Part VI: Summary of the risk management plan

Summary of risk management plan for Clefirem (Teriflunomide)

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

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

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

I. The medicine and what it is used for

Clefirem is authorised for the treatment of adult patients and paediatric 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 of administration.

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

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

II.A List of important risks and missing information

Important risks of Clefirem 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 Clefirem. 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 Hematologic effects Infections Acute Pancreatitis
Important potential risks	Teratogenicity Serious opportunistic infections, including PML
Missing information	Long term safety

II.B Summary of important risks

Important identified risks

Hepatic effects	
Evidence for linking the risk to the medicine	Product Information, European public assessment report- Risk management plan summary for originator product Aubagio
Risk factors and risk groups	Mild and moderate hepatic impairment had no impact on the pharmacokinetic 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 minimisation measures	<u>Routine risk minimisation measures:</u> SmPC: Sections 4.2, 4.3, 4.4 and 4.8 <u>Routine pharmacovigilance activities:</u>

	Targeted questionnaire (Drug induced liver injury form) Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)

Hypertension	
Evidence for linking the risk to the medicine	Product Information, European public assessment report- Risk management plan summary for originator product Aubagio.
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. 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 minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.4 and 4.8 Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)

Hematologic effects	
Evidence for linking the risk to the medicine	Product Information, European public assessment report- Risk management plan summary for originator product Aubagio.
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.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.3, 4.4 and 4.8

Hematologic effects	
	Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)

Infections	
Evidence for linking the risk to the medicine	Product Information, European public assessment report- Risk management plan summary for originator product Aubagio.
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 minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.3, 4.4 and 4.8 Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)

Acute Pancreatitis	
Evidence for linking the risk to the medicine	Product Information, European public assessment report- Risk management plan summary for originator product Aubagio.
Risk factors and risk groups	Patients with a pre-existing pancreatic disorder.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.4 and 4.8 Routine pharmacovigilance activities: Targeted questionnaire (pancreatic disorder form) Additional risk minimisation measures: None

Important potential risks

Teratogenicity	
Evidence for linking the risk to the medicine	Product Information, European public assessment report- Risk management plan summary for originator product Aubagio.
Risk factors and risk groups	Pregnant women and women of childbearing potential including adolescents.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.3 and 4.6 Routine pharmacovigilance activities: Targeted questionnaire (pregnancy reporting form) Additional risk minimisation measures: Educational Materials (HCP guide and Patient education card)

Serious opportunistic infections, including PML	
Evidence for linking the risk to the medicine	Product Information, European public assessment report- Risk management plan summary for originator product Aubagio.
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 natazilumab, 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 minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.3, 4.4 and 4.8 Routine pharmacovigilance activities: Targeted questionnaire (PML form) Additional risk minimisation measures: Educational Materials (HCP guide and Patient card)

Long term safety	
Evidence for linking the risk to the medicine	European public assessment report-Risk management plan summary for originator product Aubagio, Literature [2,3].
Risk minimisation measures	Routine risk minimisation measures: Currently there is no available information in the SmPC. 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 Clefirem.

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

There are no other studies required for Clefirem.