swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Briumvi

International non-proprietary name:	ublituximab
Pharmaceutical form:	concentrate for solution for infusion
Dosage strength(s):	25 mg/mL
Route(s) of administration:	intravenous use
Marketing authorisation holder:	Neuraxpharm Switzerland AG
Marketing authorisation no.:	69599
Decision and decision date:	approved on 6 February 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CGE	Capillary gel electrophoresis
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CIS	clinically isolated syndrome
CNS	Central nervous system
CYP	Cytochrome P450
DDI	Drug-drug interaction
DMTs	Disease-modifying therapies
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
iCIEF	Imaged capillary isoelectric focusing
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPMS	Primary Progressive Multiple Sclerosis
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
RMS	Relapsing-forms of Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious adverse event
SEC	Size exclusion chromatography
SPMS	Secondary Progressive Multiple Sclerosis

SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for ublituximab in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

2.2.2 Approved indication

Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section «Properties/Effects»).

2.2.3 Requested dosage

First and second doses
The first dose is administered as a 150 mg intravenous infusion (first infusion), followed by a 450 mg intravenous infusion (second infusion) 2 weeks later (see Table 1).

Subsequent doses
Subsequent doses are administered as a single 450 mg intravenous infusion every 24 weeks (Table 1). The first subsequent dose of 450 mg should be administered 24 weeks after the first infusion. A minimal interval of 5 months should be maintained between each dose of ublituximab.

Table 1: Dose and schedule

	Amount and volume	Infusion rate	Duration[1]
First Infusion	150 mg in 250 mL	• Start at 10 mL per hour for the first 30 minutes • Increase to 20 mL per hour for the next 30 minutes • Increase to 35 mL per hour for the next hour • Increase to 100 mL per hour for the remaining 2 hours	4 hours
Second Infusion (2 weeks later)	450 mg in 250 mL	• Start at 100 mL per hour for the first 30 minutes • Increase to 400 mL per hour for the remaining 30 minutes	1 hour
Subsequent Infusions (once every 24 weeks)[2]	450 mg in 250 mL	• Start at 100 mL per hour for the first 30 minutes • Increase to 400 mL per hour for the remaining 30 minutes	1 hour

[1]Infusion duration may take longer if the infusion is interrupted or slowed.
[2]The first subsequent infusion should be administered 24 weeks after the first infusion.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	18 October 2023
Formal control completed	15 November 2023
List of Questions (LoQ)	14 March 2024
Response to LoQ	12 June 2024
Preliminary decision	10 September 2024
Response to preliminary decision	8 November 2024
Final decision	6 February 2025
Decision	approval

3 Medical context

Multiple sclerosis (MS) is a chronic, predominantly immune-mediated, inflammatory disease of the central nervous system (CNS), affecting approximately 2.8 million individuals worldwide (MS International Federation, 2021). Around 18,000 people with MS live in Switzerland (Swiss Multiple Sclerosis Society 2021), and the prevalence has increased over the last years.
Clinically, MS starts in approximately 85% of patients as relapsing remitting MS (RRMS), with variable disease activity interspersed with periods of stability. The onset of RRMS typically occurs between the ages of 20 and 40, and the disease predominantly affects women (2 to 3 times more frequently than men). Approximately 70% of patients with RRMS develop, within the first 10 to 15 years after diagnosis, a secondary progressive MS (SPMS), which is characterised by worsening of disability in the absence or independent of relapses. Relapsing forms of MS (RMS) include patients with RRMS, patients with clinically isolated syndrome (CIS – refers to the first clinical event and evidence of dissemination of lesions in time and space on the magnetic resonance imaging (MRI) scan) and those with SPMS with superimposed relapses. There are no clear criteria that mark the transition from RRMS to SPMS. Additionally, around 15% of patients demonstrate progressive neurological deterioration without superimposed relapses at the beginning of the disease. This form is called primary progressive MS (PPMS), begins typically in the 4th or 5th decade of life and affects men equally as women. The current therapeutic approach of treating RMS involves symptomatic treatment, treatment of acute relapses, and disease modifying therapies (DMTs). The goal of a DMT is to modify the natural course of disease by reducing the rate of relapses and MRI disease activity, and delay disability progression. There are a number of DMTs available for the treatment of MS with different mechanisms of action and differentiated efficacy and safety profiles.
CD20 is a cell surface antigen found on pre-B cells, mature and memory B-cells. Antibodies directed against CD20 positive B-cells have shown to be effective treatments for MS. Ublituximab is a recombinant monoclonal antibody that targets a novel epitope on the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes. The binding of ublituximab to CD20 induces lysis of CD20 positive B-cells primarily through antibody-dependent cell-mediated cytotoxicity and also through complement-dependent cytotoxicity.

4 Quality aspects

4.1 Drug substance

Ublituximab is a recombinant IgG1 chimeric monoclonal antibody which binds to CD20. It is a potent B cell depleting antibody with both antibody dependent cytotoxicity and complement mediated mechanisms of action.
Ublituximab is expressed in the rat cell line YB2/0 using a fed-batch production process in a production bioreactor. The cell broth is harvested, and ublituximab is subsequently purified by several chromatographic steps. The purification manufacturing process also contains dedicated viral clearance steps. The fermentation and purification processes were validated and demonstrated a consistent manufacturing process that effectively reduces product- and process-related impurities. The impurity clearance validation studies are supported by the impurity levels measured in the drug substance. The characterisation of the physicochemical and biological properties of the drug substance and its impurities was performed using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity/impurity tests (e.g. size exclusion chromatography [SEC], imaged capillary isoelectric focusing [iCIEF], capillary gel electrophoresis [CGE]), protein concentration and five biological activity assays. Batch analysis data of development, clinical, and process validation batches were provided. All batch

release data comply with the drug substance specifications valid at the time of batch release. All the analytical methods are described, and the non-compendial methods were validated in accordance with ICH guidelines.
The drug substance is stored under appropriate storage conditions. No significant changes have been observed within the proposed shelf life.

4.2 Drug product

The ublituximab 25 mg/mL drug product is provided in a vial as a sterile liquid solution intended for intravenous infusion after dilution in 0.9% saline.
The drug product is formulated in an aqueous buffered solution containing sodium chloride, sodium citrate, polysorbate 80, and hydrochloric acid. All excipients comply with Pharmacopoeia quality requirements.
As the drug substance and drug product formulation and composition are identical, the finished product manufacturing process consists only of thawing, pooling and mixing of drug substance, sterile filtration, aseptic filling into vials, and stoppering followed by capping. Process validation studies were executed at commercial scale using several validation batches.
The specifications include relevant tests and limits, e.g. for appearance, pH, osmolality, particles, identity, biological activity assays, purity tests (e.g. SEC, iCIEF, CGE), protein, sterility and bacterial endotoxins. All non-compendial methods were validated in accordance with ICH guidelines.
Batch analysis data of development, clinical, and process performance qualification batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release.
The primary container for the 25 mg/mL presentation is a 10 mL Type I borosilicate clear glass vial with a chlorobutyl elastomeric stopper and an aluminium overseal with a flip-off top. All components coming into contact with the finished product comply with Ph. Eur. requirements.
The drug product is stored at 2 - 8°C. No meaningful changes have been observed under the proposed storage conditions. A shelf life of 36 months has been accepted.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf life of the drug substance and drug product is supported by data from recommended storage conditions and by accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

5 Nonclinical aspects

Regarding the marketing authorisation application for Briumvi (ublituximab), the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the EMA Assessment report provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Briumvi in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. Safety issues, namely reproductive toxicity, with ublituximab not being tolerated in pregnant monkeys, were identified in the nonclinical studies, which is of concern for human use. The safety margins are considered to be sufficient. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals. The Nonclinical Safety Specifications in the RMP adequately address these nonclinical findings and their relevance for clinical use. The information for healthcare professionals (Pregnancy/Nursing and Preclinical Data) is adequate from the Nonclinical Assessment point of view.

There are no safety concerns regarding impurities and excipients.

Based on the ERA, the risk for the environment is low.

From the nonclinical perspective, approval may be granted in the proposed indication.

6 Clinical aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA and the FDA. The available EMA assessment report (EMA/173313/2023) and the FDA report, and respective product information from the EMA and FDA, were used as a basis for the clinical and clinical pharmacology evaluation. For further details concerning clinical pharmacology, efficacy and safety, please consider chapter 8 of this report.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Briumvi, concentrate for solution for infusion was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section «Undesirable Effects». for how to report adverse reactions.

BRIUMVI

Composition

Active substances

Ublituximab.
Ublituximab is a chimeric monoclonal antibody produced in a clone of the rat myeloma cell line YB2/0 by recombinant DNA technology.

Excipients

Natrii chloridum, Natrii citras dihydricus, Polysorbatum 80, Acidum hydrochloridum (for pH adjustment), Aqua ad iniectabile.
Overall sodium content: 31.57 mg per vial.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (sterile solution).
Clear to opalescent, colourless to slightly yellow solution.
The pH of the solution is 6.3 to 6.7, and the osmolality is 340 to 380 mOsm/kg.
Each vial contains 150 mg of ublituximab in 6 ml at a concentration of 25 mg/ml.
The final concentration after dilution is approximately 0.6 mg/ml for the first infusion and 1.8 mg/ml for the second infusion and all subsequent infusions.

Indications/Uses

Briumvi is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features (see section «Properties/Effects»).

Dosage/Administration

Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions (IRRs).

Premedication for infusion-related reactions (IRR)

The following two premedications must be administered (orally, intravenously, intramuscular, or subcutaneously) prior to each infusion to reduce the frequency and severity of IRRs (see section «Warnings and precautions» for additional steps to reduce IRRs):

- 100 mg methylprednisolone or 10-20 mg dexamethasone (or an equivalent) approximately 30-60 minutes prior to each infusion;

- antihistamines (e.g. diphenhydramine) approximately 30-60 minutes prior to each infusion.

In addition, premedication with an antipyretic (e.g. paracetamol) may also be considered.

Posology

First and second doses

The first dose is administered as a 150 mg intravenous infusion (first infusion), followed by a 450 mg intravenous infusion (second infusion) 2 weeks later (see Table 1).

Subsequent doses

Subsequent doses are administered as a single 450 mg intravenous infusion every 24 weeks (Table 1). The first subsequent dose of 450 mg should be administered 24 weeks after the first infusion.
A minimal interval of 5 months should be maintained between each dose of ublituximab.

Infusion adjustments in case of IRRs

Life-threatening IRRs

If there are signs of a life-threatening or disabling IRR during an infusion, the infusion must be stopped immediately and the patient should receive appropriate treatment. Treatment must be permanently discontinued in these patients (see section «Warnings and precautions»).

Severe IRRs

If a patient experiences a severe IRR, the infusion should be interrupted immediately and the patient should receive symptomatic treatment. The infusion should be restarted only after all symptoms have resolved. When restarting, the infusion rate should be at half of the infusion rate at the time of onset of the IRR. If the rate is tolerated, the rate should be increased as described in Table 1.

Mild to moderate IRRs

If a patient experiences a mild to moderate IRR, the infusion rate should be reduced to half the rate at the onset of the event. This reduced rate should be maintained for at least 30 minutes. If the reduced rate is tolerated, the infusion rate may then be increased as described in Table 1.

Dose modifications during treatment

No dose reductions are recommended. In case of dose interruption or infusion rate reduction due to IRR, the total duration of the infusion would be increased, but not the total dose.

Delayed or missed doses

If an infusion is missed, it should be administered as soon as possible; administration after a delayed or missed dose should not wait until the next planned dose. The treatment interval of 24 weeks (with a minimum of 5 months) should be maintained between doses (see Table 1).

Special populations

Adults over 55 years old and elderly

There are limited data on efficacy and safety for patients > 55 years of age. Based on these data, a dose adjustment is not considered necessary for these patients.

Renal impairment

No dose adjustment is expected to be required for patients with renal impairment (see section «Pharmacokinetics»)

Hepatic impairment

No dose adjustment is expected to be required for patients with hepatic impairment (see section «Pharmacokinetics»).

Children and adolescents

The safety and efficacy of Briumvi in children and adolescents aged 0 to 18 years have not yet been established. No data are available.

Method of administration

After dilution, Briumvi is administered as an intravenous infusion through a dedicated line. Infusions should not be administered as an intravenous push or bolus

Table 1: Dose and schedule

	Amount and volume	**Infusion rate**	**Duration[1]**
First Infusion	150 mg in 250 ml	• Start at 10 ml per hour for the first 30 minutes • Increase to 20 ml per hour for the next 30 minutes • Increase to 35 ml per hour for the next hour • Increase to 100 ml per hour for the remaining two hours	4 hours
Second Infusion (2 weeks later)	450 mg in 250 ml	• Start at 100 ml per hour for the first 30 minutes • Increase to 400 ml per hour for the remaining 30 minutes	1 hour
Subsequent Infusions (once every 24 weeks)[2]	450 mg in 250 ml	• Start at 100 ml per hour for the first 30 minutes • Increase to 400 ml per hour for the remaining 30 minutes	1 hour

[1] Infusion duration may take longer if the infusion is interrupted or slowed.

[2] The first subsequent infusion should be administered 24 weeks after the first infusion.

Solutions for intravenous infusion are prepared by dilution of the medicinal product into an infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, to a final concentration of 0.6 mg/ml for the first infusion and 1.8 mg/ml for the second infusion and all subsequent infusions. For instructions on dilution of the medicinal product before administration, see section «Other information».

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe active infection (see section «Warnings and precautions»).
- Patients in a severely immunocompromised state (see section «Warnings and precautions»).
- Known active malignancies.
- Initiation of therapy during pregnancy.

Warnings and precautions

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion-related reactions (IRRs)

Symptoms of IRRs may include pyrexia, chills, headache, tachycardia, nausea, abdominal pain, throat irritation, erythema, and anaphylactic reaction (see section «Undesirable effects»).
Patients should premedicate with a corticosteroid and an antihistamine to reduce the frequency and severity of IRRs (see section «Dosage/Administration»). The addition of an antipyretic (e.g., paracetamol) may also be considered. Patients treated with ublituximab should be observed during infusions. Patients should be monitored for at least one hour after the completion of the first two infusions. Subsequent infusions do not require monitoring post-infusion unless IRR and/or hypersensitivity has been observed. Physicians should inform patients that IRRs can occur up to 24 hours after the infusion. For guidance regarding posology for patients experiencing IRR symptoms, see section «Dosage/Administration».

Infection

Administration must be delayed in patients with an active infection until the infection is resolved.
It is recommended to verify the patient’s immune status before dosing since severely immunocompromised patients (e.g. significant neutropenia or lymphopenia) should not be treated (see sections «Contraindications» and section «Undesirable effects»).
Ublituximab has the potential for serious, sometimes life-threatening or fatal, infections (see section «Undesirable effects»).

Most of the serious infections that occurred in controlled clinical trials in relapsing forms of multiple sclerosis (RMS) resolved. There were 3 infection-related deaths that occurred, all in patients treated with ublituximab. The infections leading to death were post-measles encephalitis, pneumonia, and post-operative salpingitis following an ectopic pregnancy.

Progressive multifocal leukoencephalopathy (PML)

John Cunningham virus (JCV) infection resulting in PML has been observed very rarely in patients treated with anti-CD20 antibodies and mostly associated with risk factors (e.g., patient population, lymphopenia, advanced age, polytherapy with immunosuppressants).
Physicians should be vigilant for the early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms, as these can be similar to MS disease.
If PML is suspected, dosing with ublituximab must be withheld. Evaluation including Magnetic Resonance Imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebro-spinal fluid (CSF) testing for JCV Desoxyribonucleic acid (DNA) and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently.

Hepatitis B virus (HBV)

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has been observed in patients treated with anti-CD20 antibodies.
HBV screening should be performed in all patients before initiation of treatment as per local guidelines. Patients with active HBV (i.e. an active infection confirmed by positive results for HBsAg and anti HB testing) should not be treated with ublituximab. Patients with positive serology (i.e. negative for HBsAg and positive for HB core antibody [HBcAb +] or who are carriers of HBV [positive for surface antigen, HBsAg+]) should consult liver disease experts before starting the treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Vaccinations

The safety of immunisation with live or live-attenuated vaccines, during or following therapy has not been studied and vaccination with live-attenuated or live vaccines is not recommended during treatment and not until B-cell repletion (see section «Properties/Effects»).
All immunisations should be administered according to immunisation guidelines at least 4 weeks prior to treatment initiation for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to treatment initiation for inactivated vaccines.

Vaccination of infants born to mothers treated with ublituximab during pregnancy

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. Depletion of B

cells in these infants may increase the risks associated with live or live-attenuated vaccines. 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 (see section «Pregnancy, lactation»).

Sodium

This medicinal product contains 31.57 mg of sodium per vial, corresponding to 1.61% of the WHO recommended maximum daily intake of sodium from food of 2 g.

Interactions

No interaction studies have been performed.

Vaccinations

The safety of immunisation with live or live-attenuated vaccines following ublituximab therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment or until B-cell repletion (see sections «Warnings and precautions» and «Pharmacodynamics»).

Immunosuppressants

It is not recommended to use other immunosuppressives concomitantly with ublituximab except corticosteroids for symptomatic treatment of relapses.
When initiating Briumvi after an immunosuppressive therapy, or when initiating an immunosuppressive therapy after Briumvi, the potential for overlapping pharmacodynamic effects should be taken into consideration (see section «Properties/Effects»). Caution should be exercised when prescribing Briumvi taking into consideration the pharmacodynamics of other disease modifying MS therapies.

Pregnancy, lactation

Women of child-bearing potential

Treatment must not be started during pregnancy (see «Contraindications»). Women of child-bearing potential must use effective contraception while receiving ublituximab and for at least 4 months after the last infusion (see below and sections «Pharmacodynamics» and «Pharmacokinetics »).

Pregnancy

Ublituximab is a monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier. Animal studies have shown reproductive toxicity (see non-clinical data).
To date, there is a limited amount of data from the use of ublituximab in pregnant women; however, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants whose mothers were treated with other anti-CD20 antibodies during pregnancy. No data on B-cell counts are available for neonates and infants exposed to ublituximab, and the possible duration of B-cell depletion in neonates and infants is unknown (see «Warnings and precautions»). Postponement of vaccination with non-live or live-attenuated vaccines should be considered in neonates and infants whose mothers received ublituximab during pregnancy.
Briumvi should not be used during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether ublituximab is excreted in breast milk. It is known that human IgGs are excreted in breast milk. There are no data on the effects of Briumvi on the breastfed infant or on milk production. A risk to the newborn/breastfed infant cannot be ruled out. The benefits of breastfeeding for the development and health of the breastfed child should be considered along with the clinical benefit of Briumvi for the mother and the potential harmful effects of Briumvi on the breastfed newborn/infant.

Fertility

The effect of ublituximab on fertility parameters in animals has not been investigated. Based on animal data, no particular hazard to the reproductive organs is apparent (see «Preclinical data»).

Effects on ability to drive and use machines

No relevant studies have been conducted. Based on the known safety profile, Briumvi is expected to have no or negligible impact on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

The most important and frequently reported adverse reactions are IRRs (45.3%) and infections (55.8%).

Tabulated list of adverse reactions

Table 2 summarises the adverse reactions that have been reported in association with the use of ublituximab. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1’000 to < 1/100), rare (≥ 1/10’000 to < 1/1’000), very rare (< 1/10’000) and not

known (cannot be estimated from the available data). Within each System Organ Class and frequency grouping, adverse reactions are presented in order of decreasing frequency.

Table 2: Adverse reactions

MedDRA System Organ Class (SOC)	Very common	Common
Infections and infestations	Upper respiratory tract infections (33.6%), Respiratory tract infections 14.9%)	Herpes virus infektionen, Lower respiratory tract infections
Blood and lymphatic system disorders		Neutropenia
Musculoskeletal and connective tissue disorders		Pain in extremity
Injury, poisoning and procedural complications	Infusion-related reactions (45.3%)[1]	

[1] Symptoms reported as IRRs within 24 hours of the infusion are described below in «Infusion-related reactions».

Description of selected adverse reactions

Infusion-related reactions (IRRs)

In active-controlled RMS trials, symptoms of IRR included pyrexia, chills, headache, tachycardia, nausea, abdominal pain, throat irritation, erythema, and anaphylactic reaction. IRRs were primarily mild to moderate in severity. The incidence of IRRs in patients treated with ublituximab was 45.3%, with the highest incidence with the first infusion (40.4%). The incidence of IRRs was 8.6% with the second infusion and decreased thereafter. 1.7% of patients experienced IRRs that led to treatment interruption. 0.4% of patients experienced IRRs that were serious. There were no fatal IRRs.

Infection

In active-controlled RMS trials, the proportion of patients who experienced a serious infection with ublituximab was 5.0% compared to 2.9% in the teriflunomide group. The overall rate of infections in patients treated with ublituximab was similar to patients who were treated with teriflunomide (55.8% vs 54.4%, respectively). The infections were predominantly mild to moderate in severity and consisted primarily of respiratory tract-related infections (mostly nasopharyngitis and bronchitis). Upper respiratory tract infections occurred in 33.6% of ublituximab treated patients and 31.8% teriflunomide treated patients. Lower respiratory tract infections occurred in 5.1% of ublituximab treated patients and 4.0% of teriflunomide treated patients.

Laboratory abnormalities

Immunoglobulins decrease

In active-controlled RMS trials, treatment with ublituximab resulted in a decrease in total immunoglobulins over the controlled period of the studies, mainly driven by the reduction in IgM. The

proportion of patients at baseline reporting IgG, IgA, and IgM below the lower limit of normal (LLN) in ublituximab treated patients was 6.3%, 0.6%, and 1.1%, respectively. Following treatment, the proportion of ublituximab treated patients reporting IgG, IgA, and IgM below the LLN at 96 weeks was 6.5%, 2.4%, and 20.9%, respectively.

Lymphocytes

In active controlled RMS trials, a transient decrease in lymphocytes was observed in 91% of ublituximab patients at Week 1. The decrease in lymphocytes was observed only once in the majority of patients treated with ublituximab and regressed by week 2; at that time, only 7.8% of the patients reported a decrease in lymphocytes. All decreases in lymphocytes were Grade 1 (< LLN-800 cells/mm^3) and 2 (between 500 and 800 cells/mm^3) in severity.

Neutrophils counts

In active-controlled RMS trials, a decrease in neutrophils counts < LLN was observed in 15% of ublituximab patients compared with 22% of patients treated with teriflunomide. The majority of the neutrophil decreases were transient (only observed once for a given patient treated with ublituximab) and were Grade 1 (between < LNN and 1500 cells/mm^3) and 2 (between 1000 and 1500 cells/mm^3) in severity. Approximately 1% of the patients in the ublituximab group had Grade 4 neutropenia vs. 0% in the teriflunomide group. One ublituximab treated patient with Grade 4 (< 500 cells/mm^3) neutropenia required specific treatment with granulocyte-colony stimulating factor.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is limited clinical trial experience in RMS with doses higher than the approved intravenous dose of ublituximab. The highest dose tested to date in RMS patients is 600 mg (Phase II dose finding study in RMS). The adverse reactions were consistent with the safety profile for ublituximab in the pivotal clinical studies.
There is no specific antidote in the event of an overdose; the infusion should be immediately interrupted and the patient should be observed for IRRs (see section «Warnings and precautions»).

Properties/Effects

ATC code

L04AG14

Mechanism of action

Ublituximab is a chimeric monoclonal antibody that selectively targets CD20-expressing cells.

CD20 is a cell surface antigen found on pre-B cells, mature and memory B cells but not expressed on lymphoid stem cells and plasma cells. The binding of ublituximab to CD20 induces lysis of CD20+ B cells primarily through antibody-dependent cell-mediated cytotoxicity (ADCC) and, to a lesser extent through complement-dependent cytotoxicity (CDC). Due to a specific glycosylation pattern of its Fc region, ublituximab displays an increased affinity for the FcγRIIIa (CD16) and antibody-dependent cellular cytolysis against B cells.

Pharmacodynamics

Treatment with ublituximab leads to rapid depletion of CD19+ cells in blood by the first day post treatment as an expected pharmacologic effect. This was sustained throughout the treatment period. For the B cell counts, CD19 is used, as the presence of ublituximab interferes with the recognition of CD20 by the assay.
In the Phase III studies, treatment with ublituximab resulted in a median reduction of 97% of CD19+ B cell counts from baseline values after the first infusion in both studies and remained depleted at this level for the duration of dosing.
In the Phase III studies, between each dose of ublituximab, 5.5% of patients showed B-cell repletion (> lower limit of normal (LLN) or baseline) at least at one time point.
The longest follow up time after the last ublituximab infusion in the Phase III studies indicates that the median time to B-cell repletion (return to baseline/LLN whichever occurred first) was 70 weeks.

Clinical efficacy

Efficacy and safety of ublituximab were evaluated in two randomised, double-blind, double-dummy, active comparator-controlled clinical trials (ULTIMATE I and ULTIMATE II), with identical design, in patients with RMS (in accordance with McDonald criteria 2010) and evidence of disease activity (as defined by clinical or imaging features) within the previous two years. Study design and baseline characteristics of the study population are summarised in Table 3.
Demographic and baseline characteristics were well balanced across the two treatment groups.
Patients were to receive either: (1) ublituximab 450 mg plus oral placebo; or (2) teriflunomide 14 mg plus placebo infusion. Oral treatment (active or placebo) was to start on Week 1 Day 1 and treatment was to continue until the last day of Week 95. Infusions (active or placebo) were to begin on Week 1 Day 1 at 150 mg then increase to 450 mg on Week 3 Day 15, and continue at 450 mg on Week 24, Week 48, and Week 72.

Table 3: Study design, demographic and baseline characteristics

Study Name	**Study 1 (ULTIMATE I) (n = 545)**	**Study 2 (ULTIMATE II) (n = 544)**
Study design		
Study population	Patients with RMS	

Disease history at screening	At least two relapses within the prior two years, one relapse within the prior year, or the presence of a T1 gadolinium (Gd)-enhancing lesion in the previous year; EDSS* between 0 and 5.5, inclusive			
Study duration	2 years			
Treatment groups	Group A: Ublituximab 450 mg IV Infusion + Oral Placebo Group B: Teriflunomide 14 mg Oral + IV Infusion Placebo			
Baseline characteristics	Ublituximab 450 mg (n = 271)	Teriflunomide 14 mg (n = 274)	Ublituximab 450 mg (n = 272)	Teriflunomide 14 mg (n = 272)
Mean age (years)	36.2	37.0	34.5	36.2
Age range (years) at inclusion	18-55	18-55	18-55	18-55
Gender distribution (% male/% female)	38.7/61.3	34.7/65.3	34.6/65.4	35.3/64.7
Mean/median disease duration since diagnosis (years)	4.9/2.9	4.5/2.5	5.0/3.2	5.0/3.7
Patients naïve to previous Disease Modifying Treatment (%)**	59.8	59.1	50.7	57.0
Mean number of relapses in the last year	1.3	1.4	1.3	1.2
Mean EDSS*	2.96	2.89	2.80	2.96
Proportion of patients with Gd-enhancing T1 lesions	43.2	42.3	51.8	49.6

* Expanded Disability Status Scale

** Patients who had not been treated with any RMS medication in the 5 years prior to randomization.

Key clinical and MRI efficacy results are presented in Table 4.

The results of these studies show that ublituximab significantly suppressed relapses and sub-clinical disease activity measured by MRI compared with oral teriflunomide 14 mg.

Table 4: Key clinical and MRI endpoints from studies ULTIMATE I and ULTIMATE II

	Study 1 (ULTIMATE I)		**Study 2 (ULTIMATE II)**	
Endpoints	Ublituximab 450 mg	Teriflunomide 14 mg	Ublituximab 450 mg	Teriflunomide 14 mg
Clinical endpoints[1]				
Annualised Relapse Rate (ARR) (primary endpoint) Relative Reduction	0.076	0.188	0.091	0.178
	59% ($p < 0.0001$)		49% ($p = 0.0022$)	
Proportion of patients Relapse-free at 96 weeks	86%	74%	87%	72%
Proportion of patients with 12-week Confirmed Disability Progression[2,3] Risk Reduction (Pooled Analysis)[4]	5.2% Ublituximab vs. 5.9% Teriflunomid			
	16% ($p = 0.5099$)			
Proportion of patients with No Evidence of Disease Activity (NEDA)	45%	15%	43%	11%
	($p < 0.0001$)[7]		($p < 0.0001$)[7]	
MRT-Endpunkte[5]				

Mean number of T1 Gd-enhancing lesions per MRI scan[6] Relative Reduction	0.016	0.491	0.009	0.250
	97% ($p < 0.0001$)		97% ($p < 0.0001$)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan[6] Relative Reduction	0.213	2.789	0.282	2.831
	92% ($p < 0.0001$)		90% ($p < 0.0001$)	

[1] Based on Modified Intent to Treat (mITT) Population, defined as all randomised patients who received at least one infusion of study medication and had one baseline and post-baseline efficacy assessment. ULTIMATE I: ublituximab (N=271), teriflunomide (N=274). ULTIMATE II: ublituximab (N=272), teriflunomide (N=272).

[2] Data prospectively pooled from Study 1 and Study 2: ublituximab (N=543), teriflunomide (N=546).

[3] Defined as an increase in EDSS score of at least 1.0 point from baseline EDSS in patients with a baseline EDSS of 5.5 or less, or at least 0.5 points in patients with a baseline EDSS of > 5.5, Kaplan-Meier estimate at week 96.

[4] Based on Hazard Ratio.

[5] Based on MRI-mITT population (mITT patients who have baseline and post-baseline MRI). ULTIMATE I: ublituximab (N=265), teriflunomide (N=270). ULTIMATE II: ublituximab (N=272), teriflunomide (N=267).

[6] At Week 96.

7 Nominal p-value.

Immunogenicity

Serum samples from patients with RMS were tested for antibodies to ublituximab during the treatment period. In clinical trials on efficacy and safety, anti-drug antibodies (ADA) were detected at one point or another in 81% of patients treated with ublituximab during the 96-week treatment phase. ADA was generally transient (at Week 96, 18.5% of patients were positive for ADA). Neutralising activity was detected in 6.4% of ublituximab-treated patients. The presence of ADA or neutralising antibodies had no observable impact on the safety or efficacy of ublituximab.

Pharmacokinetics

In the RMS studies, the pharmacokinetics (PK) of ublituximab following repeated intravenous infusions was described by a two-compartment model with first-order elimination and with PK parameters typical for an IgG1 monoclonal antibody. Ublituximab exposures increased in a dose-proportional manner (i.e., linear pharmacokinetics) over the dose range of 150 to 450 mg in patients with RMS. Administration of 150 mg ublituximab by intravenous infusion on Day 1 followed by 450 mg ublituximab by intravenous infusion over one hour on Day 15, Week 24 and Week 48 led to a geometric mean steady-state AUC of 3000 µg/ml per day (CV=28%) and a mean maximum concentration of 139 µg/ml (CV=15%).

Absorption

Ublituximab is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

Distribution

In the population pharmacokinetic analysis of ublituximab, the central volume of distribution was estimated to be 3.18 l and the peripheral volume of distribution was estimated to be 3.6 l.

Metabolism

The metabolism of ublituximab has not been directly studied, as antibodies are cleared principally by catabolism (i.e. breakdown into peptides and amino acids).

Elimination

Following intravenous infusion of 150 mg ublituximab on Day 1 followed by 450 mg ublituximab on Day 15, Week 24 and Week 48, the mean terminal elimination half-life of ublituximab was estimated to be 22 days.

Kinetics in specific patient groups

Children and adolescents

No studies have been conducted to investigate the pharmacokinetics of ublituximab in children and adolescents < 18 years of age.

Adults over 55 years old

There are no dedicated PK studies of ublituximab in patients ≥ 55 years due to limited clinical experience (see section «Dosage/Administration»).

Renal impairment

No specific studies of ublituximab in patients with renal impairment have been performed.
Patients with mild renal impairment were included in the clinical studies. There is no experience in patients with moderate and severe renal impairment. However, as ublituximab is not excreted via urine, it is not expected that patients with renal impairment require dose modification.

Hepatic impairment

No specific studies of ublituximab in patients with hepatic impairment have been performed.
Since hepatic metabolism of monoclonal antibodies such as ublituximab is negligible, hepatic impairment is not expected to impact its pharmacokinetics. Therefore, it is not expected that patients with hepatic impairment require dose modification.

Preclinical data

Non-clinical data reveal no special hazard for humans based on repeated dose toxicity studies and *in-vitro* mutagenicity studies. Carcinogenicity studies have not been conducted with ublituximab.
In an enhanced pre- and post-natal development study, pregnant cynomolgus monkeys were administered weekly intravenous doses of 30 mg/kg ublituximab (corresponding to AUC 26 times the AUC in patients at the maximum recommended dose) during either the first, second or third trimester of pregnancy, which resulted in maternal moribundity and foetal loss. Pathological observations in exposed dams involved multiple organ systems (thrombi in multiple organs, vascular necrosis in the intestine and liver, inflammation and oedema in the lungs and heart) as well as the placenta and these findings were consistent with immune-mediated adverse effects secondary to immunogenicity. Infant abnormalities were absent in dams exposed during the first trimester of pregnancy. Ublituximab-related external, visceral and skeletal abnormalities were noted in two infants from dams treated during the second trimester of pregnancy. Histopathology evaluations revealed minimal to moderate degeneration/necrosis in the brain. Foetal findings included contractures and abnormal flexion of multiple limbs and tail, shortened mandible, elongate calvarium, enlargement of ears, and/or craniomandibular abnormalities which were attributed to brain necrosis. These findings were potentially related to the immunogenic response of ublituximab in the mothers, which affected the placental exchange of nutrients.
The presence of ublituximab in mother’s milk was not assessed.

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section «Other information».

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Diluted solution for intravenous infusion

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C and subsequently for 8 hours at room temperature.
From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C and subsequently for 8 hours at room temperature, unless dilution has taken place in controlled and validated aseptic conditions

Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section «Other information».

Instructions for handling

Instructions for dilution

Briumvi should be prepared by a healthcare professional using aseptic technique. Do not shake the vial.
The product is intended for single use only.
Do not use the solution if it is discoloured or if it contains foreign particulate matter.
This medicinal product must be diluted before administration. The solution for intravenous administration is prepared by dilution of the product into an infusion bag containing isotonic sodium chloride 9 mg/ml (0.9%) solution for injection.
No incompatibilities between ublituximab and polyvinyl chloride (PVC) or polyolefin (PO) bags and intravenous administration sets have been observed.
For the first infusion, dilute one vial of product into the infusion bag (150 mg/250 ml) to a final concentration of approximately 0.6 mg/ml.
For subsequent infusions, dilute three vials of product into the infusion bag (450 mg/250 ml) to a final concentration of approximately 1.8 mg/ml.
Prior to the start of the intravenous infusion, the content of the infusion bag should be at room temperature (20-25°C).
In case an intravenous infusion cannot be completed the same day, the remaining solution should be discarded.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

Authorisation number

69599 (Swissmedic).

Packs

Briumvi 150 mg: pack of 1 vial (6 ml) (A).
Briumvi 150 mg: pack of 3 vials (6 ml) (A).

Marketing authorisation holder

Neuraxpharm Switzerland AG, Cham.

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