

## 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<sup>®</sup> (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

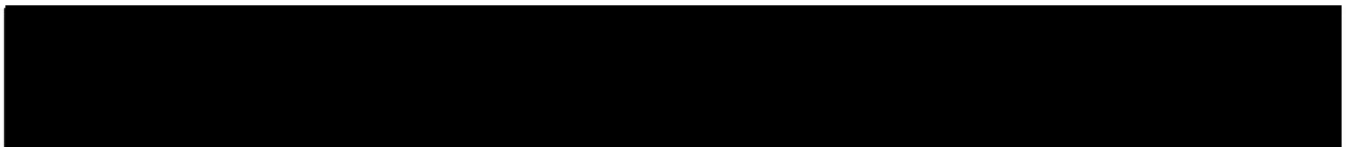
**Details of the currently approved RMP:**

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

**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

**QPPV Name:** Agata Gesiewicz



## TABLE OF CONTENT

|  |           |
|--|-----------|
| <b>LIST OF TABLES.....</b>   | <b>5</b>  |
| <b>Part I: Products Overview .....</b>   | <b>6</b>  |
| <b>Part II: Safety specification .....</b>   | <b>10</b> |
| Part II: Module SI - Epidemiology of the indication(s) and target population(s).....                                       | 10        |
| Part II: Module SII - Non-clinical part of the safety specification .....  | 10        |
| Part II: Module SIII - Clinical trial exposure.....  | 10        |
| Part II: Module SIV - Populations not studied in clinical trials.....  | 10        |
| SIV.1 Exclusion criteria in pivotal clinical studies within the development programme.....                                 | 10        |
| SIV.2 Limitations to detect adverse reactions in clinical trial development programmes.....                                | 10        |
| SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes.....      | 10        |
| Part II: Module SV - Post-authorisation experience.....  | 10        |
| SV.1 Post-authorisation exposure .....   | 10        |
| Part II: Module SVI - Additional EU requirements for the safety specification .....  | 11        |
| SVI.1 Potential for misuse for illegal purposes .....  | 11        |
| Part II: Module SVII - Identified and potential risks.....   | 12        |
| SVII.1 Identification of safety concerns in the initial RMP submission.....  | 12        |
| SVII.2 New safety concerns and reclassification with a submission of an updated RMP.....                                   | 12        |
| SVII.3 Details of important identified risks, important potential risks, and missing information.....                      | 12        |
| Part II: Module SVIII - Summary of the safety concerns.....  | 13        |
| <b>Part III: Pharmacovigilance Plan (including post-authorisation safety studies).....</b>                                 | <b>14</b> |
| III.1 Routine pharmacovigilance activities.....  | 14        |
| III.2 Additional pharmacovigilance activities .....  | 15        |
| III.3 Summary Table of additional Pharmacovigilance activities .....   | 15        |
| <b>Part IV: Plans for post-authorisation efficacy studies .....</b>  | <b>16</b> |
| <b>Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities).....</b> | <b>17</b> |
| V.1. Routine Risk Minimisation Measures.....   | 17        |
| V.2. Additional Risk Minimisation Measures .....   | 20        |
| V.3 Summary of risk minimisation measures.....   | 22        |
| <b>Part VI: Summary of the risk management plan .....</b>  | <b>28</b> |
| I. The medicine and what it is used for.....   | 28        |
| II. Risks associated with the medicine and activities to minimise or further characterise the risks .....                  | 28        |
| II.A List of important risks and missing information .....   | 29        |
| II.B Summary of important risks with additional risk minimization measures .....   | 30        |
| II.C Post-authorisation development plan.....  | 32        |

II.C.1 Studies which are conditions of the marketing authorisation..... 32

II.C.2 Other studies in post-authorisation development plan ..... 33

**Part VII: Annexes ..... 34**

Annex 1 - EudraVigilance Interface ..... 35

Annex 2 - Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme35

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan..... 35

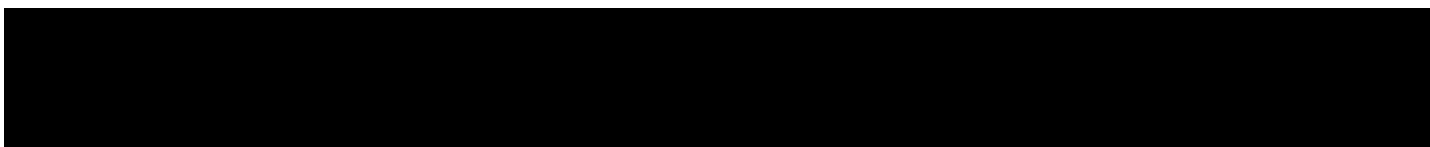
Annex 4 - Specific adverse drug reaction follow-up forms ..... 35

Annex 5 - Protocols for proposed and on-going studies in RMP part IV ..... 65

Annex 6 - Details of proposed additional risk minimisation activities (if applicable) ..... 65

Annex 7 - Other supporting data (including referenced material) ..... 68

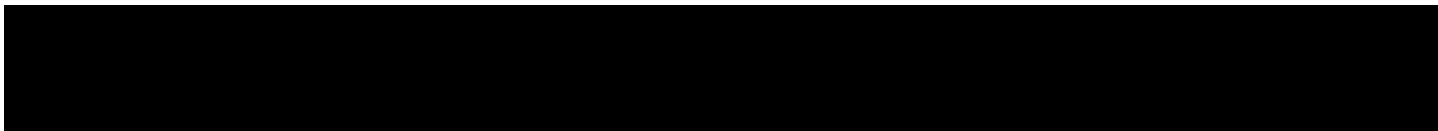
Annex 8 – Summary of changes to the risk management plan over time..... 68



**LIST OF TABLES**

Table 1: Product Overview ..... 6

Table 2: Summary of safety concerns ..... 13



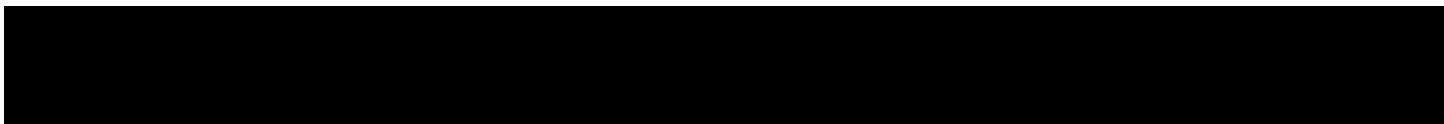
## Part I: Products Overview

Table 1: Product Overview

|   |   |
|---|---|
| <b>Active substance</b><br>(INN or common name)           | Teriflunomide   |
| <b>Pharmacotherapeutic group(s) (ATC Code)</b>            | Immunosuppressants, Selective immunosuppressants, ATC Code: L04AA31   |
| <b>Marketing Authorisation Holder</b>                     | Accord Healthcare S.L.U., Spain   |
| <b>Medicinal products to which this RMP refers</b>        | 2   |
| <b>Invented names in the European Economic Area (EEA)</b> | Teriflunomide Accord 7 mg film coated tablets<br>Teriflunomide Accord 14 mg film-coated tablets   |
| <b>Marketing authorisation procedure</b>                  | Centralised procedure (EMEA/H/C/H0005960)   |
| <b>Brief description of the product</b>                   | <p><i>Chemical class:</i></p> <p>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.</p> <p><u>Summary of mode of action:</u></p> <p>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</p> |

|   |   |
|---|---|
|   | <p>fully understood, but this is mediated by a reduced number of T-lymphocytes.</p> <p><u>Important information about its composition</u></p> <p><b><i>Teriflunomide Accord 7 mg film coated tablets</i></b></p> <p>Each film coated tablet contains 7 mg of teriflunomide.</p> <p>Excipient with known effect:</p> <p>Each tablet contains 79 mg of lactose (as monohydrate).</p> <p><b><i>Teriflunomide Accord 14 mg film coated tablets</i></b></p> <p>Each film-coated tablet contains 14 mg of teriflunomide.</p> <p>Excipient with known effect:</p> <p>Each tablet contains 72 mg of lactose (as monohydrate).</p> |
| <b>Hyperlink to the Product Information</b> | Refer to <a href="#">Module 1.3.1</a> for SmPC and PIL  |
| <b>Indications in the EEA</b>               | Teriflunomide Accord is indicated for the treatment of adult patients and paediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS).   |
| <b>Dosage in the EEA</b>                    | <p><i>Current</i></p> <p><u>Teriflunomide Accord 14 mg film coated tablets</u></p> <p><b>Posology:</b></p> <p><b>Adults</b></p> <p>In adults, the recommended dose of teriflunomide is 14 mg once daily.</p> <p><i>Paediatric population (10 years and older)</i></p> <p>In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:</p> <p>-Paediatric patients with body weight &gt;40 kg: 14 mg once daily.</p>  |

|  |   |
|--|---|
|  | <p>-Paediatric patients with body weight <math>\leq 40</math> kg: 7 mg once daily.</p> <p>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 <math>\leq 40</math> 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.</p> <p><u>Method of administration:</u></p> <p>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.</p> |
|  | <p><i>Proposed</i></p> <p><u>Teriflunomide Accord 7 mg film coated tablets</u></p> <p><b><u>Posology:</u></b></p> <p><b>Adults</b></p> <p>In adults, the recommended dose of teriflunomide is 14 mg once daily.</p> <p><i>Paediatric population (10 years and older)</i></p> <p>In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:</p> <p>-Paediatric patients with body weight <math>&gt;40</math> kg: 14 mg once daily.</p> <p>-Paediatric patients with body weight <math>\leq 40</math> kg: 7 mg once daily.</p> <p>Paediatric patients who reach a stable body weight above 40 kg should be switched to 14 mg once daily.</p> <p><u>Method of administration:</u></p>                                 |





|  |   |
|--|---|
|  | 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. |
| <b>Pharmaceutical forms and strengths</b>                          | Current<br>Film-coated tablets<br>14 mg   |
|  | Proposed<br>Film-coated tablets<br>7 mg   |
| <b>Will the product be subject to additional monitoring in EU?</b> | 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**

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.

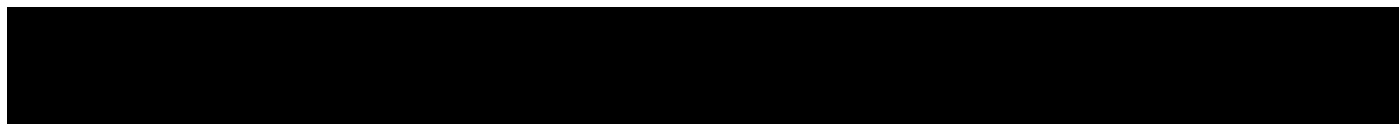
**SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes**

Not applicable.

**Part II: Module SV - Post-authorisation experience**

**SV.1 Post-authorisation exposure**

Not applicable.



**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

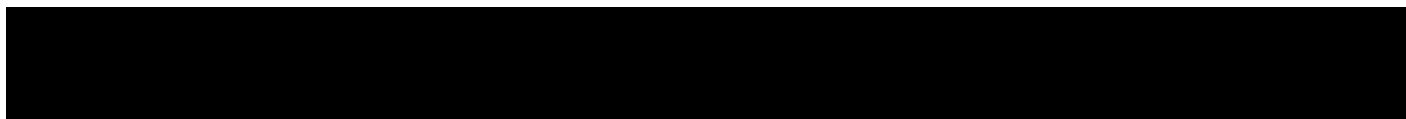
**SVII.3 Details of important identified risks, important potential risks, and missing information**

**SVII.3.1. Presentation of important identified risks and important potential risks**

Not Applicable

**SVII.3.2. Presentation of the missing information**

Not Applicable



**Part II: Module SVIII - Summary of the safety concerns**

**Table 2: Summary of safety concerns**

|                            |  |
|----------------------------|--|
| Important identified risks | <ul style="list-style-type: none"><li>• Hepatic effects</li><li>• Hypertension</li><li>• Hematologic effects</li><li>• Infections</li><li>• Acute Pancreatitis</li></ul> |
| Important potential risks  | <ul style="list-style-type: none"><li>• Teratogenicity</li><li>• Serious opportunistic infections, including PML</li></ul>   |
| Missing Information        | <ul style="list-style-type: none"><li>• None</li></ul>   |

**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:
  - o Overall patient exposure data for the respective product expressed as patient-years based on World Health Organization (WHO) defined daily dose of 14 mg.
  - o 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)
  - o 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.

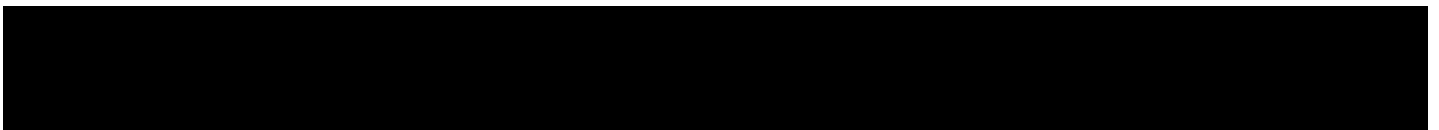
Purpose: For collection and reporting of safety information while use of Teriflunomide.  
The data and conclusions included in this report are confidential and proprietary information of Marketing Authorisation Holder

**III.2 Additional pharmacovigilance activities**

None proposed for generic MAH.

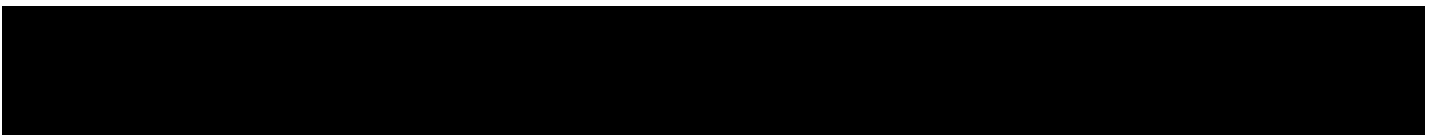
**III.3 Summary Table of additional Pharmacovigilance activities**

Not Applicable.



**Part IV: Plans for post-authorisation efficacy studies**

Not applicable





## 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   |
|-----------------------------------|--|
| <b>Important Identified Risks</b> |  |
| Hepatic Effects                   | <p><i>Routine risk communication</i></p> <p>SmPC sections 4.4, 4.3 and 4.8</p> <p>PL section 2 and 4</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <ul style="list-style-type: none"> <li>- Information to perform/monitor liver test during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4.</li> </ul> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>the prescription only status of the product.</p> |
| Hypertension                      | <p><i>Routine risk communication</i></p> <p>SmPC sections 4.4 and 4.8</p> <p>PIL section 2 and 4</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <ul style="list-style-type: none"> <li>- Information to monitor blood pressure before and during the treatment with teriflunomide is included in SmPC section 4.4 and PIL section 2.</li> </ul> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p>  |

| Safety concern       | Routine risk minimisation activities  |
|----------------------|---|
|                      | the prescription only status of the product.  |
| Haematologic effects | <p><i>Routine risk communication</i></p> <p>SmPC sections 4.4, 4.3 and 4.8</p> <p>PIL section 4</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <ul style="list-style-type: none"> <li>- 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.</li> </ul> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>the prescription only status of the product.</p> |
| Infections           | <p><i>Routine risk communication</i></p> <p>SmPC sections 4.4, 4.3 and 4.8</p> <p>PIL section 2 and 4</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <ul style="list-style-type: none"> <li>- Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4.</li> </ul> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>the prescription only status of the product.</p>         |
| Acute Pancreatitis   | <p><i>Routine risk communication</i></p> <p>SmPC section 4.4 and 4.8</p> <p>PIL section 2 and 4</p>   |

| Safety concern   | Routine risk minimisation activities  |
|--|---|
|  | <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <ul style="list-style-type: none"> <li>- 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.</li> </ul> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>the prescription only status of the product.</p> |
| <b>Important Potential Risks</b>                       |   |
| <p>Teratogenicity</p>                                  | <p><i>Routine risk communication</i></p> <p>SmPC section 4.3 and 4.6</p> <p>PIL section 2</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p> <ul style="list-style-type: none"> <li>- Information on contraception recommendations and treatment discontinuation is included in SmPC section 4.6</li> </ul> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>the prescription only status of the product.</p>     |
| <p>Serious opportunistic infections, including PML</p> | <p><i>Routine risk communication</i></p> <p>SmPC section 4.3, 4.4 and 4.8</p> <p>PIL section 2 and 4</p> <p><i>Routine risk minimisation activities recommending specific clinical measures to address the risk:</i></p>  |



| Safety concern | Routine risk minimisation activities  |
|----------------|---|
|                | <ul style="list-style-type: none"> <li>- Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4.</li> </ul> <p><i>Other routine risk minimisation measures beyond the Product Information:</i></p> <p>the prescription only status of the product.</p> |

**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

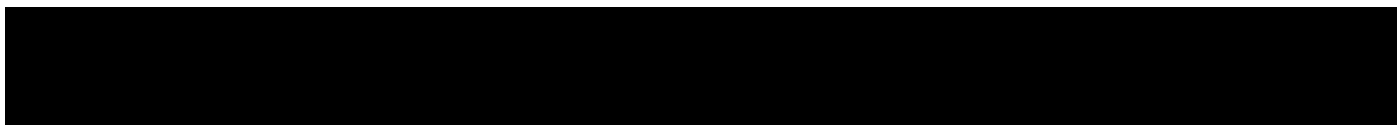
Proposed additional risk minimisation measures are listed below and are summarised in Annexure-6.

**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.



**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:**

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.

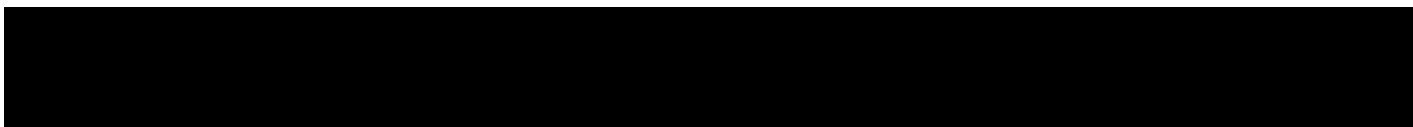
**V.3. Summary of risk minimisation measures**

**Table 4: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern**

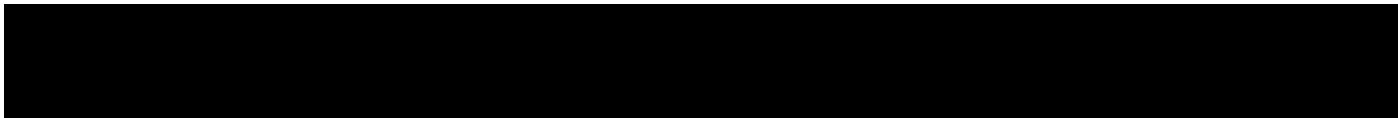
| Safety concern                    | Risk minimisation measures   | Pharmacovigilance activities  |
|-----------------------------------|--|---|
| <b>Important Identified Risks</b> |  |   |
| Hepatic Effects                   | <u>Routine risk minimisation measures:</u> <ul style="list-style-type: none"> <li>- SmPC sections 4.4, 4.3 and 4.8</li> <li>- PL section 2 and 4</li> <li>- Information to perform/monitor liver test during the treatment with teriflunomide and treatment discontinuation information</li> </ul> | <u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u><br>Specific adverse reaction follow-up questionnaire for ‘Hepatic effects.’<br><br><u>Additional pharmacovigilance activities:</u><br>None |



| Safety concern       | Risk minimisation measures   | Pharmacovigilance activities   |
|----------------------|--|--|
|                      | <p>is included in SmPC section 4.4.</p> <ul style="list-style-type: none"> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u></p> <p>Educational Materials (HCP guide and Patient card)</p>  |  |
| Hypertension         | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC sections 4.4 and 4.8</li> <li>- PIL section 2 and 4</li> <li>- Information to monitor blood pressure before and during the treatment with teriflunomide is included in SmPC section 4.4 and PIL section 2.</li> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u></p> <p>Educational Materials (HCP guide and Patient card)</p> | <p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>No Specific adverse reaction follow-up questionnaire for ‘Hypertension’.</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>None</p> |
| Haematologic effects | <p><u>Routine risk minimisation measures:</u></p>  | <p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p>  |



| Safety concern | Risk minimisation measures  | Pharmacovigilance activities   |
|----------------|---|--|
|                | <ul style="list-style-type: none"> <li>- SmPC sections 4.4, 4.3 and 4.8</li> <li>- PIL section 4</li> <li>- 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.</li> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u><br/>Educational Materials (HCP guide and Patient card)</p> | <p>No Specific adverse reaction follow-up questionnaire for ‘Haematologic effects’.</p> <p><u>Additional pharmacovigilance activities:</u><br/>None</p>  |
| Infections     | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC sections 4.4, 4.3 and 4.8</li> <li>- PIL section 2 and 4</li> <li>- Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4.</li> </ul>   | <p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>No Specific adverse reaction follow-up questionnaire for ‘Infection’.</p> <p><u>Additional pharmacovigilance activities:</u><br/>None</p> |

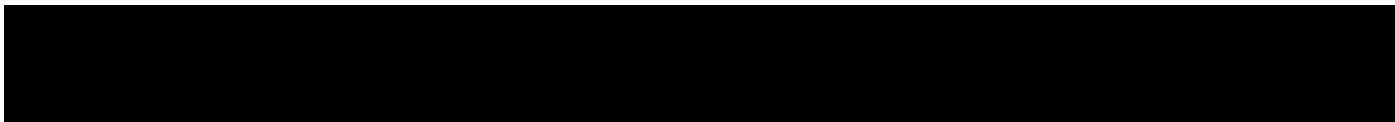




| Safety concern                   | Risk minimisation measures   | Pharmacovigilance activities  |
|----------------------------------|--|---|
|                                  | <p>- The prescription only status</p> <p><u>Additional risk minimisation measures:</u></p> <p>Educational Materials (HCP guide and Patient card)</p>   |   |
| Acute Pancreatitis               | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC section 4.4 and 4.8</li> <li>- PIL section 2 and 4</li> <li>- 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.</li> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u></p> <p>None</p> | <p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p> <p>Specific adverse reaction follow-up questionnaire for ‘Acute Pancreatitis’.</p> <p><u>Additional pharmacovigilance activities:</u></p> <p>None</p> |
| <b>Important Potential Risks</b> |  |   |
| Teratogenicity                   | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC section 4.3 and 4.6</li> </ul>   | <p><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u></p>   |

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

| <b>Safety concern</b> | <b>Risk minimisation measures</b>                   | <b>Pharmacovigilance activities</b> |
|-----------------------|---|-------------------------------------|
|                       | 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:

- 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.

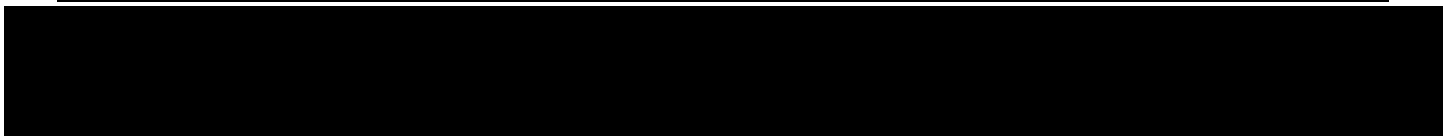
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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);

|                                   |  |
|-----------------------------------|--|
| <p>Important identified risks</p> | <ul style="list-style-type: none"> <li>• Hepatic effects</li> <li>• Hypertension</li> <li>• Hematologic effects</li> </ul> |
|-----------------------------------|--|



|                           |   |
|---------------------------|---|
|                           | <ul style="list-style-type: none"> <li>• Infections</li> <li>• Acute Pancreatitis</li> </ul>                                  |
| Important potential risks | <ul style="list-style-type: none"> <li>• Teratogenicity</li> <li>• Serious opportunistic infections, including PML</li> </ul> |
| Missing Information       | <ul style="list-style-type: none"> <li>• None</li> </ul>  |

**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).

| <b>Important Identified Risks: Hepatic Effects</b> |   |
|--|---|
| Risk minimisation measures                         | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC sections 4.4, 4.3 and 4.8</li> <li>- PL section 2 and 4</li> <li>- Information to perform/monitor liver test during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4.</li> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u></p> <p>Educational Materials (HCP guide and Patient card)</p> |
| <b>Important Identified Risks: Hypertension</b>    |   |
| Risk minimisation measures                         | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC sections 4.4 and 4.8</li> <li>- PIL section 2 and 4</li> </ul>  |

|  |   |
|--|---|
|  | <ul style="list-style-type: none"> <li>- Information to monitor blood pressure before and during the treatment with teriflunomide is included in SmPC section 4.4 and PIL section 2.</li> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u><br/>Educational Materials (HCP guide and patient card)</p> |
|--|---|

**Important Identified Risks: Haematologic effects**

|                                   |   |
|-----------------------------------|---|
| <p>Risk minimisation measures</p> | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC sections 4.4, 4.3 and 4.8</li> <li>- PIL section 4</li> <li>- 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.</li> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u><br/>Educational Materials (HCP guide and patient card)</p> |
|-----------------------------------|---|

**Important Identified Risks: Infections**

|                                   |   |
|-----------------------------------|---|
| <p>Risk minimisation measures</p> | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC sections 4.4, 4.3 and 4.8</li> <li>- PIL section 2 and 4</li> <li>- Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4.</li> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u><br/>Educational Materials (HCP guide and patient card)</p> |
|-----------------------------------|---|



| <b>Important Potential Risks: Teratogenicity</b>                                  |   |
|---|---|
| <p>Risk minimisation measures</p>   | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC section 4.3 and 4.6</li> <li>- PIL section 2</li> <li>- Information on contraception recommendations and treatment discontinuation is included in SmPC section 4.6</li> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u></p> <p>Educational Materials (HCP guide and patient card)</p>  |
| <b>Important Potential Risks: Serious opportunistic infections, including PML</b> |   |
| <p>Risk minimisation measures</p>   | <p><u>Routine risk minimisation measures:</u></p> <ul style="list-style-type: none"> <li>- SmPC section 4.3, 4.4 and 4.8</li> <li>- PIL section 2 and 4</li> <li>- Information to monitor symptoms of infections during the treatment with teriflunomide and treatment discontinuation information is included in SmPC section 4.4.</li> <li>- The prescription only status</li> </ul> <p><u>Additional risk minimisation measures:</u></p> <p>Educational Materials (HCP guide and patient card)</p> |

**II.C Post-authorisation development plan**

**II.C.1 Studies which are conditions of the marketing authorisation**

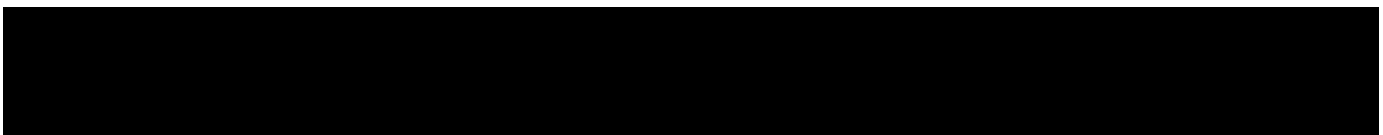
There are no studies required for Teriflunomide Accord 7 mg and 14 mg film-coated tablets.





**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.



**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?<br>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:<br>1)<br>2) | Date event stopped:<br>1)<br>2) |
|---------------------------------|---------------------------------|

|  |   |
|--|---|
| Please describe the event and details of any treatment given or investigation performed. | Outcome:  |
|  | <input type="radio"/> Recovered<br><input type="radio"/> Not Recovered<br><input type="radio"/> Recovered with Sequel<br><input type="radio"/> Recovering<br><input type="radio"/> Fatal<br><input type="radio"/> Unknown |

| Documentation of the Adverse event                      |                               |            |
|---|-------------------------------|------------|
| Main Diagnosis  |                               | Start Date |
| <i>Are the following signs and symptoms associated?</i> | <i>tick box if applicable</i> |            |
| <i>Asthenia</i>   | <input type="checkbox"/>      |            |
| <i>Fever</i>  | <input type="checkbox"/>      |            |
| <i>Pruritus</i>   | <input type="checkbox"/>      |            |
| <i>Jaundice</i>   | <input type="checkbox"/>      |            |
| <i>Joint pain</i>                                       | <input type="checkbox"/>      |            |
| <i>Abdominal pain</i>                                   | <input type="checkbox"/>      |            |
| <i>Vomiting</i>   | <input type="checkbox"/>      |            |
| <i>Skin eruption</i>                                    | <input type="checkbox"/>      | Type:      |
| <i>Purpura</i>  | <input type="checkbox"/>      |            |



## Risk Management Plan

## Teriflunomide RMP Version 3.0

|   |                          |  |
|---|--------------------------|--|
| Hepatomegaly                                    | <input type="checkbox"/> |  |
| Splenomegaly                                    | <input type="checkbox"/> |  |
| Lymph nodes                                     | <input type="checkbox"/> |  |
| Ascites   | <input type="checkbox"/> |  |
| Asterixis                                       | <input type="checkbox"/> |  |
| Coma  | <input type="checkbox"/> |  |
| Malaise (with or without loss of consciousness) | <input type="checkbox"/> |  |
| INR > 2 or prothrombin T. < 50%                 | <input type="checkbox"/> |  |
| Dizziness                                       | <input type="checkbox"/> |  |
| Hypotension                                     | <input type="checkbox"/> |  |
| Arrhythmia                                      | <input type="checkbox"/> |  |

### SERIOUSNESS OF ADVERSE EVENT(S):

|  |   |  |
|--|---|--|
| Do you consider the event to be serious?                 | <input type="radio"/> Yes                   | <input type="radio"/> No                     |
| If Yes, Reason for Seriousness:                          |   |  |
| <input type="radio"/> Patient Died                       | <input type="radio"/> Life Threatening      | <input type="radio"/> Congenital Abnormality |
| <input type="radio"/> Involved/Prolonged Hospitalisation | <input type="radio"/> Disability/Incapacity | <input type="radio"/> Medically Significant  |

### ACTION TAKEN WITH SUSPECTED DRUGS:

|                                      |                                      |                                      |  |
|--------------------------------------|--------------------------------------|--------------------------------------|--|
| <input type="radio"/> Dose Decreased | <input type="radio"/> Dose Increased | <input type="radio"/> Drug withdrawn | <input type="radio"/> Dose not changed |
| <input type="radio"/> 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           | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Hepato-biliary                    | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Allergic disease                  | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Allergy to drug                   | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Auto-Immune                       | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Heart/vascular disease            | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Respiratory disease               | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Cancer                            | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Surgical/Dental operation         | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Alcohol consumption               | <input type="checkbox"/> | <input type="checkbox"/> | Number of drinks per day                |
| Acupuncture                       | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Occupational/toxic agent exposure | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Travels to Africa                 | <input type="checkbox"/> | <input type="checkbox"/> |   |
| Travels to Asia                   | <input type="checkbox"/> | <input type="checkbox"/> |   |

**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

|                        |                          |                          |  |
|------------------------|--------------------------|--------------------------|--|
| Intravenous drug abuse | <input type="checkbox"/> | <input type="checkbox"/> |  |
| Other                  | <input type="checkbox"/> | <input type="checkbox"/> |  |

|   |                             |                              |              |
|---|-----------------------------|------------------------------|--------------|
| <b>CENTRAL LABORATORY DATA performed:</b> | NO <input type="checkbox"/> | YES <input type="checkbox"/> | <b>Date:</b> |
| <b>LOCAL LABORATORY DATA performed:</b>   | NO <input type="checkbox"/> | YES <input type="checkbox"/> | <b>Date:</b> |

| Additional TEST DATA (to be performed at local level) |                          |                          |                          |                            |           |
|---|--------------------------|--------------------------|--------------------------|----------------------------|-----------|
|   | Not Tested               | Negative result          | Positive result          | Date of test<br>MM/DD/YYYY | Titration |
| HBaAg   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti-HbsAb  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti-HbcAb  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti-Hbc/IgM Ab                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti-HAV/IgM Ab                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti-HCVAb  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| PCR-C   | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti-CMV IgM Ab                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti-EBVAb  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti-nuclear Ab                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Antinative DNA Ab                                     | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti smooth muscle Ab                                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |
| Anti mitochondrial AB                                 | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                            |           |

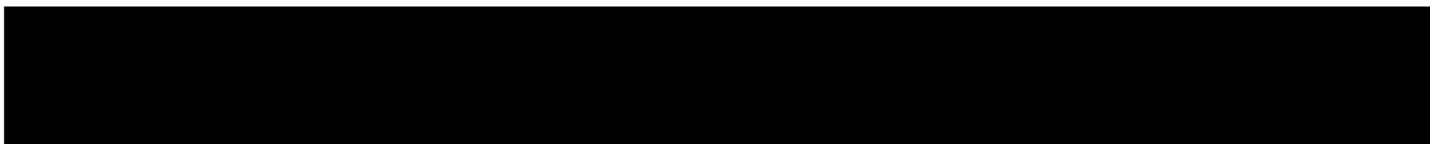
| OTHER INVESTIGATIONS |        |         |
|----------------------|--------|---------|
| Date DD/MM/YYYY      | NATURE | RESULTS |
|                      |        |         |
|                      |        |         |
|                      |        |         |

|  |                        |
|--|------------------------|
| <b>LIVER BIOPSY</b> NO <input type="checkbox"/> YES <input type="checkbox"/> | <b>DATE DD/MM/YYYY</b> |
| <i>If yes is ticked a report needs to be attached</i>                        |                        |

| LIVER IMAGING <i>If yes is ticked a report needs to be attached</i>      | DATE DD/MM/YYYY | BRIEF RESULTS |
|--|-----------------|---------------|
| ULTRASONOGRAPHY NO <input type="checkbox"/> YES <input type="checkbox"/> |                 |               |
| CT SCAN NO <input type="checkbox"/> YES <input type="checkbox"/>         |                 |               |
| MRI NO <input type="checkbox"/> YES <input type="checkbox"/>             |                 |               |

| 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 |
|------------------|------|-----------------|--------|-----------------|
|                  |      |                 |        |                 |
|                  |      |                 |        |                 |



|  |  |  |  |  |
|--|--|--|--|--|
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|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

**REPORTER DETAILS:**

|  |            |           |      |
|--|------------|-----------|------|
| Title, Name & Surname                  | Occupation | Signature | Date |
| Postal Address:<br><br>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?<br><b>Yes / No</b> | 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):**

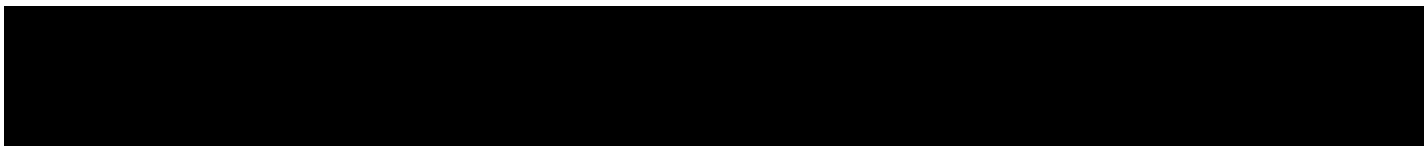
|                                 |                                 |
|---------------------------------|---------------------------------|
| Date event started:<br>1)<br>2) | Date event stopped:<br>1)<br>2) |
|---------------------------------|---------------------------------|

|  |  |
|--|--|
| Please describe the event and details of any treatment given or investigation performed. | <b>Outcome:</b><br><input type="radio"/> Recovered<br><input type="radio"/> Not Recovered<br><input type="radio"/> Recovered with Sequel<br><input type="radio"/> Recovering<br><input type="radio"/> Fatal<br><input type="radio"/> Unknown |
|--|--|



**SYMPTOMS:**

| Symptoms   | Date of Onset | Description | Outcome  |
|--|---------------|-------------|--|
| Abdominal Pain<br><input type="checkbox"/> Yes <input type="checkbox"/> No |               |             | <input type="checkbox"/> Recovered<br><input type="checkbox"/> Recovering<br><input type="checkbox"/> Continuing<br><input type="checkbox"/> Not Recovered<br><input type="checkbox"/> Recovered with Sequelae<br><input type="checkbox"/> Fatal |
| Malaise<br><input type="checkbox"/> Yes <input type="checkbox"/> No        |               |             | <input type="checkbox"/> Recovered<br><input type="checkbox"/> Recovering<br><input type="checkbox"/> Continuing<br><input type="checkbox"/> Not Recovered<br><input type="checkbox"/> Recovered with Sequelae<br><input type="checkbox"/> Fatal |
| Nausea<br><input type="checkbox"/> Yes <input type="checkbox"/> No         |               |             | <input type="checkbox"/> Recovered<br><input type="checkbox"/> Recovering<br><input type="checkbox"/> Continuing<br><input type="checkbox"/> Not Recovered<br><input type="checkbox"/> Recovered with Sequelae<br><input type="checkbox"/> Fatal |
| Vomiting<br><input type="checkbox"/> Yes <input type="checkbox"/> No       |               |             | <input type="checkbox"/> Recovered<br><input type="checkbox"/> Recovering<br><input type="checkbox"/> Continuing<br><input type="checkbox"/> Not Recovered<br><input type="checkbox"/> Recovered with Sequelae<br><input type="checkbox"/> Fatal |
| Jaundice<br><input type="checkbox"/> Yes <input type="checkbox"/> No       |               |             | <input type="checkbox"/> Recovered<br><input type="checkbox"/> Recovering<br><input type="checkbox"/> Continuing<br><input type="checkbox"/> Not Recovered<br><input type="checkbox"/> Recovered with Sequelae<br><input type="checkbox"/> Fatal |
| Fever<br><input type="checkbox"/> Yes <input type="checkbox"/> No          |               |             | <input type="checkbox"/> Recovered<br><input type="checkbox"/> Recovering<br><input type="checkbox"/> Continuing<br><input type="checkbox"/> Not Recovered<br><input type="checkbox"/> Recovered with Sequelae<br><input type="checkbox"/> Fatal |



**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

|  |  |  |  |
|--|--|--|--|
| Weight Loss<br><input type="checkbox"/> Yes <input type="checkbox"/> No        |  |  | <input type="checkbox"/> Recovered<br><input type="checkbox"/> Recovering<br><input type="checkbox"/> Continuing<br><input type="checkbox"/> Not Recovered<br><input type="checkbox"/> Recovered with Sequelae<br><input type="checkbox"/> Fatal |
| Abdominal bleeding<br><input type="checkbox"/> Yes <input type="checkbox"/> No |  |  | <input type="checkbox"/> Recovered<br><input type="checkbox"/> Recovering<br><input type="checkbox"/> Continuing<br><input type="checkbox"/> Not Recovered<br><input type="checkbox"/> Recovered with Sequelae<br><input type="checkbox"/> 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?

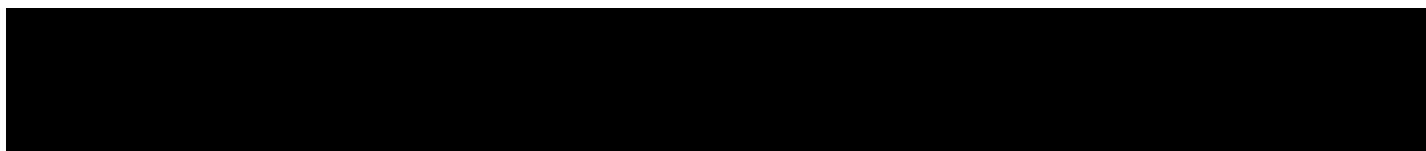
Yes, please provide details below       No

**SERIOUSNESS OF ADVERSE EVENT(S):**

|   |  |   |
|---|--|---|
| Do you consider the event to be serious?<br><br>If Yes, Reason for Seriousness:<br><input type="radio"/> Patient Died<br><input type="radio"/> Involved/Prolonged Hospitalisation | <input type="radio"/> Yes<br><br><input type="radio"/> Life Threatening<br><input type="radio"/> Disability/Incapacity | <input type="radio"/> No<br><br><input type="radio"/> Congenital Abnormality<br><input type="radio"/> Medically Significant |
|---|--|---|

**ACTION TAKEN WITH SUSPECTED DRUGS:**

|   |                                      |                                      |  |
|---|--------------------------------------|--------------------------------------|--|
| <input type="radio"/> Dose Decreased  | <input type="radio"/> Dose Increased | <input type="radio"/> Drug withdrawn | <input type="radio"/> Dose not changed |
| <input type="radio"/> Unknown   |                                      |                                      |  |
| Was Teriflunomide re-administered? <input type="checkbox"/> Yes <input type="checkbox"/> No   |                                      |                                      |  |
| Did the patient experience any adverse event, upon re-administration of Teriflunomide? <input type="checkbox"/> Yes <input type="checkbox"/> No |                                      |                                      |  |





**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

**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<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                           |                |                          |
| Cholelithiasis/<br>choledocholithiasis<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No |                |                          |
| Hepatitis<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                              |                |                          |
| Abdominal tumor<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                        |                |                          |
| Abdominal surgery<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                      |                |                          |
| Abdominal trauma<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                       |                |                          |
| Hypertriglyceridemia<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                   |                |                          |
| Hyperparathyroidism<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                    |                |                          |
| Hypercalcemia<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                          |                |                          |
| Human immunodeficiency<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                 |                |                          |
| Post-ERCP<br><input type="checkbox"/> Yes<br><input type="checkbox"/> No                              |                |                          |
| Malignancy<br>Specify: <input type="checkbox"/> Yes<br><input type="checkbox"/> No                    |                |                          |
| Other suspected disorders<br>Specify: <input type="checkbox"/> Yes<br><input type="checkbox"/> No     |                |                          |

**SOCIAL HISTORY:**

Alcohol consumption (Drinks/day) \_\_\_\_\_

Tobacco user:  Yes  No \_\_\_\_\_ pack years



**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

**MEDICATION HISTORY:**

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

| <b>Medication</b>   | <b>Start Date</b> | <b>End Date</b> | <b>Dose</b> | <b>Frequency</b> | <b>Reason for Discontinuation</b> | <b>Investigator Causality<sup>1</sup></b>  |
|---|-------------------|-----------------|-------------|------------------|-----------------------------------|--|
| Leflunomide <input type="checkbox"/> Yes<br><input type="checkbox"/> No                 |                   |                 |             |                  |                                   | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Azathioprine <input type="checkbox"/> Yes<br><input type="checkbox"/> No                |                   |                 |             |                  |                                   | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Valproic Acid <input type="checkbox"/> Yes<br><input type="checkbox"/> No               |                   |                 |             |                  |                                   | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Estrogen <input type="checkbox"/> Yes<br><input type="checkbox"/> No                    |                   |                 |             |                  |                                   | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Corticosteroids <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br>Specify: |                   |                 |             |                  |                                   | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Statins: <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br>Specify:_____   |                   |                 |             |                  |                                   | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |

<sup>1</sup> Physician assessment of relatedness to Pancreatitis

**INVESTIGATIONS:**

**Laboratory tests:**

| <b>Investigation</b>   | <b>Date</b> | <b>Baseline Values</b> | <b>Result</b> | <b>Normal High / Low</b> |
|--|-------------|------------------------|---------------|--------------------------|
| Red blood cell count <input type="checkbox"/> Yes<br><input type="checkbox"/> No           |             |                        |               |                          |
| WBC count <input type="checkbox"/> Yes<br><input type="checkbox"/> No                      |             |                        |               |                          |
| Blood urea nitrogen <input type="checkbox"/> Yes<br><input type="checkbox"/> No            |             |                        |               |                          |
| Blood glucose <input type="checkbox"/> Yes<br><input type="checkbox"/> No                  |             |                        |               |                          |
| Amylase <input type="checkbox"/> Yes<br><input type="checkbox"/> No                        |             |                        |               |                          |
| Lipase <input type="checkbox"/> Yes<br><input type="checkbox"/> No                         |             |                        |               |                          |
| Gamma GT <input type="checkbox"/> Yes<br><input type="checkbox"/> No                       |             |                        |               |                          |
| Tripsinogen Activation Peptide <input type="checkbox"/> Yes<br><input type="checkbox"/> No |             |                        |               |                          |

**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

| Investigation  | Date | Baseline Values | Result | Normal High / Low |
|--|------|-----------------|--------|-------------------|
| Alanine aminotransferase (ALT) <input type="checkbox"/> Yes<br><input type="checkbox"/> No   |      |                 |        |                   |
| Aspartate aminotransferase (AST) <input type="checkbox"/> Yes<br><input type="checkbox"/> No |      |                 |        |                   |
| Alkaline phosphatase <input type="checkbox"/> Yes<br><input type="checkbox"/> No             |      |                 |        |                   |
| Bilirubin <input type="checkbox"/> Yes<br><input type="checkbox"/> No                        |      |                 |        |                   |
| Calcium <input type="checkbox"/> Yes<br><input type="checkbox"/> No                          |      |                 |        |                   |

| Other Investigation | Date | Baseline Values | Result | Normal High / Low |
|---------------------|------|-----------------|--------|-------------------|
|                     |      |                 |        |                   |
|                     |      |                 |        |                   |
|                     |      |                 |        |                   |

**Imaging studies:**

| Investigation   | Date | Results |
|---|------|---------|
| Abdominal ultrasound <input type="checkbox"/> Yes<br><input type="checkbox"/> No                                |      |         |
| Contrast enhanced abdominal CT <input type="checkbox"/> Yes<br><input type="checkbox"/> No                      |      |         |
| Magnetic resonance imaging (MRI) <input type="checkbox"/> Yes<br><input type="checkbox"/> No                    |      |         |
| Endoscopic Retrograde Cholangiopancreatogram (ERCP) <input type="checkbox"/> Yes<br><input type="checkbox"/> No |      |         |
| Magnetic Resonance Cholangiopancreatogram (MRCP) <input type="checkbox"/> Yes<br><input type="checkbox"/> No    |      |         |

**MANAGEMENT:**

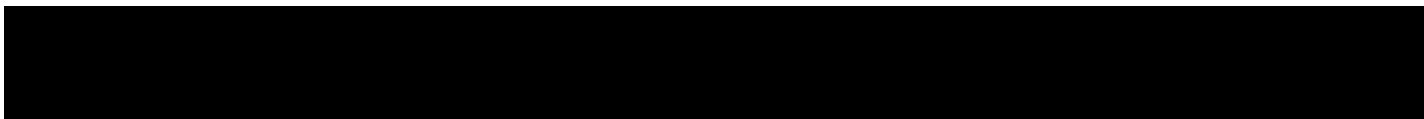
**Causal relationship**

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 |
|------------|------|-----------|-------------------------|------------|----------|
|            |      |           |                         |            |          |
|            |      |           |                         |            |          |
|            |      |           |                         |            |          |



**REPORTER DETAILS:**

|  |            |           |      |
|--|------------|-----------|------|
| Title, Name & Surname                  | Occupation | Signature | Date |
| Postal Address:<br><br>Postcode: ..... | Email:     | Tel No.   |      |

**ABBREVIATIONS**

|      |  |
|------|--|
| ALT  | Alanine aminotransferase                     |
| AST  | Aspartate aminotransferase                   |
| ERCP | Endoscopic retrograde cholangiopancreatogram |
| 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**<br>ALCOHOL: ____ DRINKS PER DAY<br>SUBSTANCE ABUSE: (specify) _____<br>HYPERTENSION: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK<br>DIABETES: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK<br>EPILEPSY: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK<br>IF YES, SPECIFY THE TYPE: ....<br>PSYCHIATRIC ILLNESS: <input type="checkbox"/> NO <input type="checkbox"/> YES<br>IF YES, SPECIFY: .....<br>SEROLOGY:<br>HIV: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK<br>HEPATITIS: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK<br>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**<br>ALCOHOL: ____ DRINKS PER DAY<br>SUBSTANCE ABUSE: (specify) _____<br>HYPERTENSION: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK  |



**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

|  |  |  |  |  |   |
|--|--|--|--|--|---|
|  |  |  |  |  | DIABETES: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK<br>EPILEPSY: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK<br>IF YES, SPECIFY THE TYPE: ....<br>PSYCHIATRIC ILLNESS: <input type="checkbox"/> NO <input type="checkbox"/> YES<br>IF YES, SPECIFY: ..... |
|  |  |  |  |  | SEROLOGY:<br>HIV: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK<br>HEPATITIS: <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> 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):

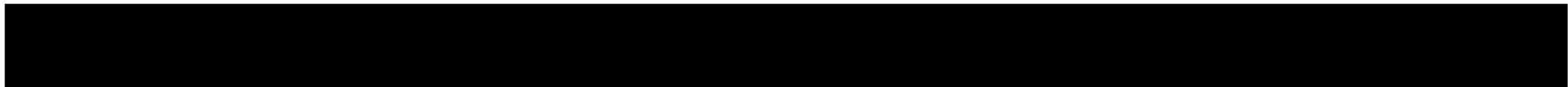
\*Include information on race, ethnicity, consanguinity or occupation if you consider it would contribute significantly to the investigation and evaluation of certain adverse findings in the pregnancy or its outcome or on the health of the fetus/child. Per local privacy law.

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

**SPECIFIC TO THE PREGNANCY PREVENTION PROGRAMME, IF APPLICABLE (e.g. valproate..)**

|  |                             |                              |                               |                              |
|--|-----------------------------|------------------------------|-------------------------------|------------------------------|
| WAS THERE A NEGATIVE PREGNANCY TEST AT TREATMENT INITIATION? | <input type="checkbox"/> NO | <input type="checkbox"/> YES | <input type="checkbox"/> UNK. | <input type="checkbox"/> NA* |
| WAS THE PATIENT GUIDE RECEIVED?                              | <input type="checkbox"/> NO | <input type="checkbox"/> YES | <input type="checkbox"/> UNK  | <input type="checkbox"/> NA* |
| WAS THE PATIENT CARD RECEIVED?                               | <input type="checkbox"/> NO | <input type="checkbox"/> YES | <input type="checkbox"/> UNK. | <input type="checkbox"/> NA* |
| WAS AN ANNUAL REVIEW COMPLETED BY A SPECIALIST?              | <input type="checkbox"/> NO | <input type="checkbox"/> YES | <input type="checkbox"/> UNK. | <input type="checkbox"/> NA* |
| WAS THE ANNUAL RISK ACKNOWLEDGMENT FORM SIGNED?              | <input type="checkbox"/> NO | <input type="checkbox"/> YES | <input type="checkbox"/> UNK. | <input type="checkbox"/> NA* |

\*Not applicable



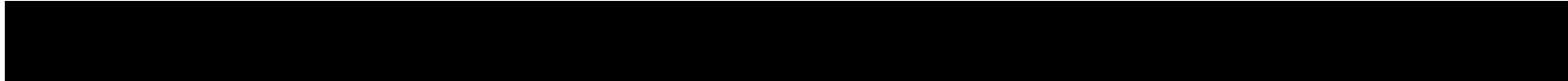


**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

**PREGNANCY INFORMATION**

|   |  |
|---|--|
| <p>DATE OF LAST MENSTRUAL PERIOD (LMP)<br/>LMP: __-__-__(DD-MMM-YY)</p> <p>ESTIMATED DATE OF DELIVERY (EDD)<br/>EDD: __-__-__(DD-MMM-YY)</p>  | <p>DATE OF POSITIVE PREGNANCY TEST (IF ANY)<br/>__-__-__(DD-MMM-YY)</p> <p>DATE OF PREVIOUS NEGATIVE PREGNANCY TEST (IF ANY)<br/>__-__-__(DD-MMM-YY)</p> |
| <p>MEDICAL ASSISTANCE / HOSPITALIZATION DURING PREGNANCY? <input type="checkbox"/> NO <input type="checkbox"/> YES<br/>DETAILS: _____</p>   | <p>MULTIPLE FETUSES/CHILDREN? <input type="checkbox"/> NO <input type="checkbox"/> YES</p>   |
| <p>IS THE OUTCOME OF CURRENT PREGNANCY KNOWN AT THE TIME OF THIS REPORT? <input type="checkbox"/> NO <input type="checkbox"/> YES</p>   |  |
| <p><b>OBSTETRICAL HISTORY</b></p>   | <p><b>NUMBER/ YEAR/COMMENTS</b></p>  |
| <p>PREVIOUS PREGNANCIES (if ectopic or molar pregnancy or other complication, please specify):</p>  |  |
| <p>LIVE BIRTHS, WITHOUT CONGENITAL ANOMALIES/ MALFORMATIONS/NEURODEVELOPMENTAL DISORDERS/ AUTISM SPECTRUM DISORDERS (ASD)</p>   |  |
| <p>LIVE BIRTHS, WITH CONGENITAL ANOMALIES/ MALFORMATIONS/NEURODEVELOPMENTAL DISORDERS/ AUTISM SPECTRUM DISORDERS (specify type of congenital anomalies/developmental disorders/ ASD :</p> |  |



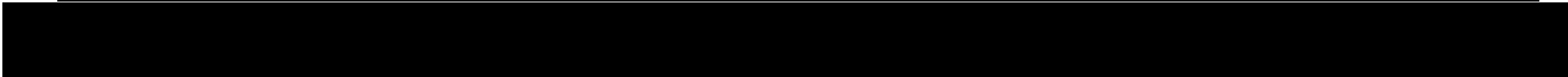


**Risk Management Plan****Teriflunomide RMP Version 3.0**

|  |  |
|--|--|
| 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  | <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY RELATION/DETAILS: ___ _  |
| CHILDREN DYING YOUNG   | <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY RELATION/DETAILS: ___ _  |
| CHROMOSOMAL ABNORMALITY  | <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY RELATION/DETAILS: ___ _  |
| DEVELOPMENTAL DELAY  | <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY RELATION/DETAILS: ___ _  |
| HEREDITARY DISEASE   | <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY RELATION/DETAILS: ___ _  |
| PERTINENT GYNECOLOGIC INFORMATION  | <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY RELATION/ DETAILS: ___ _ |
| CONSANGUINITY BETWEEN PARENTS  | <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY RELATION/ DETAILS: ___ _ |
| OTHER  | <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY: _____ _                 |

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

|   |
|---|
| <input type="checkbox"/> No <input type="checkbox"/> Yes (please complete corresponding AE form(s)) |
| THE AE OCCURRED IN THE <input type="checkbox"/> MOTHER <input type="checkbox"/> CHILD               |
| DESCRIBE ADVERSE EVENT(S):  |



**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

|  |
|--|
|  |
|--|

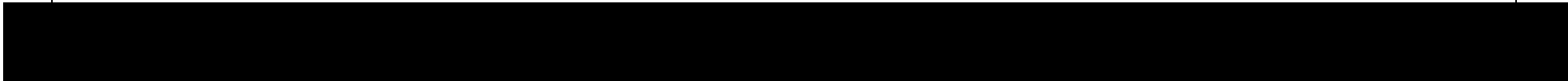
**MEDICATIONS: (include prescription & OTC medicines and pregnancy/food supplements e.g. folic acid and other vitamins, iron)**

| PRODUCTS<br>* | CAUSAL<br>RELATION<br>- SHIP<br>(YES/NO) | FETAL /<br>NEONATA<br>L<br>EXPOSURE<br>** | INDICATIO<br>N | DOSE/<br>SCHEDULE/DOS<br>E NUMBER | RO<br>U<br>TE | START<br>DATE<br>+ (DD-<br>MMM-<br>YY) | STOP<br>DATE<br>+ (DD-<br>MMM-<br>YY) | DURATIO<br>N (DAYS) | BATCH<br>NUMBER<br>(MANDATO<br>RY. IF NOT<br>AVAILABLE<br>, ENTER NA/<br>IF NOT<br>OBTAINABL<br>E AT ALL<br>ENTER NO) | SITE<br>OF<br>ADMI<br>N | SIDE<br>OF<br>ADMI<br>N |
|---------------|--|---|----------------|-----------------------------------|---------------|--|---------------------------------------|---------------------|---|-------------------------|-------------------------|
|               |  |   |                |                                   |               |  |                                       |                     |   |                         |                         |
|               |  |   |                |                                   |               |  |                                       |                     |   |                         |                         |
|               |  |   |                |                                   |               |  |                                       |                     |   |                         |                         |
|               |  |   |                |                                   |               |  |                                       |                     |   |                         |                         |
|               |  |   |                |                                   |               |  |                                       |                     |   |                         |                         |
|               |  |   |                |                                   |               |  |                                       |                     |   |                         |                         |

\*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



**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

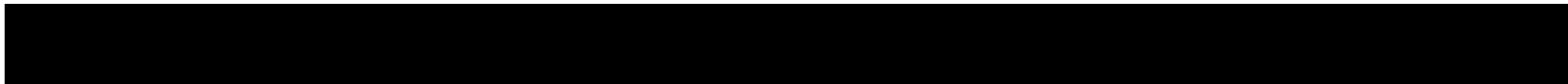
| PRODUCTS<br>* | CAUSAL<br>RELATION<br>- SHIP<br>(YES/NO) | FETAL /<br>NEONATA<br>L<br>EXPOSURE<br>** | INDICATIO<br>N | DOSE/<br>SCHEDULE/DOS<br>E NUMBER | RO<br>U<br>TE | START<br>DATE<br>+ (DD-<br>MMM-<br>YY) | STOP<br>DATE<br>+ (DD-<br>MMM-<br>YY) | DURATIO<br>N (DAYS) | BATCH<br>NUMBER<br>(MANDATO<br>RY. IF NOT<br>AVAILABLE<br>, ENTER NA/<br>IF NOT<br>OBTAINABL<br>E AT ALL<br>ENTER NO) | SITE<br>OF<br>ADMI<br>N | SIDE<br>OF<br>ADMI<br>N |
|---------------|--|---|----------------|-----------------------------------|---------------|--|---------------------------------------|---------------------|---|-------------------------|-------------------------|
| 2.            | DURING PREGNANCY                         |   | 4.             | BREAST FEEDING                    |               |  |                                       |                     |   |                         |                         |

**ADDITIONAL MEDICAL DATA**

|  |
|--|
| COMMENTS REGARDING MATERNAL HEALTH OR COMPLICATIONS DURING PREGNANCY |
|--|

**PRENATAL TESTING**

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



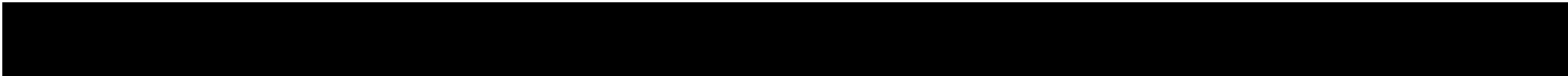
**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

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

**PREGNANCY OUTCOME**

| #CHILDREN/FETUSES: SINGLE MULTI (#_____) |     |  |             |       |                   |        |                   |                       |                   |          |                    |    |   |
|--|-----|--|-------------|-------|-------------------|--------|-------------------|-----------------------|-------------------|----------|--------------------|----|---|
| CHILD/<br>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<br>Cm               |                   |          |                    |    |   |
|  |     |  |             |       |                   |        |                   | G<br>Cm               |                   |          |                    |    |   |
|  |     |  |             |       |                   |        |                   | G<br>Cm               |                   |          |                    |    |   |



**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

|   |  |   |
|---|--|---|
| 1 | *OUTCOME: ENTER THE NUMBER APPROPRIATE TO THE PREGNANCY OUTCOME (ENTER ALL THAT APPLY)   |   |
|   | 1. LIVE BIRTH (NORMAL)<br>3. LIVE BIRTH (ABNORMAL)**<br><br>5. SPONTANEOUS ABORTION (<20 WEEKS GESTATION)<br><br>7. EARLY FETAL DEATH (20-27 WEEKS GESTATION)<br><br>9. LATE FETAL DEATH (AT LEAST 28 WEEKS GESTATION)   | 2. ELECTIVE TERMINATION<br>4. STILLBIRTH<br>6. MATERNAL DEATH (IF RESULTING IN FETAL DEATH,ADD APPROPRIATE NUMBER)<br>8. ECTOPIC PREGNANCY<br>10. LIVE BIRTH (NORMAL)-<br>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<br>(SEE SECTION 12FOR NEURO DEVELOPMENT DISORDERS): |   |
|   | IN CASE OF ABORTION, STILLBIRTHS, FETAL DEATH OR MATERNAL DEATH, WAS AN AUTOPSY PERFORMED?<br><br><input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> UNK<br><br>IF YES, PROVIDE RESULTS FOR EACH WHERE APPLICABLE   |   |
|   | <b>LABOR/DELIVERY:</b><br>MODE OF DELIVERY:<br>ANY COMPLICATIONS OF LABOR AND/OR DELIVERY <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY  |   |
|   | MEDICATION DURING LABOR <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY:   |   |



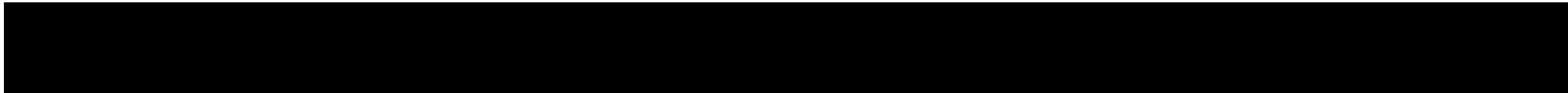
**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

|  |  |
|--|--|
|  | CLEAR AMNIOTIC FLUID <input type="checkbox"/> NO <input type="checkbox"/> YES                   NORMAL PLACENTA <input type="checkbox"/> NO <input type="checkbox"/> YES   |
|  | YES  |
|  | ADDITIONAL INFORMATION ABOUT THE NEWBORN CONDITION:<br>BREAST FEEDING <input type="checkbox"/> NO <input type="checkbox"/> YES<br>NEONATAL ILLNESS <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY: -----<br>NEED FOR RESUSCITATION <input type="checkbox"/> NO <input type="checkbox"/> YES INTRAUTERINE GROWTH<br>RESTRICTION OR IMMATURITY <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY:<br>CORRECTIVE TREATMENT RECEIVED BY NEWBORN <input type="checkbox"/> NO <input type="checkbox"/> YES, SPECIFY: -----<br>INTENSIVE CARE <input type="checkbox"/> NO <input type="checkbox"/> YES<br>TRANSFERRED TO INTENSIVE CARE UNIT OR PEDIATRIC DEPARTMENT <input type="checkbox"/> NO <input type="checkbox"/> YES<br>DURATION:<br>ADDRESS OF DEPARTMENT _____<br>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<br>cm                 |                                   |    |               |
|       |                                     |                   |          |  |          | g<br>cm                 |                                   |    |               |
|       |                                     |                   |          |  |          | g<br>cm                 |                                   |    |               |



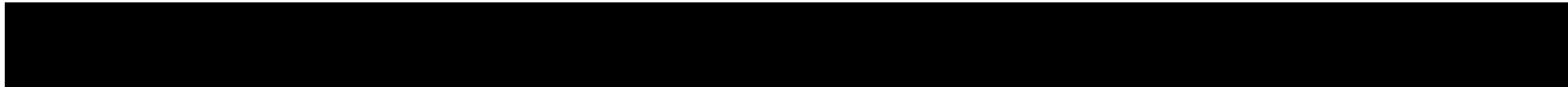
**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

|  |  |
|--|--|
|  | *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:<br><input type="checkbox"/> CONSUMER<br><input type="checkbox"/> STUDY INVESTIGATOR D LAWYER<br><input type="checkbox"/> MEDICAL DOCTOR<br><input type="checkbox"/> PHARMACIST<br><input type="checkbox"/> OTHER HCP (HEALTHCARE PROFESSIONAL) D OTHER | CITY/STATE/PROVINCE:  |
| PHONE:   | POSTAL CODE: Country: |
| DOES MOTHER AGREE TO PROVIDE INFORMATION? YES <input type="checkbox"/> NO <input type="checkbox"/>   |                       |
| DOES FATHER AGREE TO PROVIDE INFORMATION? YES <input type="checkbox"/> NO <input type="checkbox"/>   |                       |







**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?

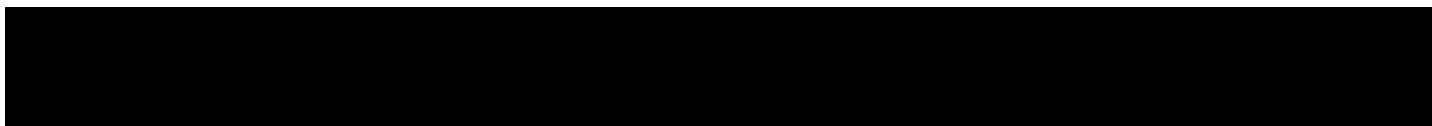
Yes     No     Unable to assess

**Clinical symptoms**

| <b>Symptoms</b>  | <b>Date of onset</b> |
|--|----------------------|
| Recent changes in personality or mood <input type="checkbox"/> Yes <input type="checkbox"/> No   |                      |
| Recent or sudden change in cognitive behaviour Example: confusion, disorientation <input type="checkbox"/> Yes <input type="checkbox"/> No |                      |
| Language or speech disturbances Example: aphasia or dysarthria <input type="checkbox"/> Yes <input type="checkbox"/> No                    |                      |
| Visual disturbances <input type="checkbox"/> Yes <input type="checkbox"/> No   |                      |
| Ataxia/loss of motor coordination/progressive weakness <input type="checkbox"/> Yes <input type="checkbox"/> No                            |                      |
| New onset of seizures <input type="checkbox"/> Yes <input type="checkbox"/> No   |                      |
| Other- if yes, please specify <input type="checkbox"/> Yes <input type="checkbox"/> No   |                      |

**EDSS score**

|                                | <b>Date</b> | <b>Score</b> |
|--------------------------------|-------------|--------------|
| Prior to the onset of symptoms |             |              |
| After the onset of symptoms    |             |              |



Laboratory and JCV information

| Test*  |  |                                 | Date | Results |
|--|--|---------------------------------|------|---------|
| JCV DNA Detection by PCR   | <input type="checkbox"/> Yes <input type="checkbox"/> No | <input type="checkbox"/> CSF    |      |         |
| Laboratory used for detection (please provide name and location) |  | <input type="checkbox"/> Plasma |      |         |
| Brain biopsy   | <input type="checkbox"/> Yes <input type="checkbox"/> No |                                 |      |         |
| Hospital facility (please provide name and location)             |  |                                 |      |         |
| CD4 count  | <input type="checkbox"/> Yes <input type="checkbox"/> No |                                 |      |         |
| CD8 count  | <input type="checkbox"/> Yes <input type="checkbox"/> No |                                 |      |         |

\*Please provide copies of test results

**Other Investigation**

| Other Investigation | Date | Baseline Values | Result | Normal High/<br>Low |
|---------------------|------|-----------------|--------|---------------------|
|                     |      |                 |        |                     |
|                     |      |                 |        |                     |
|                     |      |                 |        |                     |
|                     |      |                 |        |                     |
|                     |      |                 |        |                     |
|                     |      |                 |        |                     |
|                     |      |                 |        |                     |
|                     |      |                 |        |                     |
|                     |      |                 |        |                     |
|                     |      |                 |        |                     |

Imaging information

|  | Date   | Results |
|--|--|---------|
| Was Brain MRI performed prior to the start of          | <input type="checkbox"/> Yes <input type="checkbox"/> No |         |
| Was Brain MRI performed for PML diagnosis?             | <input type="checkbox"/> Yes <input type="checkbox"/> No |         |
| Was Brain CT performed prior to the start of symptoms? | <input type="checkbox"/> Yes <input type="checkbox"/> No |         |
| Was Brain CT performed for PML diagnosis?              | <input type="checkbox"/> Yes <input type="checkbox"/> No |         |





**DRUG HISTORY**

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

| Medication   | Date of 1 <sup>st</sup> Course | Date of Last Course | No. of Courses | Dose/Route | Reason for Discontinuation | Reporter Causality <sup>1</sup>  |
|--|--------------------------------|---------------------|----------------|------------|----------------------------|--|
| alemtuzumab <input type="checkbox"/> Yes<br>(if not the drug being reported) <input type="checkbox"/> No |                                |                     |                |            |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |

| Medication   | Start Date | End Date | Dose/Route | Frequency | Reason for Discontinuation | Reporter Causality <sup>1</sup>  |
|--|------------|----------|------------|-----------|----------------------------|--|
| teriflunomide <input type="checkbox"/> Yes<br>(if not the drug being reported) <input type="checkbox"/> No |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| natalizumab <input type="checkbox"/> Yes<br><input type="checkbox"/> No                                    |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| fingolimod <input type="checkbox"/> Yes<br><input type="checkbox"/> No                                     |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| dimethyl fumarate <input type="checkbox"/> Yes<br><input type="checkbox"/> No                              |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Interferon beta (any product) <input type="checkbox"/> Yes<br><input type="checkbox"/> No                  |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| glatiramer acetate <input type="checkbox"/> Yes<br><input type="checkbox"/> No                             |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| mitoxantrone <input type="checkbox"/> Yes<br><input type="checkbox"/> No                                   |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Corticosteroids (most recent course) <input type="checkbox"/> Yes<br><input type="checkbox"/> No           |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Other MS Therapies <input type="checkbox"/> Yes<br>Specify: <input type="checkbox"/> No                    |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Other MS Therapies <input type="checkbox"/> Yes<br>Specify: <input type="checkbox"/> No                    |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |



**Risk Management Plan**

**Teriflunomide RMP Version 3.0**

| Medication  | Start Date | End Date | Dose/Route | Frequency | Reason for Discontinuation | Reporter Causality <sup>1</sup>  |
|---|------------|----------|------------|-----------|----------------------------|--|
| Other MS Therapies <input type="checkbox"/> Yes<br>Specify: <input type="checkbox"/> No |            |          |            |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |

<sup>1</sup>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 <sup>1</sup>  |
|---|------------|----------|------|-----------|----------------------------|--|
| rituximab <input type="checkbox"/> Yes<br><input type="checkbox"/> No   |            |          |      |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| efalizumab <input type="checkbox"/> Yes<br><input type="checkbox"/> No  |            |          |      |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| leflunomide <input type="checkbox"/> Yes<br><input type="checkbox"/> No   |            |          |      |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| Methotrexate <input type="checkbox"/> Yes<br><input type="checkbox"/> No  |            |          |      |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |
| <b>Other Immunosuppressive or</b> <input type="checkbox"/> Yes<br><b>chemotherapeutic agents (e.g.,</b> <input type="checkbox"/> No<br><b>cyclophosphamide,</b><br><b>tacrolimus,</b><br><b>azathioprine,</b><br><b>mycophenolate,</b><br><b>cyclosporine)</b><br>Please specify: |            |          |      |           |                            | Related <input type="checkbox"/><br>Unrelated <input type="checkbox"/><br>Unknown <input type="checkbox"/> |

<sup>1</sup>Physician's assessment of relatedness to PML

**Abbreviations**

|      |                                    |
|------|------------------------------------|
| AIDS | Acquired immunodeficiency syndrome |
| CMV  | Cytomegalovirus                    |
| CT   | Computed tomography                |
| DNA  | Deoxyribonucleic acid              |

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

## **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;



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