Summary of risk management plan for Briumvi (ublituximab)
Based on EU-RMP Version 1.2
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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 minimise them.
The RMP summary of “Briumvi” 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 médicament” 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 “Briumvi” in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. “Neuraxpharm Switzerland GmbH, Cham” is fully responsible for the accuracy and correctness of the content of the published summary RMP of “Briumvi”.

Summary of risk management plan for Briumvi (ublituximab)

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

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

This summary of the RMP for Briumvi 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 Swiss Public Assessment Report (SwissPAR).

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

I. The medicine and what it is used for

Briumvi is authorised for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see SmPC for the full indication). It contains ublituximab as the active substance and it is given by intravenous infusion. Ublituximab is a glycoengineered murine/human chimeric anti-CD20 monoclonal antibody that targets an epitope of the B-lymphocyte antigen CD20 expressed on the cell membranes of lymphocytes.

Further information about the evaluation of Briumvi's benefits can be found in Briumvi's SwissPAR, including in its plain-language summary, available on the Swissmedic website.

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

Important risks of Briumvi, together with measures to minimise such risks and the proposed studies for learning more about Briumvi'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 addition to these measures, information about adverse events is collected continuously and regularly analysed, 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 Briumvi is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Briumvi 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 Briumvi. 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	Infusion-related reactions
Important potential risks	Serious infections, including opportunistic infections (e.g., PML and HBV reactivation) Malignancy

Missing information	Long-term safety of ublituximab treatment Safety in pregnancy and lactation, including foetal risks

II.B Summary of important risks

Important identified risk: Infusion-related reactions	
Evidence for linking the risk to the medicine	TG1101-RMS301, TG1101-RMS302, TG1101-RMS201 and their extension studies.
Risk factors and risk groups	Infusion-related reactions occur most often during the first infusion in patients who have not had this type of infusion before.
Risk minimisation measures	**Routine risk communication:** SmPC: Sections 4.2, 4.4, 4.8 PL: Section 2, 3, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Treatment with other medicines such as a corticosteroid and antihistamine to mitigate possible side effects such as infusion-related reactions are required before each infusion; medicines used to reduce fever may also be used. • Appropriate medical support should be available for the management of severe reactions such as serious infusion related reactions. • Patients should be observed for at least one hour after completion of the first two infusions of ublituximab for any symptom of infusion-related reaction. Physicians should inform patients that an infusion-related reaction can occur up to 24 hours after the infusion. Sections 4.2 and 4.4 of the SmPC include more detailed information. **Other risk minimisation measures beyond the Product**

	Information: ***Medicine's legal status*:** Ublituximab is a medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk: Serious infections, including opportunistic infections (e.g., PML and HBV reactivation)	
Evidence for linking the risk to the medicine	TG1101-RMS301, TG1101-RMS302, TG1101-RMS201 and their extension studies. Opportunistic infections including PML and HBV reactivation are a class risk for anti-CD20 monoclonal antibodies; however, no cases of PML have been observed in the RMS studies with ublituximab.
Risk factors and risk groups	Previous or concomitant medicines that affect the immune system, such as chemotherapy, immunosuppressants or other medicines used to treat multiple sclerosis, can be important contributing factors. In patients with a history of hepatitis B virus (HBV) infection, anti-CD20 antibody therapy may trigger HBV reactivation.
Risk minimisation measures	**Routine risk communication:** SmPC: Sections 4.3, 4.4, 4.8 PL: Sections 2, 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Administration of ublituximab must be delayed in patients with an active infection until the infection is resolved. • For progressive multifocal leukoencephalopathy (PML; a very rare and life-threatening brain infection), physicians should be alerted for the

	early signs and symptoms which can include any new onset or worsening of neurological signs or symptoms. If PML is suspected, dosing with ublituximab must be withheld and an appropriate diagnostic evaluation should be performed. Magnetic Resonance Imaging (MRI) findings may be apparent before clinical signs or symptoms. If PML is confirmed, ublituximab must be discontinued permanently. • Hepatitis B virus screening should be performed before initiation of treatment with ublituximab as per local guidelines because patients with active Hepatitis B virus infection should not be treated with ublituximab. Patients with positive serology (blood serum diagnostic); carriers of Hepatitis B virus should be referred to a liver disease expert before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. Sections 4.3 and 4.4 of the SmPC include more detailed information **Other risk minimisation measures beyond the Product Information:** ***Medicine's legal status:*** Ublituximab is a medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation long-term safety study (TG1101-RMS402)

Important potential risk: Malignancy	
Evidence for linking the risk to the medicine	A potential risk of malignancy has been observed with another anti-CD20 antibody. A weight of evidence approach (including review of the non-clinical and clinical findings with ublituximab and a comprehensive literature review on the biology and mechanism of action) has not revealed data to suggest that treatment with ublituximab would support or induce proliferation of transformed cells possibly leading to neoplasia.
Risk factors and risk groups	No risk factors have been identified.
Risk minimisation measures	**Routine risk communication:** SmPC: Section 4.3 **Routine risk minimisation measures:** Patients should be asked whether they have an active cancer because patients with a known active cancer should not be treated with ublituximab. **Other risk minimisation measures beyond the Product Information:** ***Medicine's legal status*:** Ublituximab is a medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Post-authorisation long-term safety study (TG1101-RMS402)

Missing information: Long-term safety of ublituximab treatment	
Risk minimisation measures	**Routine risk communication:** None **Routine risk minimisation activities recommended specific clinical measures to address the risk:** None **Other risk minimisation measures beyond the Product Information:** ***Medicine's legal status*:** Ublituximab is a medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Post-authorisation long-term safety study (TG1101-RMS402) Open Label Extension Study of ublituximab in subjects with Relapsing MS (TG1101-RMS303)

Missing information: Safety in pregnancy and lactation, including foetal risks	
Risk minimisation measures	**Routine risk communication:** SmPC: Sections 4.4, 4.6, 5.3 PL: Section 2 **Routine risk minimisation measures:** • Women of childbearing potential should be instructed that they should use contraception while receiving ublituximab and for at least 4 months after the last infusion of ublituximab. • It is unknown whether ublituximab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short

	period. Afterwards, ublituximab could be used during breast-feeding if clinically needed. • In infants of mothers treated with ublituximab during pregnancy, live or live-attenuated vaccines should not be administered before the recovery of B-cell counts has been confirmed. Measuring CD19-positive B-cell levels in neonates and infants prior to vaccination is recommended. Inactivated vaccines may be administered as indicated prior to recovery from B-cell depletion, however, assessment of vaccine immune responses, including consultation with a qualified specialist, should be considered to determine whether a protective immune response was mounted. The safety and timing of vaccination should be discussed with the infant's physician. Sections 4.4 and 4.6 of the SmPC includes more detailed information. **Other risk minimisation measures beyond the Product Information:** ***Medicine's legal status*:** Ublituximab is a medicinal product subject to restricted medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Post-authorisation pregnancy and infant outcomes safety studies (TG1101-RMS403 and TG1101-RMS404)

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 ublituximab.

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

Long-term surveillance of ublituximab-treated patients with multiple sclerosis

Purpose of the study:

- to characterise the long-term safety of ublituximab in RMS patients, with a primary objective to estimate the incidence rates of serious infections and malignancies.

A registry study of pregnancy and infant outcomes in patients treated with ublituximab

Purpose of the study:

- to further characterise the safety of ublituximab in RMS patients when used during pregnancy, including follow-up of infants exposed to ublituximab during pregnancy.

A study to characterize the safety of Briumvi use in pregnant patients with multiple sclerosis using data from an administrative healthcare claims database

Purpose of the study:

- to characterize the safety of Briumvi use in pregnant patients with multiple sclerosis and their infants using data from an administrative healthcare claims database

Open Label Extension Study of ublituximab in subjects with Relapsing MS

Purpose of the study:

- to evaluate the long-term safety and efficacy of ublituximab treatment in subjects with relapsing forms of MS for subjects previously treated in studies TG1101-RMS301 and TG1101- RMS302