ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Briumvi 150 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

Ublituximab is a chimeric monoclonal antibody produced in a clone of the rat myeloma cell lineYB2/0 by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion [sterile solution]

Clear to opalescent, and 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.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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 5.1).

4.2. Posology and method of 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

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 4.4 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;
- Antihistaminic (eg. 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 4.4).

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

Based on the limited data available (see section 5.1 and section 5.2), no dose adjustment is considered necessary in patients over 55 years of age.

Renal impairment

No dose adjustment is expected to be required for patients with renal impairment (see section 5.2).

Hepatic impairment

No dose adjustment is expected to be required for patients with hepatic impairment (see section 5.2).

Paediatric population

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 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.

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 6.6.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe active infection (see section 4.4).
- Patients in a severely immunocompromised state (see section 4.4).
- Known active malignancies.

4.4. Special warnings and precautions for use

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 IRR may include pyrexia, chills, headache, tachycardia, nausea, abdominal pain, throat irritation, erythema, and anaphylactic reaction (see section 4.8).

Patients should premedicate with a corticosteroid and an antihistamine to reduce the frequency and severity of IRRs (see section 4.2). 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 4.2.

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 4.3 and 4.8).

Ublituximab has the potential for serious, sometimes life-threatening or fatal, infections (see section 4.8).

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 Deoxyribonucleic acid (DNA) and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently.

Hepatitis B virus (HBV) reactivation

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 5.1).

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 4.6).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

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 4.4 and 5.1).

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 5.1 Pharmacodynamic effects). Caution should be exercised when prescribing Briumvi taking into consideration the pharmacodynamics of other disease modifying MS therapies.

4.6. Fertility, pregnancy and lactation

Women of child-bearing potential

Women of child-bearing potential should use effective contraception while receiving ublituximab and for at least 4 months after the last infusion (see below and sections 5.1 and 5.2).

Pregnancy

Ublituximab is a monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier.

There is a limited amount of data from the use of ublituximab in pregnant women. Postponing vaccination with live or live-attenuated vaccines should be considered for neonates and infants born to mothers who have been exposed to ublituximab during pregnancy. No B-cell count data have been collected in neonates and infants exposed to ublituximab and the potential duration of B-cell depletion in neonates and infants is unknown (see section 4.4).

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy.

Reproductive toxicity was observed in a pre- and post-natal development studies (see section 5.3).

Briumvi should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus.

Breast-feeding

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.

Fertility

Preclinical data reveal no special hazard on reproductive organs based on studies of general toxicity in cynomolgus monkeys (see section 5.3).

4.7. Effects on ability to drive and use machines

Briumvi has no or negligible influence on the ability to drive and use machines.

4.8. 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	Uncommon
Infections and infestations	Upper respiratory tract infections, Respiratory tract infections	Herpes virus infections, Lower respiratory tract infections	Encephalitis, Meningitis, Meningoencephalitis
Blood and lymphatic system disorders		Neutropenia	
Musculoskeletal and connective tissue disorders		Pain in extremity	
Injury, poisoning and procedural complications	Infusion-related reactions[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

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 majority of lymphocyte decreases were observed only once for a given patient treated with ublituximab and resolved by Week 2 at which 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 <LLN 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9. 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 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressants, 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.

Pharmacodynamic effects

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 and safety

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)	0.076	0.188	0.091	0.178
Relative Reduction	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]	5.2% ublituximab vs. 5.9% teriflunomide			
Risk Reduction (Pooled Analysis)[4]	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]	
MRI Endpoints[5]				
Mean number of T1 Gd-enhancing lesions per MRI scan[6]	0.016	0.491	0.009	0.250
Relative Reduction	97% ($p < 0.0001$)		97% ($p < 0.0001$)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan[6]	0.213	2.789	0.282	2.831
Relative Reduction	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 of 1.0 point or more from the baseline EDSS score for patients with baseline score of 5.5 or less, or 0.5 or more when the baseline score is greater than 5.5, Kaplan-Meier estimates 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. 81% of ublituximab-treated patients tested positive for anti-drug antibodies (ADA) at one or

more timepoints during the 96-week treatment period in clinical efficacy and safety trials. 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with ublituximab in one or more subsets of the paediatric population in the treatment of multiple sclerosis (see section 4.2 for information on paediatric use).

5.2. Pharmacokinetic properties

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.

Biotransformation

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.

Special populations

Paediatrics

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 4.2).

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.

5.3. Preclinical safety 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Sodium citrate (E 331)
Polysorbate 80 (E 433)
Hydrochloric acid (for pH adjustment) (E 507)
Water for injections

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life

Unopened vial

3 years

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°C - 8°C and subsequently for 8 hours at room temperature, unless dilution has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not shake or 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 6.3.

6.5. Nature and contents of container

6 ml concentrate in a glass vial. Pack size of 1 or 3 vials.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other 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°C – 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.

7. MARKETING AUTHORISATION HOLDER

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí – Barcelona
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1730/001
EU/1/23/1730/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 May 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLYAND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Samsung Biologics Co., Ltd.
300 Songo bio-daero Yeonsu-gu
Incheon, South Korea 21987

Name and address of the manufacturer responsible for batch release

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí
Barcelona - Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Briumvi 150 mg concentrate for solution for infusion
ublituximab
150 mg/6ml
For intravenous use after dilution

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 150 mg ublituximab in 6 ml (25 mg/ml)

3. LIST OF EXCIPIENTS

Sodium chloride
Sodium citrate
Polysorbate 80
Hydrochloric acid
Water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
150 mg/6 ml
1 vial
3 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after dilution.
Do not shake the vial.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí – Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1730/001 (1-vial pack)
EU/1/23/1730/002 (3-vials pack)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTION ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Briumvi 150 mg concentrate for solution for infusion sterile concentrate
ublituximab
For intravenous IV use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 mg/6 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Briumvi 150 mg concentrate for solution for infusion
ublituximab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Briumvi is and what it is used for

What Briumvi is

Briumvi contains the active substance ublituximab. It is a type of protein called a monoclonal antibody. Antibodies work by attaching to specific targets in your body.

What Briumvi is used for

Briumvi is used to treat adults with relapsing forms of multiple sclerosis (RMS), where the patient has flare-ups (relapses) followed by periods with milder or no symptoms.

What is Multiple Sclerosis

Multiple Sclerosis (MS) affects the central nervous system, especially the nerves in the brain and spinal cord. In MS, white blood cells called B cells that are part of the immune system (the body's defence system) work incorrectly and attack a protective layer (called myelin sheath) around nerve cells, causing inflammation and damage. Breakdown of the myelin sheath stops the nerves from working properly and causes symptoms of MS. Symptoms of MS depend on which part of the central nervous system is affected and can include problems with walking and balance, muscle weakness, numbness, double vision and blurring, poor coordination and bladder problems.

In relapsing forms of MS, the patient has repeated attacks of symptoms (relapses) that can appear suddenly within a few hours, or slowly over several days. The symptoms disappear or improve between relapses but damage may build up and lead to permanent disability.
How does Briumvi work?

Briumvi works by attaching to a target called CD20 on the surface of B cells. B cells are a type of white blood cell which are part of the immune system. In multiple sclerosis, the immune system attacks the protective layer around nerve cells. B cells are involved in this process. Briumvi targets and removes the B cells and thereby reduces the chance of a relapse, relieves symptoms and slows down the progression of the disease.

2. What you need to know before you are given Briumvi

You must not be given Briumvi:

- if you are **allergic** to ublituximab or any of the other ingredients of this medicine (listed in section 6),
- if you are suffering from a severe infection,
- if you have been told that you have severe problems with your immune system, or
- if you have cancer.

If you are not sure, talk to your doctor before you are given Briumvi.

Warnings and precautions

Talk to your doctor before you are given Briumvi if any of the following apply to you. Your doctor may decide to delay your treatment with Briumvi, or may decide you cannot receive Briumvi if:

- you have an **infection**. Your doctor will wait until the infection is resolved before giving you Briumvi.
- you have ever had **hepatitis B** or are a carrier of the hepatitis B virus. This is because medicines like Briumvi can cause the hepatitis B virus to become active again. Before your Briumvi treatment, your doctor will check if you are at risk of hepatitis B infection. Patients who have had hepatitis B or are carriers of the hepatitis B virus will have a blood test and will be monitored by a doctor for signs of hepatitis B infection.
- you have recently been given any vaccine or might be given a vaccine in the near future.
- you have **cancer** or if you have had cancer in the past. Your doctor may decide to delay your treatment.

Infusion-related reactions

- The most common side effect of Briumvi treatment are infusion-related reactions, types of allergic reactions that develop during or shortly after a medicine is given. These can be serious.
- Symptoms of an infusion-related reaction may include:
  - itchy skin
  - hives
  - redness of the face or skin
  - throat irritation
  - trouble breathing
  - swelling of tongue or throat
  - wheezing
  - chills
  - fever
  - headache
  - dizziness
  - feeling faint
  - nausea
  - abdominal (belly) pain
  - rapid heartbeat.

- **Tell your doctor or nurse straight away if you have or think you may have any infusion-related reaction**. Infusion-related reactions can happen during the infusion or up to 24 hours after the infusion.
- To reduce the risk of infusion-related reaction, your doctor will give you other medicines before each infusion of Briumvi (see section 3) and you will be closely monitored during the infusion.
- If you get an infusion reaction, your doctor may need to stop or slow down the rate of infusion.

Infections

- Talk to your doctor before you are given Briumvi if you have or think you have an infection. Your doctor will wait until the infection is resolved before giving you Briumvi.
- You might get infections more easily with Briumvi. This is because the immune cells that Briumvi targets also help to fight infection.
- **Tell your doctor or nurse straight away if you have an infection or any of the following signs of infection during or after Briumvi treatment:**
  - fever or chills
  - cough that does not go away
  - herpes (such as cold sore, shingles or genital sores)
- **Tell your doctor or nurse straight away if you think your MS is getting worse or if you notice any new symptoms.** This is because of a very rare and life-threatening brain infection, called 'progressive multifocal leukoencephalopathy' (PML), which can cause symptoms similar to those of MS. PML can occur in patients taking medicines like Briumvi, and other medicines used for treating MS.
- **Tell your partner or carer** about your Briumvi treatment. They might notice symptoms of PML that you do not, such as memory lapses, trouble thinking, difficulty walking, sight loss, changes in the way you talk, which your doctor may need to investigate.

Vaccinations

- Tell your doctor if you have recently been given any vaccine or might be given a vaccine in the near future.
- Your doctor will check if you need any vaccinations before you start your treatment with Briumvi. You should receive a type of vaccine called a live or live attenuated vaccines at least 4 weeks before you start treatment with Briumvi. While you are being treated with Briumvi, you should not be given live or live attenuated vaccines until your doctor tells you that your immune system is no longer weakened.
- When possible, you should receive other types of vaccine called inactivated vaccines at least 2 weeks before you start treatment with Briumvi. If you would like to receive any inactivated vaccines while you are being treated with Briumvi, talk to your doctor.

Children and adolescents

Briumvi is not intended to be used in children and adolescents under 18 years old. This is because it has not yet been studied in this age group.

Other medicines and Briumvi

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular tell your doctor:

- if you are taking, have recently taken or might take medicines that affect your immune system, such as chemotherapy, immunosuppressants (except corticosteroids) or other medicines used to treat MS. This is because these may have an added effect on the immune system.
- if you plan to have any vaccinations (see "Warnings and Precautions" above).

If any of the above apply to you (or you are not sure), talk to your doctor before you are given Briumvi.

Pregnancy and breast-feeding

- Tell your doctor before being given Briumvi if you are pregnant, think that you might be pregnant or are planning to have a baby. This is because Briumvi may cross the placenta and affect your baby.
- Do not use Briumvi if you are pregnant unless you have discussed this with your doctor. Your doctor will consider the benefit of you taking Briumvi against the risk to your baby.
- If you have a baby and you received Briumvi during your pregnancy, it is important to tell your baby's doctor about receiving Briumvi so they can recommend when your baby should get vaccinated.
- It is not known whether Briumvi passes into your breast milk. Talk to your doctor about the best way to feed your baby if you take Briumvi.

Contraception for women

If you are able to become pregnant (conceive), you must use contraception:
- during treatment with Briumvi and
- for at least 4 months after your last infusion of Briumvi.

Driving and using machines

Briumvi is unlikely to affect your ability to drive and use machines.

Briumvi contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free.'

3. How Briumvi is given

Briumvi will be given to you by a doctor or nurse who is experienced in the use of this treatment. They will watch you closely while you are being given this medicine. This is in case you get any side effects. You will always be given Briumvi as a drip (intravenous infusion).

Medicines you will have before you are given Briumvi

Before you are given Briumvi, you will receive other medicines to prevent or reduce possible side effects such as infusion-related reactions (see sections 2 and 4 for information about infusion-related reactions).

You will receive a corticosteroid and an antihistamine before each infusion and you may also receive other medicines to reduce fever.

How much and how often you will be given Briumvi

- The first dose of Briumvi will be 150 mg. This infusion will last 4 hours.
- The second dose of Briumvi will be 450 mg given 2 weeks after the first dose. This infusion will last 1 hour.
- Subsequent dosing of Briumvi will be 450 mg given 24 weeks after the first dose and every 24 weeks thereafter. These infusions will last 1 hour.

How Briumvi is given

- Briumvi will be given to you by a doctor or a nurse. Briumvi must be diluted before it is given to you. Dilution will be done by a healthcare professional. It will be given as an infusion into a vein (intravenous infusion).
- You will be closely monitored while you are being given Briumvi and for at least 1 hour after the first two infusions have been given. This is in case you have any side effects such as infusion-related reactions. The infusion may be slowed, temporarily stopped, or permanently stopped if you have an infusion-related reaction, depending on how serious it is (see sections 2 and 4 for information about infusion-related reactions).

If you miss an infusion of Briumvi

- If you miss an infusion of Briumvi, talk to your doctor to arrange to have it as soon as possible. Do not wait until your next planned infusion.
- To get the full benefit of Briumvi, it is important that you receive each infusion when it is due.

If you stop Briumvi treatment

- It is important to continue your treatment for as long as you and your doctor decide that it is helping you.
- Some side effects can be related to having low levels of B cells. After you stop Briumvi treatment, you may still experience such side effects until your B cells return to normal levels.
- Before your start any other medicines, tell your doctor when you had your last Briumvi infusion.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported with Briumvi:

Serious side effects

Infusion-related reactions

- Infusion-related reactions are the most common side effect of Briumvi treatment (very common: may affect more than 1 in 10 people). In most cases these are mild reactions, but some serious reactions can happen.
- **Tell your doctor or nurse straight away if you experience any signs or symptoms of an infusion-related reaction during the infusion or up to 24 hours after the infusion.**
  Symptoms can include, but are not limited to:
  - itchy skin
  - hives
  - redness of the face or skin
  - throat irritation
  - trouble breathing
  - swelling of tongue or throat
  - wheezing
  - chills
  - fever
  - headache
  - dizziness
  - feeling faint
  - nausea
  - abdominal (belly) pain

- rapid heartbeat.

- If you have an infusion-related reaction, you will be given medicines to treat it and the infusion may need to be slowed down or stopped. When the reaction has stopped, the infusion may be continued. If the infusion-related reaction is life-threatening, your doctor will permanently stop your treatment with Briumvi.

Infections

- You might get infections more easily with Briumvi. Some of them might be serious. The following infections have been seen in patients treated with Briumvi in MS:
  - **Very common** (may affect more than 1 in 10 people)
    - upper respiratory tract infections (nose and throat infections)
    - respiratory tract infections (infection of the airways)
  - **Common** (may affect up to 1 in 10 people)
    - lower respiratory tract infections (infection of the lungs such as bronchitis or pneumonia)
    - herpes infections (cold sore or shingles)
  - **Uncommon** (may affect up to 1 in 100 people)
    - Infection of the lining around the brain and spine (meningitis), infection of the brain (encephalitis) or both (meningoencephalitis).

- Tell your doctor or nurse straight away if you notice any of these signs of infection:
  - fever or chills
  - cough which does not go away
  - herpes (such as cold sore, shingles or genital sores)
  - headache with fever, neck stiffness, sensitivity to light, nausea, confusion, seizures, personality change, incoordination (ataxia), altered consciousness and/or coma. These may be symptoms of an infection of the lining around the brain and spine (meningitis), an infection of the brain (encephalitis) or both (meningoencephalitis), which can be fatal.

  Your doctor will wait until the infection is resolved before giving you Briumvi.

Other side effects

Common (may affect up to 1 in 10 people)
- neutropenia (low levels of neutrophils, a type of white blood cell)
- pain in extremity (arms or legs)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Briumvi

Store in a refrigerator (2°C – 8°C).

Briumvi will be stored by the healthcare professionals at the hospital or clinic under the following conditions:
- This medicine is not to be used after the expiry date which is stated on the outer carton and the vial label after 'EXP'. The expiry date refers to the last day of that month.

- This medicine is to be stored in a refrigerator (2°C - 8°C). It is not to be frozen. The vial is to be kept in the outer carton in order to protect from light.

It is recommended that the product is used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the healthcare professional and would normally not be longer than 24 hours at 2°C - 8°C and subsequently 8 hours at room temperature.

Do not throw away any medicines via wastewater. These measures will help to protect the environment.

6. Contents of the pack and other information

What Briumvi contains

- The active substance is ublituximab. Each vial contains 150 mg of ublituximab in 6 ml at a concentration of 25 mg/ml.
- The other ingredients are sodium chloride, sodium citrate, polysorbate 80, hydrochloric acid and water for injections.

What Briumvi looks like and contents of the pack

- Briumvi is a clear to opalescent, and colourless to slightly yellow solution.
- It is supplied as a concentrate for solution for infusion.
- This medicine is available in packs containing 1 or 3 vials (glass vials of 6 ml concentrate). Not all pack sizes may be marketed

Marketing Authorisation Holder

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí – Barcelona
Spain

Manufacturer

Neuraxpharm Pharmaceuticals, S.L.
Avda. Barcelona 69
08970 Sant Joan Despí
Barcelona - Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Neuraxpharm Belgium
Tél/Tel: +32 (0)2 732 56 95

България
Neuraxpharm Pharmaceuticals, S.L.
Тел.: +34 93 475 96 00

Česká republika
Neuraxpharm Bohemia s.r.o.
Tel: +420 739 232 258

Lietuva
Neuraxpharm Pharmaceuticals, S.L.
Tel:+34 93 475 96 00

Luxembourg/Luxemburg
Neuraxpharm France
Tél/Tel: +32 474 62 24 24

Magyarország
Neuraxpharm Hungary Kft.
Tel.: +36 (30) 542 2071

Danmark
Neuraxpharm Sweden AB
Tlf.: +46 (0)8 30 91 41
(Sverige)

Deutschland
neuraxpharm Arzneimittel GmbH
Tel: +49 2173 1060 0

Eesti
Neuraxpharm Pharmaceuticals, S.L.
Tel: +34 93 475 96 00

Ελλάδα
Brain Therapeutics IKE
Τηλ: +302109931458

España
Neuraxpharm Spain, S.L.U.
Tel: +34 93 475 96 00

France
Neuraxpharm France
Tél: +33 1.53.62.42.90

Hrvatska
Neuraxpharm Pharmaceuticals, S.L.
Tel: +34 93 602 24 21

Ireland
Neuraxpharm Ireland Ltd
Tel: +353 1 428 7777

Ísland
Neuraxpharm Sweden AB
Sími: +46 (0)8 30 91 41
(Svíþjóð)

Italia
Neuraxpharm Italy S.p.A.
Tel: +39 0736 980619

Κύπρος
Brain Therapeutics IKE
Τηλ: +302109931458

Latvija
Neuraxpharm Pharmaceuticals, S.L.
Tel: +34 93 475 96 00

Malta
Neuraxpharm Pharmaceuticals, S.L.
Tel.:+34 93 475 96 00

Nederland
Neuraxpharm Netherlands B.V.
Tel.: +31 85 4891 608

Norge
Neuraxpharm Sweden AB
Tlf:+46 (0)8 30 91 41
(Sverige)

Österreich
Neuraxpharm Austria GmbH
Tel.:+ 43 (0) 1 208 07 40

Polska
Neuraxpharm Polska Sp. z.o.o.
Tel.: +48 783 423 453

Portugal
Neuraxpharm Portugal, Unipessoal Lda
Tel: +351 910 259 536

România
Neuraxpharm Pharmaceuticals, S.L.
Tel: +34 93 475 96 00

Slovenija
Neuraxpharm Pharmaceuticals, S.L.
Tel: +34 93 475 96 00

Slovenská republika
Neuraxpharm Slovakia a.s.
Tel: +421 255 425 562

Suomi/Finland
Neuraxpharm Sweden AB
Puh/Tel: +46 (0)8 30 91 41
(Ruotsi/Sverige)

Sverige
Neuraxpharm Sweden AB
Tel: +46 (0)8 30 91 41

This leaflet was last revised

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Read the SmPC for additional information.

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 2 weeks later (second infusion).

- Subsequent doses

Subsequent doses of Briumvi 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 minimum interval of 5 months should be maintained between each dose of Briumvi.

Figure 1: Dose and Schedule of Briumvi

First infusion	Second infusion	Subsequent infusions
Day 1	Day 15	Every 24 weeks
		

Management of IRRs before the infusion

- Briumvi treatment should be initiated and supervised by an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion-related reactions (IRRs).

- Premedication for IRRs

  The following two premedications must be administered prior to each Briumvi infusion to reduce the frequency and severity of IRRs:
  - 100 mg methylprednisolone or 10-20 mg dexamethasone (or an equivalent) approximately 30-60 minutes prior to each Briumvi infusion;
  - Antihistaminic (eg. Diphenhydramine) approximately 30-60 minutes prior to each Briumvi infusion;

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

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 discoloured or if the solution contains foreign particulate matter.
- Briumvi medicinal product must be diluted before administration. Solutions of Briumvi for intravenous administration are prepared by dilution of the product into an infusion bag

containing isotonic 0.9% sodium chloride. 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.

Method of administration

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

Table 1: Dose and Schedule of Briumvi

	Amount and Volume	Infusion Rate	Duration
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.

Management of IRRs during and after the infusion

Patients should be monitored during the infusion and for at least one hour after the completion of the first two infusions.

During the infusion

- Infusion Adjustments in case of IRRs

  In case of IRRs during any infusion, see the following adjustments.

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. Briumvi must be permanently discontinued in these patients (see section 4.3).

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, begin at half of the infusion rate at the time of onset of the IRR. If the rate is tolerated, increase the rate 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.

After the infusion

- Patients treated with Briumvi should be observed for at least one hour after the completion of the first two infusions for any symptom of an IRR.
- Physicians should alert patients that an IRR can occur within 24 hours of infusion.

Shelf life

Unopened vial

3 years

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°C - 8°C and subsequently for 8 hours at room temperature, unless dilution has taken place in controlled and validated aseptic conditions.
- In the event an intravenous infusion cannot be completed the same day, the remaining solution should be discarded.