EU Risk Management Plan

For

Teriflunomide Accord 7 mg film-coated tablets

Teriflunomide Accord 14 mg film-coated tablets

(Teriflunomide)

RMP version to be assessed as part of this application:

RMP Version number	3.0
Data lock point for this RMP	22-Nov-2023
Date of final sign off	11-Dec-2023

Rationale for submitting an RMP: Risk Management Plan (RMP) has been updated in line with the authority comment and with the reference product Aubagio® (Teriflunomide) Risk management plan published by EMA.

Summary of significant changes in this RMP: Significant changes have been done in the following sections of this RMP: Part II (SVII and SVIII), Part (V), Part VI (IIA) and Part VII (Annex 8)

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

RMP Version number	Approved with procedure	Date of approval (opinion date)
1.2	Centralised procedure (EMEA/H/C/005960/0000)	15-Sep-2022

[redacted]

QPPV Name: Agata Gesiewicz

[redacted]

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Part I: Products Overview

Table 1: Product Overview

Active substance (INN or common name)	Teriflunomide
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressants, Selective immunosuppressants, ATC Code: L04AA31
Marketing Authorisation Holder	Accord Healthcare S.L.U., Spain
Medicinal products to which this RMP refers	2
Invented names in the European Economic Area (EEA)	Teriflunomide Accord 7 mg film coated tablets Teriflunomide Accord 14 mg film-coated tablets
Marketing authorisation procedure	Centralised procedure (EMEA/H/C/H0005960)
Brief description of the product	*Chemical class*: Teriflunomide is an orally available immunomodulatory agent used to treat relapsing multiple sclerosis. Teriflunomide is associated with transient serum enzyme elevations during therapy and with rare instances of acute liver injury.
	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 ***Teriflunomide Accord 7 mg film coated tablets*** Each film coated tablet contains 7 mg of teriflunomide. Excipient with known effect: Each tablet contains 79 mg of lactose (as monohydrate). ***Teriflunomide Accord 14 mg film coated tablets*** Each film-coated tablet contains 14 mg of teriflunomide. Excipient with known effect: Each tablet contains 72 mg of lactose (as monohydrate).
Hyperlink to the Product Information	Refer to Module 1.3.1 for SmPC and PIL
Indications in the EEA	Teriflunomide Accord is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS).
Dosage in the EEA	*Current* Teriflunomide Accord 14 mg film coated tablets **Posology:** **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.

[redacted]

	-Paediatric patients with body weight ≤40 kg: 7 mg once daily. Teriflunomide Accord is only available as 14 mg film-coated tablets. Thus, it is not possible to administer Teriflunomide Accord to paediatric patients with body weight ⩽ 40 kg 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. Paediatric patients who reach a stable body weight above 40 kg should be switched to 14 mg once daily. Method of administration: The film-coated tablets are for oral use. The tablets should be swallowed whole with some water. Film coated tablets can be taken with or without food.
	Proposed Teriflunomide Accord 7 mg film coated tablets **Posology:** **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. Method of administration:

	The film-coated tablets are for oral use. The tablets should be swallowed whole with some water. Film coated tablets can be taken with or without food.
Pharmaceutical forms and strengths	Current Film-coated tablets 14 mg
	Proposed Film-coated tablets 7 mg
Will the product be subject to additional monitoring in EU?	No

[redacted]

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

Not applicable.

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

SV.1 Post-authorisation exposure

Not applicable.

[redacted]

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Not applicable

Part II: Module SVII - Identified and potential risks

There is a published European Public Assessment Report (EPAR) available for the medicinal product Aubagio® (Teriflunomide) published by EMA website on 22-Aug-2023. There is no change proposed by MAH in these safety concerns mentioned in Module SVIII which is in-line with EPAR of Aubagio® (Teriflunomide).

Hence this section remains "Not applicable".

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable

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

Not applicable

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

SVII.3.2. Presentation of the missing information

Not Applicable

[redacted]

Part II: Module SVIII - Summary of the safety concerns

Table 2: 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

[redacted]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for this medicinal product. Additionally, following activities shall be carried out as per D156 joint CHMP and PRAC response assessment report and D180 authority assessment report.

- 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 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.

*Accord being a generic MAH, PSUR requirements will be followed as per EURD list.

In addition, MAH proposed specific adverse reaction targeted questionnaire for following risks, in line with the reference product:

- Hepatic Effects,
- Acute Pancreatitis
- Teratogenicity
- Serious opportunistic infections, including PML

Targeted follow-up questionnaire forms are appended in Annexure-4 of this RMP.

Purpose: For collection and reporting of safety information while use of Teriflunomide.

III.2 Additional pharmacovigilance activities

None proposed for generic MAH.

III.3 Summary Table of additional Pharmacovigilance activities

Not Applicable.

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable

[redacted]

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Table 3: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Hepatic Effects	*Routine risk communication* SmPC sections 4.4, 4.3 and 4.8 PL section 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* - Information to perform/monitor liver test during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. *Other routine risk minimisation measures beyond the Product Information:* the prescription only status of the product.
Hypertension	*Routine risk communication* SmPC sections 4.4 and 4.8 PIL section 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* - Information to monitor blood pressure before and during the treatment with teriflunomide is included in SmPC section 4.4 and PIL section 2. *Other routine risk minimisation measures beyond the Product Information:*

Safety concern	**Routine risk minimisation activities**
	the prescription only status of the product.
Haematologic effects	*Routine risk communication* SmPC sections 4.4, 4.3 and 4.8 PIL section 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* - Instruction to perform complete blood cell count before and during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. *Other routine risk minimisation measures beyond the Product Information:* the prescription only status of the product.
Infections	*Routine risk communication* SmPC sections 4.4, 4.3 and 4.8 PIL section 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* - Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. *Other routine risk minimisation measures beyond the Product Information:* the prescription only status of the product.
Acute Pancreatitis	*Routine risk communication* SmPC section 4.4 and 4.8 PIL section 2 and 4

[redacted]

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: - Information to monitor symptoms of symptoms of pancreatitis during the treatment with teriflunomide and treatment discontinuation information If pancreatitis is confirmed, is included in SmPC section 4.4. *Other routine risk minimisation measures beyond the Product Information:* the prescription only status of the product.
Important Potential Risks	
Teratogenicity	*Routine risk communication* SmPC section 4.3 and 4.6 PIL section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* - Information on contraception recommendations and treatment discontinuation is included in SmPC section 4.6 *Other routine risk minimisation measures beyond the Product Information:* the prescription only status of the product.
Serious opportunistic infections, including PML	*Routine risk communication* SmPC section 4.3, 4.4 and 4.8 PIL section 2 and 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:*

[redacted]

Safety concern	Routine risk minimisation activities
	- Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. *Other routine risk minimisation measures beyond the Product Information:* the prescription only status of the product.

V.2. Additional Risk Minimisation Measures

Additional Risk Minimisation Measures have been proposed for following risks as per reference medicinal product Aubagio® (Teriflunomide)

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

Proposed additional risk minimisation measures are listed below and are summarised in Annexure-6.

Additional risk minimisation 1

- **HCP guide:**

Objectives:

To increase an awareness of healthcare professionals regarding risk of hepatic effects, hypertension, hematologic effects, infections, teratogenicity, and serious opportunistic infections, including PML with use of Teriflunomide.

[redacted]

Rationale for the additional risk minimisation activity:

To minimize the frequency of ADRs related with 'hepatic effects, hypertension, hematologic effects, infections, teratogenicity, and serious opportunistic infections, including PML' by increasing awareness of healthcare professionals.

Target audience and planned distribution path:

The target audience for HCP checklist will primarily be specialists (neurologists) and MS nurses who may be approached by the patient for ongoing follow up care and other healthcare professionals who may prescribe Teriflunomide initially are also in scope. The final target audience and distribution path has to be agreed with the respective National Competent Authority Prior to launch in each Member State.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance including but not limited to internal signal management activity and analysis of ADR reports to assess compliance with Summary of product Characteristics recommendation will allow assessing and judging the success of the risk minimisation measures.

Additional risk minimisation 2

- **Patient card**

Objectives:

To increase an awareness of patients regarding the risk of hepatic effects, hypertension, hematologic effects, Infections, teratogenicity and serious opportunistic infections, including PML with use of Teriflunomide.

Rationale for the additional risk minimisation activity:

[redacted]

To minimize the frequency of ADRs related with 'hepatic effects, hypertension, hematologic effects, infections, teratogenicity, and serious opportunistic infections, including PML' by increasing an awareness of healthcare professionals

Target audience and planned distribution path:

Patients who are taking the Teriflunomide, their care takers and Physician and other healthcare professionals who may prescribe Teriflunomide. The final target audience and distribution path has to be agreed with the respective National Competent Authority Prior to launch in each Member State.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance including analysis of ADR reports to assess compliance with Summary of product Characteristics recommendation will allow assessing and judging the success of the risk minimisation measures.

V.3. Summary of risk minimisation measures

Table 4: 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 minimisation measures: - SmPC sections 4.4, 4.3 and 4.8 - PL section 2 and 4 - Information to perform/monitor liver test during the treatment with teriflunomide and treatment discontinuation information	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for 'Hepatic effects. Additional pharmacovigilance activities: None

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	
Hypertension	Routine risk minimisation measures: - SmPC sections 4.4 and 4.8 - PIL section 2 and 4 - Information to monitor blood pressure before and during the treatment with teriflunomide is included in SmPC section 4.4 and PIL section 2. - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: No Specific adverse reaction follow-up questionnaire for 'Hypertension'. Additional pharmacovigilance activities: None
Haematologic effects	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	- SmPC sections 4.4, 4.3 and 4.8 - PIL section 4 - Instruction to perform complete blood cell count before and during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. - The prescription only status <u>Additional risk minimisation measures</u>: Educational Materials (HCP guide and Patient card)	No Specific adverse reaction follow-up questionnaire for 'Haematologic effects'. <u>Additional pharmacovigilance activities</u>: None
Infections	<u>Routine risk minimisation measures</u>: - SmPC sections 4.4, 4.3 and 4.8 - PIL section 2 and 4 - Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4.	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection</u>: No Specific adverse reaction follow-up questionnaire for 'Infection'. <u>Additional pharmacovigilance activities</u>: None

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	- The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)	
Acute Pancreatitis	Routine risk minimisation measures: - SmPC section 4.4 and 4.8 - PIL section 2 and 4 - Information to monitor symptoms of symptoms of pancreatitis during the treatment with teriflunomide and treatment discontinuation information If pancreatitis is confirmed, is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for 'Acute Pancreatitis'. . Additional pharmacovigilance activities: None
Important Potential Risks		
Teratogenicity	Routine risk minimisation measures: - SmPC section 4.3 and 4.6	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	- PIL section 2 - Information on contraception recommendations and treatment discontinuation is included in SmPC section 4.6 - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patients card)	Specific adverse reaction follow-up questionnaire for 'Teratogenicity'. Structured analyses of cases reporting pregnancy exposure will be submitted regularly, at harmonised submission dates (3-year cycle) synchronised with Teriflunomide PSUR submission requirements. Additional pharmacovigilance activities: None
Serious opportunistic infections, including PML	Routine risk minimisation measures: - SmPC section 4.3, 4.4 and 4.8 - PIL section 2 and 4 - Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire for 'Serious opportunistic infections, including PML'. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Educational Materials (HCP guide and Patients card)	

Part VI: Summary of the risk management plan

Summary of risk management plan for Teriflunomide Accord 7 mg and 14 mg film-coated tablets (Teriflunomide)

This is a summary of the risk management plan (RMP) for Teriflunomide Accord 7 mg and 14 mg film-coated tablets. The RMP details important risks of Teriflunomide Accord 7 mg and 14 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Teriflunomide Accord 7 mg and 14 mg film-coated tablets' risks and uncertainties (missing information).

Teriflunomide Accord 7 mg and 14 mg film-coated tablets summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Teriflunomide Accord 7 mg and 14 mg film-coated tablets should be used.

Teriflunomide Accord 7 mg and 14 mg film-coated tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Teriflunomide Accord 7 mg and 14 mg film-coated tablets RMP.

I. The medicine and what it is used for

Teriflunomide Accord is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS).
It contains teriflunomide as the active substance and it is given by oral route.
Further information about the evaluation of 'Teriflunomide Accord 7 mg and 14 mg film-coated tablets' benefits can be found in Teriflunomide Accord 7 mg and 14 mg film-coated tablets EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/teriflunomide-accord .

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Teriflunomide Accord 7 mg and 14 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Teriflunomide Accord 7 mg and 14 mg film-coated tablets risks, are outlined below.

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

[redacted]

- 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 patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Teriflunomide Accord 7 mg and 14 mg film-coated tablets, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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

If important information that may affect the safe use of Teriflunomide Accord 7 mg and 14 mg film-coated tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Teriflunomide Accord 7 mg and 14 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Accord 7 mg and 14 mg film-coated tablets. 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);

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 with additional risk minimization measures

The safety information in the proposed Product Information is aligned to the reference medicinal product Aubagio® (Teriflunomide).

Important Identified Risks: Hepatic Effects	
Risk minimisation measures	Routine risk minimisation measures: - SmPC sections 4.4, 4.3 and 4.8 - PL section 2 and 4 - Information to perform/monitor liver test during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)
Important Identified Risks: Hypertension	
Risk minimisation measures	Routine risk minimisation measures: - SmPC sections 4.4 and 4.8 - PIL section 2 and 4

[redacted]

	- Information to monitor blood pressure before and during the treatment with teriflunomide is included in SmPC section 4.4 and PIL section 2. - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and patient card)
Important Identified Risks: Haematologic effects	
Risk minimisation measures	Routine risk minimisation measures: - SmPC sections 4.4, 4.3 and 4.8 - PIL section 4 - Instruction to perform complete blood cell count before and during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and patient card)
Important Identified Risks: Infections	
Risk minimisation measures	Routine risk minimisation measures: - SmPC sections 4.4, 4.3 and 4.8 - PIL section 2 and 4 - Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and patient card)

[redacted]

Important Potential Risks: Teratogenicity	
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.3 and 4.6 - PIL section 2 - Information on contraception recommendations and treatment discontinuation is included in SmPC section 4.6 - The prescription only status Additional risk minimisation measures: Educational Materials (HCP guide and patient card)
Important Potential Risks: Serious opportunistic infections, including PML	
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.3, 4.4 and 4.8 - PIL section 2 and 4 - Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4. - The prescription only status Additional risk minimisation measures: Educational Materials (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 required for Teriflunomide Accord 7 mg and 14 mg film-coated tablets.

[redacted]

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

There are no studies which are conditions of the marketing authorization or specific obligation of Teriflunomide Accord 7 mg and 14 mg film-coated tablets.

[redacted]

Targeted Follow-Up Questionnaire for Hepatic Effects

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

DETAILS OF THE ADVERSE EVENT(S):

Date event started: 1) 2)	Date event stopped: 1) 2)

Please describe the event and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

Documentation of the Adverse event		
Main Diagnosis		**Start Date**
Are the following signs and symptoms associated?	*tick box if applicable*	
Asthenia	☐	
Fever	☐	
Pruritus	☐	
Jaundice	☐	
Joint pain	☐	
Abdominal pain	☐	
Vomiting	☐	
Skin eruption	☐	Type:
Purpura	☐	

[redacted]

Hepatomegaly	☐	
Splenomegaly	☐	
Lymph nodes	☐	
Ascites	☐	
Asterixis	☐	
Coma	☐	
Malaise (with or without loss of consciousness)	☐	
INR>2 or prothrombin T.<50%	☐	
Dizziness	☐	
Hypotenslon	☐	
Arrhythmia	☐	

SERIOUSNESS OF ADVERSE EVENT(S):

Do you consider the event to be serious? ○ Yes ○ No

If Yes, Reason for Seriousness:

○ Patient Died ○ Life Threatening ○ Congenital Abnormality

○ Involved/Prolonged Hospitalisation ○ Disability/Incapacity ○ Medically Significant

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased ○ Dose Increased ○ Drug withdrawn ○ Dose not changed

○ Unknown

CONCOMITANT MEDICATION (incl. herbal or self-medication):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

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	☐	☐	

[redacted]

Intravenous drug abuse	☐	☐	
Other	☐	☐	

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 result**	**Positive result**	**Date of test MM/DD/YYYY**	**Titration**
HBaAg	☐	☐	☐		
Anti-HbsAb	☐	☐	☐		
Anti-HbcAb	☐	☐	☐		
Anti-Hbc/lgM Ab	☐	☐	☐		
Anti-HAV/lgM Ab	☐	☐	☐		
Anti-HCVAb	☐	☐	☐		
PCR-C	☐	☐	☐		
Anti-CMV lgM Ab	☐	☐	☐		
Anti-EBVAb	☐	☐	☐		
Anti-nuclear Ab	☐	☐	☐		
Antinative DNA Ab	☐	☐	☐		
Anti smooth muscle Ab	☐	☐	☐		
Anti mitochondrial AB	☐	☐	☐		

OTHER INVESTIGATIONS		
Date DD/MM/YYY	**NATURE**	**RESULTS**

LIVER BIOPSY NO ☐ **YES** ☐ *If yes is ticked a report needs to be attached*	**DATE DD/MM/YYYY**	
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 DRUG POSSIBLY SUSPECTED OF INDUCING Liver Injury					
Name	**Indication**	**Daily Dose**	**Route**	**Start Date**	**End date**

Laboratory Tests	**Date**	**Baseline Values**	**Result**	**Normal High/Low**

[redacted]

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

Targeted Follow-Up Questionnaire for Acute Pancreatitis

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

DETAILS OF THE ADVERSE EVENT(S):

Date event started: 1) 2)	Date event stopped: 1) 2)

Please describe the event and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

[redacted]

SYMPTOMS:

Symptoms	Date of Onset	Description	Outcome
Abdominal Pain □ Yes □No			□Recovered □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 □Fatal

[redacted]

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

Any known results of genetic tests indicating an increased risk for pancreatitis?

□ Yes, please provide details below □ No

Any anatomic anomalies potentially associated with pancreatitis?

□ Yes, please provide details below □ No

SERIOUSNESS OF ADVERSE EVENT(S):

Do you consider the event to be serious? If Yes, Reason for Seriousness: ○ Patient Died ○ Involved/Prolonged Hospitalisation	○ Yes ○ Life Threatening ○ Disability/Incapacity	○ No ○ Congenital Abnormality ○ Medically Significant

ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased ○ Dose Increased ○ Drug withdrawn ○ Dose not changed

○ Unknown
Was Teriflunomide re-administered? □Yes □No
Did the patient experience any adverse event, upon re-administration of Teriflunomide? □Yes □No

[redacted]

CONCOMITANT MEDICATION (incl. herbal or self-medication):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					

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		
Hepatitis	☐ Yes ☐ No		
Abdominal tumor	☐ Yes ☐ No		
Abdominal surgery	☐ Yes ☐ No		
Abdominal trauma	☐ Yes ☐ No		
Hypertriglyceridemia	☐ Yes ☐ No		
Hyperparathysoidism	☐ Yes ☐ No		
Hypercalcemia	☐ Yes ☐ No		
Human immunodeficiency	☐ Yes ☐ No		
Post-ERCP	☐ Yes ☐ No		
Malignancy Specify:	☐ Yes ☐ No		
Other suspected disorders Specify:	☐ Yes ☐ No		

SOCIAL HISTORY:

Alcohol consumption (Drinks/day) _____
Tobacco user: ☐Yes ☐No _____ pack years

MEDICATION HISTORY:

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[1]
Leflunomide □ Yes □ No						Related □ Unrelated □ Unknown □
Azathioprine □ Yes □ No						Related □ Unrelated □ Unknown □
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 □

[1] Physician assessment of relatedness to Pancreatitis

INVESTIGATIONS:

Laboratory tests:

Investigation	Date	Baseline Values	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				

[redacted]

Investigation		Date	Baseline Values	Result	Normal High / Low
Alanine aminotransferase (ALT)	□ Yes □ No				
Aspartate aminotransferase (AST)	□ Yes □ No				
Alkaline phosphatase	□ Yes □ No				
Bilirubin	□ Yes □ No				
Calcium	□ Yes □ No				

Other Investigation	Date	Baseline Values	Result	Normal High / Low

Imaging studies:

Investigation		Date	Results
Abdominal ultrasound	□ Yes □ No		
Contrast enhanced abdominal CT	□ Yes □ No		
Magnetic resonance imaging (MRI)	□ Yes □ No		
Endoscopic Retrograde Cholangiopancreatogram (ERCP)	□ Yes □ No		
Magnetic Resonance Cholangiopancreatogram (MRCP)	□ Yes □ No		

MANAGEMENT:

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

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

Medication	Dose	Frequency	Route of Administration	Start date	End date

[redacted]

REPORTER DETAILS:

Title, Name & Surname	Occupation	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

ABREVIATIONS

ALT	Alanine aminotransferase
AST	Asoartate aminotransferase
ERCP	Endoscopic retroQrade cholanQiopancreatoQram
MRCP	Magnetic resonance cholangiopancreatogram
RoA	Route of administration

Targeted Follow-Up Questionnaire for Teratogenicity (Pregnancy)

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

EXPOSED PATIENT DETAILS:

Who was exposed: ☐Mother☐Father

Initials	Age	Gender:	Weight	Height	Date of Birth	Ethnicity

Parent information at the time of pregnancy					
	AGE/ BIRTH DATE	**RH (RHESUS) FACTOR**	**HT/ UNIT**	**WT / UNIT**	**SIGNIFICANT MEDICAL CONDITIONS***
MOTHER					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 THE TYPE: .... PSYCHIATRIC ILLNESS: □ NO □ YES IF YES, SPECIFY: .....
					SEROLOGY: HIV: □ NO □ YES □ UNK HEPATITIS: □ 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

[redacted]

					DIABETES: □ NO □ YES □ UNK EPILEPSY: □ NO □ YES □ UNK IF YES, SPECIFY THE TYPE: .... PSYCHIATRIC ILLNESS: □ NO □ YES IF YES, SPECIFY: .....
					SEROLOGY: HIV: □ NO □ YES □ UNK HEPATITIS: □ NO □ YES □ UNK

PARENT INFORMATION AT THE TIME OF PREGNANCY
OTHER HISTORY (including thyroid disorders, asthma, allergic disease, heart disease, sexual transmitted disorder, education level, learning difficulties, congenital malformations, environmental exposures):

*Include infomration on race, ethnicity, consanguinity or occupation if you consider it would contrubute significantly to the investigation and evaluation of certain advese findings in the pregnancy or uts outcome or ont the health of the fetus/child. Per local privacy law.
** Mention if mother quit smoling or materially reduced her usage before or during pregnancy and when

SPECIFIC TO THE PREGNNACY 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 ACKNOWLEDGMENT FORM SIGNED?	□ NO	□ YES	□ UNK.	□ NA*

*Not applicable

IMMUNIZATION / GYNECOLOGY

IMMUNIIZATION/GYNECOLOGY	
MATERNAL IMMUNIZATION	**GYNECOLOGICAL DETAILS**
RUBELLA: □ NO □ YES □ UNK. TOXOPLASMOSIS: □ NO □ YES □ UNK. CMV: □ NO □ YES □ UNK.	WERE CONTRACEPTIVE METHODS USED: □ NO □ YES□UNK IF YES, SPECIFY: CONTRACEPTION 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 (EG., DRUG DRUG INTERACTION, EPISODE OF GI DISORDER, ...): □ NO □ YES □ UNK NORMAL MENSTRUAL CYCLES: □ NO □ YES □ UNK INFERTILITY: □ NO □ YES □ UNK IF TREATMENT SPECIFY:

[redacted]

PREGNANCY INFORMATION

DATE OF LAST MENSTRUAL PERIOD (LMP) LMP: __-___-__(DD-MMM-YY) ESTIMATED DATE OF DELIVERY (EDD) EDD: __-___-__ (DD-MMM-YY)	DATE OF POSITIVE PREGNANCY TEST (IF ANY) __-___-__ (DD-MMM-YY) DATE OF PREVIOUS NEGATIVE PREGNANCY TEST (IF ANY) __-___-__ (DD-MMM-YY)
MEDICAL ASSISTANCE / HOSPITALIZATION DURING PREGNANCY? □ NO □ YES DETAILS: _____	MULTIPLE FETUSES/CHILDREN? □ NO □ YES
IS THE OUTCOME OF CURRENT PREGNANCY KNOWN AT THE TIME OF THIS REPORT? □ NO □ YES	
OBSTETRICAL HISTORY	**NUMBER/ YEAR/COMMENTS**
PREVIOUS PREGNANCIES (if ectopic or molar pregnancy or other complication, please specify):	
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 :	

SPONTANEOUS ABORTIONS PRIOR TO 20 WEEKS GESTATION (specify gestational age):	
ELECTIVE TERMINATION (FETAL DEFECTS) (specify gestational age):	
ELECTIVE TERMINATION (NO FETAL DEFECTS OR UNKNOWN) (specify gestational age):	
FETAL DEATHS (>20 WEEKS GESTATION) (specify gestational age, cause(s)/Post Mortem findings):	

MATERNAL/PATERNAL/RELATIVES (including grand-parents) 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: _____ _

ADERSE EVENT (OTHER THAN ABNORMAL PRGNANCY OUTCOMES) INVLOVED DURING THE PREGNANCY?

□ No □ Yes (please complete corresponding AE form(s))
THE AE OCCURRED IN THE □ MOTHER □ CHILD
DESCRIBE ADVERSE EVENT(S):

[redacted]

MEDICATIONS: (include prescription & OTC medicines and pregnancy/food supplements e.g. folic acid and other vitamins, iron)

PRODUCTS *	CAUSAL RELATION - SHIP (YES/NO)	FETAL / 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	SIDE OF ADMIN

*If any medications were possibly involved in the occurrence of the reported disorder; specify action taken & outcome **Fetal Exposure: Select All the Numbers (below) that apply for Fetal Exposure

+Stop And Start Dates: If exact dates are unavailable, provide gestation weeks of exposure or trimesters of exposure.

1. PRIOR TO OR AT TIME OF CONCEPTION 3. LABOR AND DELIVERY

[redacted]

PRODUCTS *	CAUSAL RELATION - SHIP (YES/NO)	FETAL / 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	SIDE OF ADMIN
2. DURING PREGNANCY 4. BREAST FEEDING											

ADDITIONAL MEDICAL DATA

COMMENTS REGARDING MATERNAL HEALTH OR COMPLICATIONS DURINGPREGNANCY

PRENATAL TESTING

Specify below or check if none				
EXAMINATION	**DATE DD-MMM-YY**	**Normal (√)**	**Abnormal (√)**	**Specify abnormalities**
AMNIOCENTESIS				
ALPHA FETAL PROTEIN (AND OTHER SERUM MARKERS)				

[redacted]

CHORIONIC VILLI SAMPLING				
FETAL STRESS TEST				
UTERINE ULTRASOUND (please describe)				
GENETIC SCREENING (specify:				
OTHER (specify:_____)				

PREGNANCY OUTCOME

#CHILDREN/FETUSES: SINGLE MULTI (#_____)												
CHILD/ FETUS	Sex	DATE OF DELIVERY, ABORTION, TERMINATION OR FETAL DEATH (DD-MMM-YY)	APGAR SCORE		DELIVERY MODE (✓)		WEEK OF GESTATION	BIRTH WEIGHT & LENGTH	HEAD CIRCUM (CMS)	*OUTCOME	CONGENITAL ANOMALY		NEONATE DEATH (age at death, specify cause)
			1 MIN	5 MIN	VAG	C-SECT					YES**	NO	
								G Cm					
								G Cm					
								G Cm					

1	*OUTCOME: ENTER THE NUMBER APPROPRIATE TO THE PREGNANCY OUTCOME (ENTER ALL THAT APPLY)
	1. LIVE BIRTH (NORMAL) 2. ELECTIVE TERMINATION 3. LIVE BIRTH (ABNORMAL)** 4. STILLBIRTH 5. SPONTANEOUS ABORTION (<20 WEEKS GESTATION) 6. MATERNAL DEATH (IF RESULTING IN FETAL DEATH,ADD APPROPRIATE NUMBER) 7. EARLY FETAL DEATH (20-27 WEEKS GESTATION) 8. ECTOPIC PREGNANCY 9. LATE FETAL DEATH (AT LEAST 28 WEEKS GESTATION) 10. LIVE BIRTH (NORMAL)-DEVELOPMENTAL DISORDERS**
	**OF NOTE, CONGENITAL ANOMALIES INCLUDE MALFORMATIONS AND ABNORMAL FUNCTIONS EITHER BEING OBSERVABLE AT BIRTH OR LATER DURING THE CHILD DEVELOPMENT. IF PREGNANCY OUTCOME INVOLVES CONGENITAL ANOMALY AT BIRTH OR DEVELOPMENTAL DISORDERS, SPECIFY (SEE SECTION 12FOR NEURO DEVELOPMENT DISORDERS):
	IN CASE OF ABORTION, STILLBIRTHS, FETAL DEATH OR MATERNAL DEATH, WAS AN AUTOPSY PERFORMED? □ NO □ YES □ UNK IF YES, PROVIDE RESULTS FOR EACH WHERE APPLICABLE
	LABOR/DELIVERY: MODE OF DELIVERY: ANY COMPLICATIONS OF LABOR AND/OR DELIVERY □ NO □YES, SPECIFY
	MEDICATION DURING LABOR □ NO □YES, SPECIFY:

[redacted]

	CLEAR AMNIOTIC FLUID □NO □ YES NORMAL PLACENTA □ NO □ YES
	ADDITIONAL INFORMATION ABOUT THE NEWBORN CONDITION: BREAST FEEDING □ NO □ YES NEONATAL ILLNESS □ NO □ YES, SPECIFY: ---------- NEED FOR RESUSCITATION □ NO □ YES INTRAUTERINE GROWTH RESTRICTION OR IMMATURITY □ 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)

PEDIATRIC ASSESSMENT

CHILD	**CHILD AGE AT THE TIME OF ASSESSMENT**	**MOTOR DEVELOPMENT**		**NEUROLOGICAL AND BEHAVIOURAL DEVELOPMENT**		**GROWTH WEIGHT &LENGTH***	**OTHER TYPE OF CONGENITAL ANOMALY***		**IF * SPECIFY.**
		NORMAL	**DELAYED***	**NORMAL**	**DELAYED***		**YES***	**NO**	
						g cm			
						g cm			
						g cm			

[redacted]

	*SPECIFY MEDICAL EVENTS THAT LED TO MEDICAL OFFICE/ER VISIT OR HOSPITALIZATION OR CONGENITAL ANOMALY NOT IDENTIFIED AT BIRTH OR DEVELOPMENTAL DISORDERS/AUTISM SPECTRUM DISORDERS,
	PRINTED NAME:_____ SIGNATURE: _____ DATE: _____ _

REPORTER INFORMATION:

NAME (first/last):	STREET:
OCCUPATION: □ CONSUMER □ STUDY INVESTIGATOR D LAWYER □ MEDICAL DOCTOR □ PHARMACIST □OTHER HCP (HEALTHCARE PROFESSIONAL) D OTHER	CITY/STATE/PROVINCE:
PHONE:	POSTAL CODE: Country:
DOES MOTHER AGREE TO PROVIDE INFORMATION? YES □ NO □ DOES FATHER AGREE TO PROVIDE INFORMATION? YES □ NO □	

[redacted]

Targeted Follow-Up Questionnaire for Serious Opportunistic Infections, Including PML

***PLEASE DO NOT LEAVE ANY FIELD BLANK. STRIKE IT OUT IF INFORMATION IS 'NOT AVAILABLE' OR 'NOT APPLICABLE'.**

1.PATIENT DETAILS:

Initials	Age	Gender:	Weight	Height	Date of Birth	Hospital Ref.

If female, is the patient pregnant? **Yes / No**	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

2.SUSPECTED DRUG(S):

Drug/Brand Name	Manufacturer & Batch No.	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.						
2.						

3.DETAILS OF THE ADVERSE EVENT(S):

Date event started: 1) 2)	Date event stopped: 1) 2)

Please describe the event and details of any treatment given or investigation performed.	Outcome: ○ Recovered ○ Not Recovered ○ Recovered with Sequel ○ Recovering ○ Fatal ○ Unknown

4.SERIOUSNESS OF ADVERSE EVENT(S):

Do you consider the event to be serious? ○ Yes ○ No

If Yes, Reason for Seriousness:

○ Patient Died	○ Life Threatening	○ Congenital Abnormality
○ Involved/Prolonged Hospitalisation	○ Disability/Incapacity	○ Medically Significant

5.ACTION TAKEN WITH SUSPECTED DRUGS:

○ Dose Decreased ○ Dose Increased ○ Drug withdrawn ○ Dose not changed

○ Unknown

[redacted]

DRUG BEING REPORTED

Name:_____

PML-RELATED QUESTIONS

PML Diagnosis

Please indicate whether the diagnosis of PML is
□Suspected □ Confirmed □ Indeterminate If indeterminate, what is the differential diagnosis?

Please indicate basis for diagnosis (check all that apply) □ Brain biopsy □ CSF PCR □ MRI

Causal relationship

Is there a reasonable possibility that PML diagnosis is associated with the use of the drug being reported?
□ Yes □ No □ Unable to assess

Clinical symptoms

Symptoms			**Date of onset**
Recent changes in personality or mood	□ Yes	□ No	
Recent or sudden change in cognitive behaviour Example: confusion, disorientation	□ Yes	□ No	
Language or speech disturbances Example: aphasia or dvsarthria	□ 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	

EDSS score

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

[redacted]

Laboratory and JCV information

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

*Please provide copies of test results

Other Investigation

Other Investigation	Date	Baseline Values	Result	Normal High/ Low

Imaging information

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

[redacted]

PML treatment

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

Medication	Dose	Frequency	Route	Start Date	End Date

MEDICAL HISTORY
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		
Leukemia/Lymphoma	□ Yes	□ No		
Other Malignancies Please specify:	□ Yes	□ No		
Opprotunistic infection(s) (e.g CMV) Specify:_____	□ Yes	□ No		
Tuberculosis	□ Yes	□ No		
Organ transplant Please specify:	□ Yes	□ No		
Other autoimmune disease {e.g. SLE, Sjogren's, Behcet's, RA, psoriasis....) Please specify:	□ Yes	□ No		

Please indicate if the patient had prior JCV testing

Relevant investigations			Date	Results
JCV DNA testing <u>before</u> current illness (please provide the name of laboratory where the test was performed)	□ Yes □ No	□ CSF		
		□ Plasma		
JCV Serology	□ Yes □ No			

[redacted]

DRUG HISTORY

Please indicate 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[1]
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[1]
teriflunomide (if not the drug being reported) □ Yes □ No						Related □ Unrelated □ Unknown □
natalizumab □ Yes □ No						Related □ Unrelated □ Unknown □
fingolimod □ Yes □ No						Related □ Unrelated □ Unknown □
dimethyl fumarate □ Yes □ No						Related □ Unrelated □ Unknown □
Interferon beta (any product) □ Yes □ No						Related □ Unrelated □ Unknown □
glatiramer acetate □ Yes □ No						Related □ Unrelated □ Unknown □
mitoxantrone □ Yes □ No						Related □ Unrelated □ Unknown □
Corticosteroids (most recent course) □ Yes □ No						Related □ Unrelated □ Unknown □
Other MS Therapies □ Yes □ No Specify:						Related □ Unrelated □ Unknown □
Other MS Therapies □ Yes □ No Specify:						Related □ Unrelated □ Unknown □

[redacted]

Medication	Start Date	End Date	Dose/ Route	Frequency	Reason for Discontinuation	Reporter Causality[1]
Other MS Therapies □Yes □ No Specify:						Related □ Unrelated □ Unknown □

[1]**Physician's assessment of relatedness to PML**

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 immunodeficiency syndrome
CMV	Cytomegalovirus
CT	Computed tomoaraohy
DNA	Deoxyribonucleic acid

[redacted]

EDSS	Expanded disability status scale
HIV	Human immunodeficiency virus
JCV	John Cunningham Virus
MRI	Maanetic resonance imaaina
PCR	Polymerase chain reaction

[redacted]

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not applicable

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 Accord Teriflunomide is marketed, at launch and after launch, all healthcare professionals who are expected to use Accord Teriflunomide are provided with the following items:

- Summary of Product Characteristics (SmPC)
- HCP guide
- Patients 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 fetus.

- 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 Accord Healthcare by calling or contacting [to be filled in at national level with the relevant contact details] irrespective of adverse outcomes observed.

- 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 Patient Card content with the patient/legal representative regularly at each consultation at least annually during treatment;
4. To encourage patients to contact their MS physician and/or General Practitioner if they experience any of the signs and symptoms discussed in the Patient Card;

[redacted]

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 labeling information and includes the following key elements:

- 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
    - 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 including girls and their parents/ caregivers
    - To use effective contraception during and after treatment with teriflunomide
    - That your doctor will provide counselling on the potential risks to the fetus 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 or girls
    - to contact your doctor when the girl experiences 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 become pregnant:
    - To remind both patients and HCPs about the accelerated elimination procedure
- To remind patients to show the Patient Education 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 PIL thoroughly