Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Teriflunomide*14 mg film-coated tablets:

*in RMS-AT:

- **Teriflunomid ratiopharm 14 mg Filmtabletten (for procedure AT/H/1225/001/DC);**
- **Teriflunomid Actavis 14 mg Filmtabletten (for procedure AT/H/1226/001/DC);**
- **Teruma 14 mg Filmtabletten (for procedure AT/H/1251/001/DC).**

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

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

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

I. The Medicine and What It is used for

Teriflunomide is authorised 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 taken orally.

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

Important risks of Teriflunomide, together with measures to minimise such risks and the proposed studies for learning more about Teriflunomide's 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, 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 is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Teriflunomide are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Teriflunomide. 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).

List of important risks and missing information	
Important identified risks	• Hepatic effects • Hypertension • Haematologic effects • Infections • Acute pancreatitis
Important potential risks	• Teratogenicity • Serious opportunistic infections, including progressive multifocal leukoencephalopathy (PML)
Missing information	• Long-term safety in paediatric patients

II.B Summary of Important Risks

Important identified risk: Hepatic effects	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8 and 5.2. SmPC section 4.4 where advice is given on monitoring of the liver function. PL sections 2 and 4. Prescription only medicine. The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Additional risk minimisation measures: Educational Material for Health Care Professionals (HCP): HCP education/discussion guide; Educational Material for Patients: Patient education card.
Important identified risk: Hypertension	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. SmPC section 4.4 where advice is given on blood pressure monitoring. PL sections 2 and 4. Prescription only medicine. The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Additional risk minimisation measures: Educational Material for Health Care Professionals (HCP): HCP education/discussion guide; Educational Material for Patients: Patient education card.
Important identified risk: Haematologic Effects	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4, 4.8 and 5.1. SmPC section 4.4 where advice is given on blood cell count monitoring. PL sections 2 and 4. Prescription only medicine. The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Additional risk minimisation measures: Educational Material for Health Care Professionals (HCP): HCP education/discussion guide; Educational Material for Patients: Patient education card.

Important identified risk: Infections	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8. PL sections 2 and 4. Prescription only medicine. The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Additional risk minimisation measures: Educational Material for Health Care Professionals (HCP): HCP education/discussion guide; Educational Material for Patients: Patient education card.
Important identified risk: Acute pancreatitis	
Risk minimisation measures	Routine risk minimisation measures: SmPC section s 4.4 and 4.8. PL sections 2 and 4. Prescription only medicine. The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Additional risk minimisation measures: None.
Important potential risk: Teratogenicity	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.6 and 5.3. SmPC sections 4.3 and 4.6 where advice is given on clinical measures in women who become pregnant (or who intend to become pregnant). PL section 2. Prescription only medicine. The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Additional risk minimisation measures: Educational Material for Health Care Professionals (HCP): HCP education/discussion guide; Educational Material for Patients: Patient education card.

Important potential risk: Serious opportunistic infections, including progressive multifocal leukoencephalopathy (PML)	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3, 4.4 and 4.8. PL sections 2 and 4. Prescription only medicine. The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Additional risk minimisation measures: Educational Material for Health Care Professionals (HCP): HCP education/discussion guide; Educational Material for Patients: Patient education card.
Missing information: Long-term safety in paediatric patients	
Risk minimisation measures	Routine risk minimisation measures: Prescription only medicine. The treatment should be initiated and supervised by a physician experienced in the management of multiple sclerosis. Additional risk minimisation measures: None.

II.C Post-Authorisation Development Plan

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

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

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

There are no studies required for Teva's Teriflunomide (Teriflunomid ratiopharm, Teriflunomid Actavis and Teruma).

The following studies are conducted for the active substance by the reference product's Marketing Authorisation Holder (sanofi-aventis groupe):

- International Pregnancy exposure registry of teriflunomide OBS12751 (EU/ROW);
- Teriflunomide pregnancy exposure registry in the US/Canada OBS13499;
- EFC11759 - Open label period of a multicenter, randomized, double blind, parallel group trial to evaluate efficacy, safety, tolerability and pharmacokinetics of teriflunomide in comparison to placebo followed by a long-term open label extension phase, in children and adolescents 10 to 17 years of age with MS with relapses (open label extension period).