beyond the recommendation contained in the Product Information.

To address the risks of hepatic effects, hypertension, hematologic effects, infections, teratogenicity, and serious opportunistic infections, including PML, the MAH proposes patient card to ensure that special information regarding the patient's current therapy and its important risks (e.g. potential life-threatening interactions with other therapies) is held by the patient at all times and reaches the relevant HCP as appropriate. It contains the minimum necessary information to convey the key minimisation message(s) and the required mitigating action, in any circumstances, including emergency.

Rationale for the Additional Risk Minimisation Activity/aRMM tool(s):

The MAH considers it is necessary to educate HCPs and patients/caregivers about specific risks, their early symptoms and the best course of action to be taken when these appear beyond the recommendation contained in the Product Information.

Target Audience and Planned Distribution Path:

HCPs and patients

Plans for Evaluating the Effectiveness of the Interventions and Criteria for Success:

Effectiveness of additional RMMs/aRMM tools has been evaluated on annual basis since MA approval. After MA approval, in accordance with the Regulation (EC) No. 726/2004, Directive 2001/83 EC and the Guideline on good pharmacovigilance practices (GVP) – Modules V and XVI, the MAH has evaluated the effectiveness of aRMM in annual effectiveness evaluation reports. This evaluation considered the objective(s), the selected process and the outcome indicators of the additional risk minimization measures for teriflunomide. The evaluation included an examination of the delivery of the risk minimisation measures in routine clinical practice. Outcome indicators (i.e. adverse reaction frequency and/or severity; other safety-related outcomes) were the key endpoints when assessing the attainment of risk minimisation measures objectives.

Results of Effectiveness Evaluation

After evaluation of all information available to Viatris within the period from 09-Nov-2023 to 08-Nov-2024,

including individual case safety reports (ICSRs) from Viatris' global safety database, global literature, PSUR outcome, outcome of signal detection activities, health authority websites, results of interventional and non-interventional studies and EudraVigilance data, no new significant data have become available that may change the safety or benefit-risk profile of teriflunomide. The risk minimization measures in place for this product are considered adequate and no further actions are needed for the time being.

V.3 Summary of Risk minimisation measures

Table 5: Part V.3- Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Hepatic effects	Routine risk minimization measures: SmPC: Sections 4.2, 4.3, 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimization measures/aRMM tools: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for drug-induced liver injury. Additional pharmacovigilance activities: None
Hypertension	Routine risk minimization measures: SmPC: Sections 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimization measures/aRMM tools: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities only
Hematologic effects	Routine risk minimization measures: SmPC: Sections 4.3, 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimization measures/aRMM tools: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities only
Infections	Routine risk minimization measures: SmPC: Sections 4.3, 4.4, and 4.8 PL: Sections 2 and 4 Additional risk minimization measures/aRMM tools: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities only

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Acute Pancreatitis	Routine risk minimization measures: SmPC: Sections 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimization measures/aRMM tools: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for pancreatic disorder. Additional pharmacovigilance activities: None
Important Potential Risks		
Teratogenicity	Routine risk minimization measures: SmPC: Sections 4.3 and 4.6 PL: Section 2 Additional risk minimization measures/aRMM tools: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Continuous collection and follow-up on all cases of pregnancy with exposure to teriflunomide using specific follow-up forms; Regular submission of cumulative structured analyses of all collected pregnancy cases within PSURs. Additional pharmacovigilance activities: None
Serious opportunistic infections, including PML	Routine risk minimization measures: SmPC: Sections 4.3, 4.4, and 4.8 PL: Sections 2 and 4 Additional risk minimization measures/aRMM tools: Educational Materials (HCP education/discussion guide and patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for PML. Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Teriflunomide Mylan and Tergio (teriflunomide)

This is a summary of the risk management plan (RMP) for Teriflunomide Mylan and Tergio. The RMP details important risks of teriflunomide, how these risks can be minimised, and how more information will be obtained about teriflunomide's risks and uncertainties (missing information).

Teriflunomide Mylan and Tergio's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Teriflunomide Mylan should be read in the context of all the information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Teriflunomide Mylan's and Tergio's RMP.

I. The Medicine and What it is Used For

Teriflunomide Mylan is authorised for the treatment of adult and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) and Tergio is authorised for the treatment of adult and paediatric patients aged 10 years and older (body weight > 40 kg) with relapsing remitting multiple sclerosis. It contains teriflunomide as the active substance and it is given by oral route.

Further information about the evaluation of Teriflunomide Mylan's benefits can be found in Teriflunomide Mylan's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Teriflunomide Mylan and Tergio, together with measures to minimise such risks are outlined below.

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

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

In the case of Teriflunomide Mylan and Tergio, these routine measures are supplemented with additional risk minimisation measures tools, mentioned under relevant risks below.

II.A List of Important Risks and Missing Information

Important risks of Teriflunomide Mylan and Tergio are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Teriflunomide Mylan and Tergio. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine/use in special patient populations etc.).

Table 6: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	• Hepatic effects • Hypertension • Hematologic effects • Infections • Acute Pancreatitis
Important Potential Risks	• Teratogenicity • Serious opportunistic infections, including PML
Missing Information	None

II.B Summary of Important Risks

Table 7: Part VI.2- Hepatic effects

Risk Minimisation Measures	Routine risk minimisation measures SmPC: Sections 4.2, 4.3, 4.4, and 4.8 PL: Sections 2 and 4 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for Drug induced liver injury. Additional risk minimisation measures/aRMM tools HCP guide and patient card

Table 8: Part VI.2- Hypertension

Risk Minimisation Measures	Routine risk minimisation measures SmPC: Sections 4.4 and 4.8 PL: Sections 2 and 4 Additional risk minimisation measures/aRMM tools HCP guide and patient card

Table 9: Part VI.2- Hematologic effects

Risk Minimisation Measures	Routine risk minimisation measures SmPC: Sections 4.3, 4.4, and 4.8 PL: Sections 2 and 4 Additional risk minimisation measures/aRMM tools HCP guide and patient card

Table 10: Part VI.2- Infections

Risk Minimisation Measures	Routine risk minimisation measures SmPC: Sections 4.3, 4.4, and 4.8 PL: Sections 2 and 4 Additional risk minimisation measures/aRMM tools HCP guide and patient card

Table 11: Part VI.2- Acute Pancreatitis

Risk Minimisation Measures	Routine risk minimisation measures SmPC: Sections 4.4 and 4.8 PL: Sections 2 and 4 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for Pancreatic disorder. Additional risk minimisation measures/aRMM tools Not applicable as there are no additional risk minimisation measures for this safety concern

Table 12: Part VI.3- Teratogenicity

Risk Minimisation Measures	Routine risk minimisation measures SmPC: Sections 4.3 and 4.6 PL: Section 2 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Continuous collection and follow-up on cases of pregnancy with exposure to teriflunomide using specific follow-up forms; Regular submission of cumulative structured analyses of all collected pregnancy cases within PSURs. Additional risk minimisation measures/aRMM tools HCP guide and patient card

Table 13: Part VI.3- Serious opportunistic infections, including PML

Risk Minimisation Measures	Routine risk minimisation measures SmPC: Sections 4.3, 4.4, and 4.8

	PL: Sections 2 and 4 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for PML. Additional risk minimisation measures/aRMM tools HCP guide and patient card

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Teriflunomide Mylan and Tergio.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Teriflunomide Mylan and Tergio.

PART VII: ANNEXES

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Specific adverse reaction follow-up questionnaires for the risks:

- Hepatic effects (Drug induced liver injury)
- Acute pancreatitis (Pancreatic disorder form)
- Teratogenicity (Pregnancy reporting form)
- Serious opportunistic infections, including PML (PML form)

Hepatic effects (Drug induced liver Injury form)

Viatris case no.:	Date of report	Study ID (if applicable)	Patient ID (if applicable) Country of Origin
Reporter name: Reported type: MD □ Nurse □ Pharmacist □ Other, please specify: □	Reporter telephone	Reporter email	Country of case

Previous relevant history and concurrent disorders			
	No	**Yes**	Specify details-ONSET Date DD/MM/YYYY
Is the patient pregnant	□	□	
Hepato-biliary	□	□	
Allergic disease	□	□	
Allergy to drug	□	□	
Auto-Immune	□	□	
Heart/vascular disease	□	□	
Respiratory disease	□	□	
Cancer	□	□	
Surgical/Dental operation	□	□	
Alcohol consumption	□	□	Number of drinks per day

Acupuncture	□	□	
Occupational/toxic agent exposure	□	□	
Travels to Africa			
Travels to Asia	□	□	
Intravenous drug abuse	□	□	
Other	□	□	

Documentation of the adverse event		
Main diagnosis:		**Start Date (DD/MM/YYYY)**
Are the following signs and symptoms associated?	Tick box if applicable □	
Asthenia	□	
Fever	□	
Pruritus	□	
Jaundice	□	
Joint pain	□	
Abdominal pain	□	
Vomiting	□	
Skin eruption	□	**Type:**
Purpura	□	
Hepatomegaly	□	
Splenomegaly	□	
Lymph nodes	□	
Ascites	□	
Asterixis	□	
Coma	□	
Malaise (with or without loss of consciousness)	□	
INR >2 or prothrombin T.<50%	□	
Dizziness	□	
Hypotension	□	
Arrhythmia	□	

Central Laboratory Data performed:	**NO □**	**Yes □**	**Date:**
Local Laboratory Data performed:	**NO □**	**Yes □**	**Date:**

Additional Test Data (to be performed at local level)					
	Not tested	Negative	Positive result	Date of test DD/MM/YYY	Titration
HBa Ag	□	□	□		
Anti-Hbs Ab	□	□	□		
Anti-Hbc Ab	□	□	□		
Anti-Hbc /IgM Ab	□	□	□		
Anti-HAV /IgM Ab	□	□	□		
Anti-HCV Ab	□	□	□		
PCR-C	□	□	□		
Anti-CMV IgM Ab	□	□	□		

Additional Test Data (to be performed at local level)					
	Not tested	Negative	Positive result	Date of test DD/MM/YYY	Titration
Anti-EBV Ab	□	□	□		
Anti-nuclear Ab	□	□	□		
Antinative DNA Ab	□	□	□		
Anti-smooth muscle Ab	□	□	□		
Anti-mitochondrial AB	□	□	□		

Other investigations		
Date DD/MM/YYYY	**Nature**	**Results:**

Liver Biopsy No □ Yes □ Date: DD/MM/YYYY **If yes is ticked a report needs to be attached**

Liver Imaging if Yes is ticked a report needs to be attached	**Date: DD/MM/YYYY**	**Brief Results**
Ultrasonography No □ Yes □		
CT Scan No □ Yes □		
MRI No □ Yes □		

Concomitant or previous drugs possibly suspected of inducing liver injury					
Name	Indication	Daily Dose	Route	Start Date	End Date

Laboratory Tests	**Date DD/MM/YYYY**	**Baseline Values**	**Result**	**Normal High/Low**

Laboratory Tests	Date DD/MM/YYYY	Baseline Values	Result	Normal High/Low

Acute pancreatitis (Pancreatic disorder form)

Viatris case no.:	Date of report	Study ID (if applicable)	Patient ID (if applicable)
Reporter name: Reported type: MD □ Nurse □ Pharmacist □ Other □, please specify:	Reporter telephone	Reporter email	Country of case

1. Patient Information:

Patient's Initials		
Patient's age		
Date of birth DOB (DD/MM/YY)		
Gender	□ M	□ F
Known allergies		

Report type

Study:	□ No	□ Yes	If yes, please specify:	Study number: Protocol number: Investigator name: Patient number:
Spontaneous:	□ No	□ Yes		

2. Drug being reported

Name: _____

3. SYPMTOMS

Were any of the following symptoms associated with the event:			
Symptoms	**Date of Onset**	**Description**	**Outcome**
Abdominal pain □ Yes			□ Recovered

Were any of the following symptoms associated with the event:			
Symptoms	**Date of Onset**	**Description**	**Outcome**
□ No			□ Recovering □ Continuing □ Not recovered □ Recovered with sequelae □ Fatal
Malaise □ Yes □ No			□ Recovered □ Recovering □ Continuing □ Not recovered □ Recovered with sequelae □ Fatal
Nausea □ Yes □ No			□ Recovered □ Recovering □ Continuing □ Not recovered □ Recovered with sequelae □ Fatal
Vomiting □ Yes □ No			□ Recovered □ Recovering □ Continuing □ Not recovered □ Recovered with sequelae □ Fatal
Jaundice □ Yes □ No			□ Recovered □ Recovering □ Continuing □ Not recovered □ Recovered with sequelae □ Fatal
Fever □ Yes □ No			□ Recovered □ Recovering □ Continuing □ Not recovered □ Recovered with sequelae

Were any of the following symptoms associated with the event:			
Symptoms	**Date of Onset**	**Description**	**Outcome**
			□ Fatal
Weight loss □ Yes □ No			□ Recovered □ Recovering □ Continuing □ Not recovered □ Recovered with sequelae □ Fatal
Abdominal bleeding □ Yes □ No			□ Recovered □ Recovering □ Continuing □ Not recovered □ Recovered with sequelae □ Fatal

4. Any known results of genetic tests indicating an increased risk for pancreatitis ?
□ Yes, please provide details below □ No

5. Any anatomic anomalies potentially associated with pancreatitis ?
□ Yes, please provide details below □ No

6. **Past medical history**

Please indicate if the patient had or has one or more of the following conditions

Condition	**Date diagnosed**	**Treatment (if available)**
Pancreatitis □ Yes □ No		
Cholelithiasis/choledocholithiasis □ Yes □ No		

Condition		Date diagnosed	Treatment (if available)
Hepatitis	□ Yes □ No		
Abdominal tumor	□ Yes □ No		
Abdominal surgery	□ Yes □ No		
Abdominal trauma	□ Yes □ No		
Condition		**Date diagnosed**	**Treatment (if available)**
Hypertriglyceridemia	□ Yes □ No		
Hyperparathyroidism	□ Yes □ No		
Hypercalcemia	□ Yes □ No		
Human immunodeficiency virus	□ Yes □ No		
Post-ERCP	□ Yes □ No		
Malignancy (specify):	□ Yes □ No		
Other suspected disorder specify:	□ Yes □ No		

7. **Social history**

Alcohol consumption □ Yes □ No (If yes, Drinks/day)_____
Tobacco user: □ Yes □ No ____pack years

8. Medication history

8.1 Please indicate if the patient has taken one or more of the following medications

Medication	Start Date	End Date	Dose	Frequency	Reason for discontinuation	Investigator causality
Leflunomide □ Yes □ No						□ Related □ Unrelated □ Unknown
Azathioprine □ Yes □ No						□ Related □ Unrelated □ Unknown

Medication	Start Date	End Date	Dose	Frequency	Reason for discontinuation	Investigator causality
Valproic acid □ Yes □ No						□ Related □ Unrelated □ Unknown
Estrogen □ Yes □ No						□ Related □ Unrelated □ Unknown
Corticosteroids □ Yes □ No Specify: _____						□ Related □ Unrelated □ Unknown
Statins □ Yes □ No Specify: _____						□ Related □ Unrelated □ Unknown

9. Investigations

9.1 Laboratory tests

Investigation	Date	Baseline value	Result	Normal High/low
Red blood cell count □ Yes □ No				
WBC count □ Yes □ No				
Blood urea nitrogen □ Yes □ No				
Blood glucose □ Yes □ No				
Amylase □ Yes □ No				
Lipase □ Yes □ No				
Gamma GT □ Yes □ No				
Tripsinogen activation peptide □ Yes □ No				
Alanine aminotransferase (ALT) □ Yes □ No				
Aspartate Aminotransferase □ Yes □ No				

Investigation	**Date**	**Baseline value**	**Result**	**Normal High/low**
(AST)				
Alkaline phosphatase □ Yes □ No				
Bilirubin □ Yes □ No				
Calcium □ Yes □ No				
Other Investigation	**Date**	**Baseline value**	**Result**	**Normal High/low**

9.2 Imaging studies

Investigation	**Date**	**Results**
Abdominal ultrasound □ Yes □ No		
Contrast enhanced Abdominal CT □ Yes □ No		
Magnetic resonance Imaging (MRI) □ Yes □ No		
Endoscopic retrograde Cholangiopacreatogram (ERCP) □ Yes □ No		
Magnetic resonance Cholangiopacreatogram (MRCP) □ Yes □ No		

10. Action taken with teriflunomide as result of the adverse events:

Drug withdrawn □ Dose reduced □ Dose not changed □

Was teriflunomide re-administration? □ Yes □ No

Did the patient experience any adverse event, upon re- administration of teriflunomide?

11. Management

11.1. Causal relationship

Is there a reasonable possibility that the pancreatic disorder is associated with the use of the drug being reported?

□ Yes □ No □ Unable to assess

11.2. Has any treatment been given to the patient to treat pancreatitis? □ Yes □ No

Medication	Dose	Frequency	RoA	Start date	End date

12. Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ERCP	Endoscopic retrograde Cholangiopacreatogram
MRCP	Magnetic resonance Cholangiopacreatogram
RoA	Route of administration

Teratogenicity (Pregnancy reporting form)

Targeted Follow-up Form (coversheet)

Please provide the below requested information in the dedicated sections of the support used to provide the data (i.e., safety collection form or Sanofi Portal). Information that has already been provided at previous times of reporting, and has not changed in the meantime, does not need to be provided again but any additional information in any sections will be very helpful.

Medical History/Risk Factors:

MS History:

- Date of diagnosis
- Number of relapses (please also detail number of relapses during pregnancy when applicable)
- Date of last relapse
- Most recent EDSS score / EDSS score prior to and during pregnancy if applicable
- Day to day activity prior to event with regards to mobility, sensory and motor disturbances, blurred vision, and self-grooming.

Description of the Reported Event(s)/Clinical Course:

Which documents are available:

- Hospital notes
- Death certificate
- Investigation results
- Other

Discharge summary should be attached if needed/applicable.

PREGNANCY / DRUG EXPOSURE VIA PARENT DATA COLLECTION FORM

Information that has already been provided at previous times of reporting, and has not changed in the meantime, does not need to be provided again but any additional information in any sections will be very helpful.

1. **Date report received:**

Company received date:	□ Initial □ Follow-up	**Date form completed by reporter**
Case number	**Product received/product code**	**Viatris/CRO contact**
Local ID **Global PV ID**		**Name:** **Telephone:**
Source	**Study information (if applicable)**	**Who received medication?**
Spontaneous/unsolicited (includes pregnancy registry) **Study/solicited (includes PSP/MRP)**	**Study ID/Registry ID: Center ID:** **Patient ID:** **Treatment ID:**	□ Mother Initials_____ (First , Middle, last) □ Father Initials_____ (First , Middle, last)

For Viatris use only

2. Reporter information

Name (first/last):	Street:
Occupation: □ Consumer □ Study investigator □ Lawyer □ Medical doctor □ Pharmacist	City/state/province:

□ Other HCP (Healthcare professional) □ Other		
Phone: Email address: Email address for patient (if patient is not the reporter):	Postal code:	Country:
Pediatrician contact information Name (first/last):	Phone:	Email address:
Does Mother agree to provide information? □ Yes □ No Does Father agree to provide information? □ Yes □ No		

3. Parent information at the time of pregnancy					
	Age/birth date For clinical study, year of birth to be collected only	**RH (Rhesus) Factor**	**Height (HT)/ Unit**	**Weight (WT)/ Unit**	**Past and Current Significant Medical conditions***
Mother				Pre-pregnancy weight:	Smoking history: _____Cigarettes per day** Alcohol: _____Drinks per day** Substance abuse** : (specify)_____ Hypertension: □ No □ Yes □ Unk Diabetes: □ No □ Yes □ Unk Epilepsy: □ No □ Yes □ Unk If yes specify type: _____ Psychiatric illness: □ No □ Yes □ Unk If yes specify type: _____
				Weight gain during pregnancy:	_____ Serology : □ No □ Yes □ Unk HIV seropositivity: □ No □ Yes □ Unk Hepatitis infection: □ No □ Yes □ Unk _____ Other history (including thyroid disorders, asthma, allergic disease, heart disease, sexual transmitted disorder, education level, learning difficulties, congenital malformations, environmental exposures):

Father					Smoking history: _____Cigarettes per day** Alcohol: _____Drinks per day Substance abuse : (specify)_____ Hypertension: □ No □Yes □ Unk Diabetes: □ No □Yes □ Unk Epilepsy: □ No □ Yes □ Unk If yes specify type: _____ Psychiatric illness: □ No □ Yes □ Unk If yes specify type: _____ _____ Serology : □ No □ Yes □ Unk HIV seropositivity: □ No □Yes □ Unk Hepatitis infection: □ No □Yes □ Unk _____ Other history* (including thyroid disorders, asthma, allergic disease, heart disease, sexual transmitted disorder, education level, learning difficulties, congenital malformations, environmental exposures):

*Include information on race, ethnicity, consanguinity, or occupation if you consider it would contribute significantly to the investigation and evaluation of certain adverse findings in the pregnancy or its outcome or on the health of the fetus/child; per local privacy laws.

** Mention if mother quit smoking or materially reduced her usage before or during pregnancy and when.

4. Specific to the pregnancy prevention programme, if applicable (e.g. valproate….)

- Was there a negative pregnancy test at treatment initiation? □ No □ Yes □ Unk □ NA *
- Was the patient guide received: □ No □ Yes □ Unk □ NA *
- Was the patient card received? □ No □ Yes □ Unk □ NA *
- Was an annual review completed by a specialist: □ No □ Yes □ Unk □ NA *
- Was the annual risk acknowledgement form signed? □ No □ Yes □ Unk □ NA *

*Not applicable

5. Immunization/Gynaecology

Material immune status	Gynaecological details
Rubella: □ No □ Yes □ Unk Toxoplasmosis: □ No □ Yes □ Unk CMV: □ No □ Yes □ Unk	Were contraceptive methods used: □ No □ Yes □ Unk If yes, specify contraceptive type: □ Oral □ Local □ IUCD Contraception name: _____

	Contraception dose: _____ Contraception start and stop dates:_____ Details of possible cause to contraception failure: _____ Non-compliance with primary method (e.g., hormonal/IUD) □ No □ Yes □ Unk Non-compliance with barrier method □ No □ Yes □ Unk Other (e.g., drug drug interaction, episode of GI disorder….) □ No □ Yes □ Unk Relevant gynecological history: Abnormal menstrual cycles □ No □ Yes □ Unk If yes, specify: Infertility □ No □ Yes □ Unk If yes, specify: History of gynecological surgery □ No □ Yes □ Unk If yes, specify: Sequelae of infections □ No □ Yes □ Unk If yes, specify:

6. Pregnancy information

Date of last menstrual period (LMP) LMP: —/—/— (DD-MMM-YY) Estimated date of delivery (EDD) EDD: —/—/— (DD-MMM-YY) _____ Medical assistance/hospitalization during pregnancy? □ No □ Yes Details:_____	Date of positive pregnancy test (If any) : —/—/— (DD-MMM-YY) Date of previous negative pregnancy test (If any) : —/—/— (DD-MMM-YY) _____ Multiple fetuses/children? □ No □ Yes
Is the outcome of the current pregnancy known at the time of this report? □ No □ Yes	
Obstetrical history	**Number/Year/comments**
Number of Previous pregnancies (including below obstetrical histories)_____	
Live births, without congenital anomalies/malformations/neurodevelopmental disorders/autism spectrum disorders (ASD)	

Live births, with congenital anomalies/malformations/neurodevelopmental disorders/autism spectrum disorders (specify type of congenital anomalies/developmental disorders/ASD):_____	
Ectopic pregnancy	
Spontaneous abortions prior to 20 weeks gestation (specify gestational age and identified cause, if any):	
Elective termination (foetal defects) (specify gestational age and identified defects):	
Elective termination (no foetal defects or unknown) (specify gestational age):	
Foetal deaths (>20 weeks gestation) (specify gestational age, cause(s)/post-mortem findings):	

Maternal/paternal/relatives (including grandparents) history:

Congenital malformation	□ No	□ Yes, specify relation/details:
Children dying young	□ No	□ Yes, specify relation/details:
Chromosomal abnormality	□ No	□ Yes, specify relation/details:
Developmental delay	□ No	□ Yes, specify relation/details:
Hereditary disease	□ No	□ Yes, specify relation/details:
Pertinent gynecologic information	□ No	□ Yes, specify relation/details:
Consanguinity between parents	□ No	□ Yes, specify relation/details:
Other	□ No	□ Yes, specify relation/details:

7. Adverse event (Other than abnormal pregnancy outcomes) involved during the pregnancy?	
□ No □ Yes (please complete corresponding AE form(s))	
The AE occurred in the □ Mother □ Child	GLOBAL PV DATABASE NUMBER FOR CHILD REPORT #
Describe Adverse event(s) here and include corrective treatments in the next section:	

8. Medications: (include prescription & OTC medicines and pregnancy/food supplements e.g., folic acid and other vitamins, iron)											
Products* (List Viatris drugs first)	**Causal relationship (Yes/No)**	**Foetal/ neonatal exposure ****	**Indication**	**Dose/ schedule/ Dose number**	**Route**	**Start date (DD-MMM-YY)**	**Stop date (DD-MMM-YY)**	**Duration (Days)**	**Batch number (Mandatory. If not available, enter NA/if not obtainable at all enter NO**	**Site of admin**	**Site of admin**

*If any medications were possibly involved in the occurrence of the reported disorder: specify action taken & outcome
** Foetal exposure: Select All numbers (below) that apply for foetal exposure

1. Prior to or at any time of conception
2. During pregnancy
3. Labour and delivery
4 . Breast feeding

+Stop and start dates: If exact dates are unavailable, provide gestation weeks of exposure or trimesters of exposure.

9. Additional medical data

Comments regarding maternal health or complications during pregnancy: (E.G. EVIDENCE OF GESTATIONAL DIABETES, INFECTIONS, PREECLAMPSIA, DEPRESSION/ANXIETY)

10. Prenatal testing

Specify below or check if none □

Examination	Date (DD-MMM-YY)	Normal √	Abnormal √	Specify abnormalities
Amniocentesis				
Alpha foetal protein (and other serum markers)				
Chronic villi sampling				
Foetal Nonstress test				
Uterine ultrasound (please describe)				
Genetic screening (specify:_____)				
Other (specify:_____)				

11. Pregnancy outcome

children/foetuses: □ single □ multi (#_____)

Child/ Foetus	Sex	Date of delivery, abortion, termination or foetal death (DD-MMM-YY)	Apgar score			Delivery mode (√)		Week of gestation (Weeks Of Amenorrhea)	Birth Weight & Length	Head Circum (cms)	***Outcome	Congenital Anomaly****		Neonate death (age at death, specify cause)
			1 MIN	5 MIN	10 MIN (IF <7 AT 5 MIN)	VAG	C-Sect*					Yes	No	
									g cm					
									g cm					
									g cm					
									g cm					
									g					

									cm					

* C section: if yes, please provide reason:
**Outcome : enter the number appropriate to the pregnancy outcome (enter all that apply)
1. Live birth (normal)
2. Spontaneous abortion (<20 weeks gestation)
3. Elective termination.
4. Ectopic pregnancy
5. Early foetal death (20-27 weeks gestation)
6. Late foetal death (at least 28 weeks gestation)
7. Stillbirth.
8. Maternal death (If resulting in foetal death, add appropriate number)

***ANY CONGENITAL ANOMALY OR DEVELOPMENTAL DISORDERS IDENTIFIED AT BIRTH, SPECIFY HERE.
Congenital anomaly identified at birth ☐ YES, SPECIFY HERE ☐ NO

IN CASE OF ANY CONGENITAL ANOMALY, OR DEVELOPMENTAL DISORDERS/AUTISM SPECTRUM DISORDERS NOT IDENTIFIED AT BIRTH SPECIFY IN SECTION 12.

IN CASE OF ABORTION, STILL BIRTHS, FETAL DEATH OR MATERNAL DEATH, WAS AN AUTOPSY PERFORMED?
☐ NO ☐ YES ☐ UNK

IF YES, PROVIDE RESULTS FOR EACH WHERE APPLICABLE:

Labour/Delivery:

Any complications of labour and/or delivery □ No □ Yes , specify:
Medication during labour □ No □ Yes , specify:
Clear amniotic fluid □ No □ Yes
Normal placenta □ No □ Yes
Abnormality of umbilical cord vessel and gases □ No □ Yes, specify for each child/fetus:
Umbilical artery
pH:
PCO2:
PO2:

Additional information about the newborn condition:
Breastfeeding □ No □ Yes, specify duration and capture maternal medications in section 8
Neonatal illness □ No □ Yes , specify:
Need for resuscitation □ No □ Yes
Intrauterine growth restriction or immaturity □ No □ Yes , specify:
Hospitalisation: □ No □ Yes
Medications: □ No □ Yes , specify:
Corrective treatment received by newborn □ No □ Yes , specify:
Intensive care □ No □ Yes
Transferred to Intensive care unit or pediatric department □ No □ Yes duration:

Address of department: Infant to be followed up by (doctor's name and address):

12. Pediatric assessment

Child #	**Child age at the time of assessment** (with unit)	**Motor development**		**Neurological and behavioural development**		**Growth weight & Length ***	**congenital anomaly not yet identified at birth**		***specify abnormalities**
		Normal	Delayed	Normal	Delayed		Yes	No	
						g cm			
						g cm			
						g cm			
* Specify medical events that led to medical office/ER visit or hospitalisation or congenital anomaly not identified at birth or developmental disorders/autism spectrum disorders									
Printed name: Email address: Occupation: Signature: Date:									

Serious opportunistic infections, including progressive multifocal leukoencephalopathy (PML) (PML form)

1. Patient Information:

Patient's Initials or other identifier		
Patient's Age		
Date of birth DOB (DD/MM/YY)		
Gender	□ M	□ F

Report type

Study:	□ No	□ Yes	If yes, please specify:	Study number: Protocol number: Investigator name: Patient number:
Spontaneous:	□ No	□ Yes		

2. Drug being reported

Name: _____

3. PML-Related questions

3.1 PML Diagnosis

3.1.1. Please indicate whether the diagnosis of PML is

□ suspected □ confirmed □ indeterminate

If indeterminate, what is the differential diagnosis?

_____

_____

3.1.2 Please indicate basis for diagnosis (check all that apply)

□ Brain biopsy □ CSF PCR □ MRI

3.2 Causal relationship

Is there a reasonable possibility that PML diagnosis is associated with the use of drug being reported?

□ Yes □ No □ Unable to assess

3.3 Clinical symptoms

Symptoms		Date of onset
Recent changes in personality or mood	□ Yes □ No	
Recent or sudden change in cognitive behaviours Example: confusion, disorientation	□ Yes □ No	
Language or speech disturbances Example: aphasia or dysarthria	□ Yes □ No	
Visual disturbances	□ Yes □ No	
Ataxia/loss of motor coordination/progressive weakness	□ Yes □ No	
New onset of seizures	□ Yes □ No	
Other-if yes, please specify	□ Yes □ No	

3.4 EDSS score

	Date	Score
Prior to the onset of symptoms		
After the onset of symptoms		

3.5 Laboratory and JCV information

Test*		Date	Results
JCV DNA detection by PCR □ Yes □ No	□ CSF		
Laboratory used for detection (please provide name and location)	□ Plasma		
Brain biopsy □ Yes □ No Hospital facility (please provide name and location)			
CD4 count □ Yes □ No			
CD8 count □ Yes □ No			

***Please provide copies of test results**

3.6 Other investigation

Other Investigation	Date	Baseline values	Result	Normal High/Low

3.7 Imaging information

	Date	Results
Was Brain MRI performed prior to the start of symptoms? □ Yes □ No		

	Date	Results
Was Brain MRI performed for PML diagnosis? □ Yes □ No		
Was Brain CT performed prior to the start of symptoms? □ Yes □ No		
Was Brain CT performed for PML diagnosis? □ Yes □ No		

3.8 PML treatment

Has any treatment been given to the patient to treat PML? □ Yes □ No

Medication	Dose	Frequency	Route	Start date	End date

4. Medical history

4.1. Please indicate if the patient had or has one or more of the following conditions

Relevant medical information	Date	Treatment (if available)
HIV or AIDs □ Yes □ No		
Leukaemia/Lymphoma □ Yes □ No Other malignancies □ Yes □ No Please specify:_____		
Opportunistic infection(s) (e.g. CMV) □ Yes □ No Specify: _____		
Tuberculosis □ Yes □ No		
Organ transplant □ Yes □ No Please specify: _____		
Other autoimmune disease □ Yes □ No (e.g., SLE, Sjogren's, Bechet's, RA, psoriasis….) Please specify: _____		

4.2. Please indicate if the patient had prior JCV testing

Relevant investigations		Date	Results
JCV DNA testing before current illness □ Yes □ No	□ CSF		

Relevant investigations		**Date**	**Results**
(please provide the name of laboratory where the test was performed)	□ Plasma		
JCV Serology □ Yes □ No			

5.Drug history

5.1 Please indicate if any treatment the patient received/receiving for multiple sclerosis

Medication	**Date of 1st course**	**Date of last course**	**No. of courses**	**Dose/ Route**	**Reason for discontinuation**	**Reporter causality**
Lemtrada (alemtuzumab) (if not the drug being reported) □ Yes □ No						□ Related □ Unrelated □ Unknown

Medication	**Start Date**	**End Date**	**Dose/ Route**	**Frequency**	**Reason for discontinuation**	**Reporter causality**
Teriflunomide □ Yes □ No (if not the drug being reported)						□ Related □ Unrelated □ Unknown
Natalizumab □ Yes □ No						□ Related □ Unrelated □ Unknown
Fingolimod □ Yes □ No						□ Related □ Unrelated □ Unknown
Dimethyl fumarate □ Yes □ No						□ Related □ Unrelated □ Unknown
Interferon beta □ Yes □ No (any product)						□ Related □ Unrelated □ Unknown
Glatiramer acetate □ Yes □ No						□ Related □ Unrelated □ Unknown
Mitoxantrone □ Yes □ No						□ Related □ Unrelated □ Unknown

Corticosteroids □ Yes (most recent course) □ No						□ Related □ Unrelated □ Unknown
Other MS Therapies □ Yes □ No Specify: _____						□ Related □ Unrelated □ Unknown
Other MS Therapies □ Yes □ No						□ Related □ Unrelated □ Unknown

5.2 Please indicate if the patient has taken one or more of the following medications

Medication	**Start Date**	**End Date**	**Dose**	**Frequency**	**Reason for Discontinuation**	**Reporter Causality[1]**
Rituximab □ Yes □ No						□ Related □ Unrelated □ Unknown
Efalizumab □ Yes □ No						□ Related □ Unrelated □ Unknown
Leflunomide □ Yes □ No						□ Related □ Unrelated □ Unknown
Methotrexate □ Yes □ No						□ Related □ Unrelated □ Unknown
Other immunosuppressive or chemotherapeutic agents (e.g., cyclophosphamide, tacrolimus, azathioprine, mycophenolate, cyclosporine) Please specify: □ Yes □ No						□ Related □ Unrelated □ Unknown

[1] Physician's assessment of relatedness to PML

Abbreviations

AIDS	**Acquired immunodefiency syndrome**
CMV	**Cytomegalovirus**
CT	**Computed tomography**
DNA	**Deoxyribose nucleic acid**
EDSS	**Expanded disability status scale**
HIV	**Human immunodeficiency virus**
JCV	**John Cunningham virus**
MRI	**Magnetic resonance imaging**
PCR	**Polymerase chain rection**

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where teriflunomide is marketed, at launch and after launch, all healthcare professionals who are expected to use teriflunomide are provided with the following items:

- Summary of Product Characteristics (SmPC)
- HCP guide
- Patient Card

The HCP guide will include the following key elements:

1. HCPs should discuss with their patients the specific safety concerns of teriflunomide detailed below including the tests and precautions needed for safe use at first prescription, and regularly during treatment as follows:

- Risk of hepatic effects
  - Liver function tests are needed prior to the start of treatment and periodically during treatment.
  - To educate the patient about the signs and symptoms of liver disease and the need to report to their HCP if they experience any of them.
- Potential risk of teratogenicity
  - To remind women of child-bearing potential (WOCP) including adolescents/their parents-caregivers that teriflunomide is contraindicated in pregnant women and in WOCP not using an effective contraception during and after treatment.
  - To assess regularly the potential for pregnancy in female patients including patients below 18 years old.
  - To tell female children and/or parents/caregivers of female children about the need to contact the prescribing physician once the female child under TERIFLUNOMIDE treatment experiences menses. Counselling should be provided to the new patients of child-bearing potential about contraception and the potential risk to the foetus.
  - To check pregnancy status before starting treatment.
  - To educate female patients of child-bearing potential on the need for effective contraception during and after treatment with teriflunomide.
  - To remind patients to inform their doctor immediately if they stop contraception, or prior to changing contraceptive measures.
  - If female patients become pregnant despite using contraceptive measures, they should stop teriflunomide and contact their doctor immediately who should:
    - Consider and discuss with the patient the accelerated elimination procedure,
    - Report any pregnancy case to <marketing authorisation holder> by calling <local number> or visiting <URL>, irrespective of adverse outcomes observed.
- Contact <marketing authorization holder> for information regarding the measurement of teriflunomide plasma concentration.
- Risk of hypertension
  - To check for a history of hypertension and that blood pressure should be appropriately managed during treatment

  - The need for blood pressure checks before treatment and periodically during treatment,
- Risk of haematologic effects
  - To discuss the risk of decreased blood cell counts (affecting mainly white blood cells) and the need for complete blood cell counts before treatment and periodically during treatment based on signs and symptoms.
- Risk of infections/serious infections
  - To discuss the need to contact the doctor in the event of signs/symptoms of infection, or if the patient takes other medicines that affect the immune system. If serious infection occurs, consider the accelerated elimination procedure.

2. A reminder to provide patients/legal representative with a Patient Card, including filling-in their contact details, and to provide replacement Patient Cards as necessary.
3. A reminder to discuss the content of the Patient Card content with the patient/legal representative regularly at each consultation at least annually during treatment.
4. To encourage patients to contact their multiple sclerosis (MS) physician and/or General Practitioner if they experience any of the signs and symptoms discussed in the Patient Card.
5. At prescription renewal, adverse events are checked, ongoing risks and their prevention are discussed, and checks are made to ensure adequate monitoring is taking place.

The Patient Card is aligned with labelling information and includes the following key elements:

1. A reminder for both patients and all HCPs involved in their treatment that the patient is being treated with teriflunomide, a medicine which:
   - Should not be used in pregnant women.
   - Requires concomitant use of effective contraception in women of child-bearing potential (WOCP).
   - Requires a pregnancy status check before treatment.
   - Affects liver function.
   - Affects blood cell counts and the immune system.
   - Information to educate the patient about important side effects and to pay attention to certain signs and symptoms which might indicate liver disease or infection, and if any of these occur, to contact their doctor/HCP promptly.
   - To remind female patients to tell their doctor if breast-feeding.
   - A reminder for women of child-bearing potential (WOCP) including girls and their parents/ caregivers:
     - to use effective contraception during and after treatment with teriflunomide
     - that their doctor will provide counselling on the potential risks to the foetus and on the need for effective contraception.
     - to stop treatment with teriflunomide immediately if they suspect they might be pregnant and also to contact their doctor immediately.
   - A reminder for parents/caregivers of girls
     - to contact their doctor when the girl experience menses for the first time in order to get counselling about the potential risk to the fetus and the need for contraception.
   - If women of child-bearing potential (WOCP) become pregnant:
     - To remind both patients and HCPs about the accelerated elimination procedure
   - To remind patients to show the Patient Card to Doctors/HCPs involved with their medical care (especially in the event of medical emergencies and/or if new Doctors/HCPs are involved.)
   - To record the first date of prescription and the contact details of their prescriber
   - To encourage the patients to read the PL thoroughly.