Summary of the Risk Management Plan (RMP) for AUBAGIO®

AUBAGIO® (teriflunomide)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of Aubagio® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Aubagio ® in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis (suisse) sa is fully responsible for the accuracy and correctness of the content of this published summary RMP of Aubagio®.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for AUBAGIO (Teriflunomide)

This is a summary of the RMP for AUBAGIO. The RMP details important risks of AUBAGIO how these risks can be minimized, and how more information will be obtained about AUBAGIO's risks and uncertainties (missing information).

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

This summary of the RMP for AUBAGIO 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 AUBAGIO's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

AUBAGIO is indicated for the treatment of adult and pediatric patients aged 10 years and older with relapsing remitting multiple sclerosis (MS) (see SmPC for the full indication). It contains teriflunomide as the active substance and it is given by oral route.

Further information about the evaluation of AUBAGIO's benefits can be found in AUBAGIO's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/aubagio

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of AUBAGIO, together with measures to minimize such risks and the proposed studies for learning more about AUBAGIO's risks, are outlined in the next sections.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of AUBAGIO, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (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 AUBAGIO is not yet available, it is listed under "missing information" outlined in the next section.

II.A List of important risks and missing information

Important risks of AUBAGIO are risks that need special risk management activities to further investigate or minimize 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 AUBAGIO. 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 (eg, on the long-term use of the medicine);

Table 37 - List of important risks and missing information

Important identified risks	Hepatic effects
	Hypertension
	Hematologic effects
	Infections
	Acute Pancreatitis
Important potential risks	Teratogenicity
	Serious opportunistic infections, including PML
Missing information	None

PML: Progressive Multifocal Leukoencephalopathy.

II.B Summary of important risks

Table 38 - Important identified risk with corresponding risk minimization activities: **Hepatic effects**

Hepatic effects	
Evidence for linking the risk to the medicine	Literature, clinical data
Risk factors and risk groups	Mild and moderate hepatic impairment had no impact on the PK of teriflunomide (POP6507). Patients with severe hepatic impairment have been excluded from teriflunomide clinical trials. Other possible theoretical risk factors: concomitant treatment with hepatotoxic agents (including alcohol), viral infections (including viral hepatitis), gall bladder disease.
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.2, 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient education card).

EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; PK: Pharmacokinetic; SmPC: Summary of Product Characteristics

Table 39 - Important identified risk with corresponding risk minimization activities: **Hypertension**

Hypertension	
Evidence for linking the risk to the medicine	Literature, clinical data
Risk factors and risk groups	Patients with prior history of hypertension, prior anti-hypertensive treatment or receiving concomitant drugs causing hypertension (eg, NSAID, OCs). Presence of concomitant cardiovascular risk factors such as obesity, diabetes. 1 There was no evidence of an increased risk of hypertension regarding intrinsic (age, gender, race, BMI) and extrinsic (region, territory, previous disease modifying MS therapy, selected concomitant medications) factors.
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.2, 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient education card).

BMI: Body Mass Index; EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; NSAID: Non-Steroidal Anti-Inflammatory Drug; OC: Oral Contraceptive; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 40 - Important identified risk with corresponding risk minimization activities: **Hematologic effects**

Hematologic effects	
Evidence for linking the risk to the medicine	Literature, non-clinical data and clinical data.
Risk factors and risk groups	Patients with pre-existent neutropenia, combination with other neutropenic or lymphopenic drug. Patients with pre-existent thrombocytopenia. Combination with other thrombopenic drugs or drugs increasing the bleeding risk. There was no evidence of increased risk of hematologic effects or hemorrhages in patients treated with teriflunomide 7 or 14 mg compared to those receiving placebo regarding intrinsic (age, gender, race, BMI, baseline EDSS) and extrinsic (region, territory, previous disease modifying MS therapy, selected concomitant medications) factors.

Hematologic effects	
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient education card).

BMI: Body Mass Index; EDSS: Expanded Disability Status Scale; EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 41 - Important identified risk with corresponding risk minimization activities: **Infections**

Infections	
Evidence for linking the risk to the medicine	Literature, non-clinical data and clinical data.
Risk factors and risk groups	Patients with pre-existent neutropenia, concomitant treatment with other neutropenic or immunosuppressive agents, history of repetitive infections. The analysis of intrinsic or extrinsic factors did not identify any further particular risk group or risk factor for infections.
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Materials (HCP education/discussion guide and patient education card).

EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 42 - Important identified risk with corresponding risk minimization activities: **Acute pancreatitis**

Acute pancreatitis	
Evidence for linking the risk to the medicine	Literature, non-clinical data, clinical data, postmarketing experience.
Risk factors and risk groups	Patients with a pre-existing pancreatic disorder.
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: None

EU: European Union; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 43 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: **Teratogenicity**

Teratogenicity	
Evidence for linking the risk to the medicine	Literature, non-clinical studies with leflunomide and teriflunomide (embryo-fetal toxicity studies).
Risk factors and risk groups	Pregnant women and women of childbearing potential including adolescents.
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 4.3 and 4.6 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Educational Materials (HCP education/discussion guide and patient education card).
Additional pharmacovigilance activities	International Pregnancy exposure registry of teriflunomide OBS12751 (EU/ROW). Teriflunomide pregnancy exposure registry in the US/Canada OBS13499

EU: European Union; HCP: Healthcare Professional; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; ROW: Rest of the World; SmPC: Summary of Product Characteristics; US: United States.

Table 44 - Important potential risk with corresponding risk minimization activities:

Serious opportunistic infections, including PML

Serious opportunistic infections, including PML	
Evidence for linking the risk to the medicine	Literature, non-clinical data, clinical data.
Risk factors and risk groups	In patients with rituximab-associated PML, most cases developed in patients with underlying disorders known to predispose toward development of PML, chiefly lymphoproliferative disorders, patients with HIV infection and autoimmune disorders. With natalizumab, risk factors for PML include duration of treatment (number of natalizumab infusions) and prior use of immunosuppressive agents (eg, mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate)
Risk minimization measures	Routine risk minimization measures: SmPC: Sections 3.3, 4.4 and 4.8 PIL: Sections 2 and 4 Legal status: Prescription should be initiated and supervised by physicians experienced in the management of MS (restricted medical prescription in EU). Additional risk minimization measures: Educational Material (HCP education/discussion guide and patient education card).

EU: European Union; HCP: Healthcare Professional; HIV: Human Immunodeficiency Virus; MS: Multiple Sclerosis; PIL: Patient Information Leaflet; PML: Progressive Multifocal Leukoencephalopathy; SmPC: Summary of Product Characteristics

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of AUBAGIO.

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

Table 45 - Other studies in post-authorization development plan

Teriflunomide pregnancy exposure registry in the US/Canada OBS13499 (Category-3)
Purpose of the study: To monitor reports of use and/or AEs in pregnancy, and pregnancy outcomes.
International pregnancy exposure registry of teriflunomide OBS12751 (EU/ROW) (Category-3)
Purpose of the study: To monitor reports of use and/or AEs in pregnancy, and pregnancy outcomes.

AE: Adverse Event; EU: European Union; ROW: Rest of the World; US: United States.