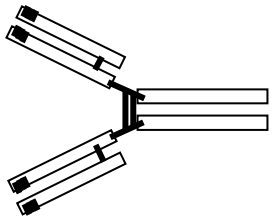
NAME OF THE MEDICINE

OCREVUS™



ocrelizumab (rch)

CAS: 637334-45-3

OCREVUS (ocrelizumab) is a recombinant humanised anti-CD20 monoclonal antibody (IgG1 subtype).

DESCRIPTION

OCREVUS is supplied in a single-dose vial containing 10 mL of preservative-free concentrate solution for infusion. Each vial contains 300 mg of ocrelizumab (30 mg/mL) with the following excipients: sodium acetate trihydrate, trehalose dihydrate, acetic acid – glacial, polysorbate 20 and water for injections.

PHARMACOLOGY

Pharmacodynamics

Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20-expressing B-cells.

The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in multiple sclerosis (MS) are not fully elucidated but is presumed to involve immunomodulation through the reduction in the number and function of CD20-expressing B-cells. Following cell surface binding, it is hypothesised that ocrelizumab selectively depletes CD20-expressing B-cells through antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis. It is presumed that the capacity of B-cell reconstitution and pre-existing humoural immunity are preserved since the cell surface antigen CD20 is expressed on pre-B cells and mature and memory B cells, but not on lymphoid stem cells and plasma cells. In addition, total numbers of cells of the innate immune system and total T-cell numbers are not affected.

Treatment with OCREVUS leads to rapid depletion of CD19+ B-cells in blood by 14 days post-treatment (first time-point of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period. For the B-cell counts, CD19 is used as the presence of OCREVUS interferes with the detection of CD20 by the assay.

In the Phase III studies, between each dose of OCREVUS, up to 5% of patients showed B-cell repletion (> lower limit of normal (LLN) or baseline) at least at one time point. The extent and duration of B-cell depletion was consistent in the primary progressive MS (PPMS) and relapsing forms of MS (RMS) trials.

The longest follow up time after the last OCREVUS infusion (Phase II WA21493, n=51) indicates that the median time to B-cell repletion (return to baseline/LLN, whichever occurred first) was 72 weeks (range 27-175 weeks). Ninety percent of all patients had their B-cells repleted to LLN or baseline by approximately two and a half years after the last infusion.

Pharmacokinetics

Pharmacokinetics of ocrelizumab in the MS studies were described by a two compartment model with time-dependent clearance, and with pharmacokinetic (PK) parameters typical for an IgG1 monoclonal antibody. Clearance and central volume were estimated at 0.17 L/day and 2.78 L, peripheral volume and inter-compartment clearance at 2.68 L and 0.294 L/day, and initial time-dependent clearance at 0.0489 L/day which declined with a half-life of 33 weeks. The overall exposure (area under curve (AUC) over the 24 week dosing intervals) was identical in the 2 x 300 mg PPMS study and the 1 x 600 mg RMS studies, as expected given an identical dose was administered. AUCτ after the fourth dose of 600 mg OCREVUS was 3510 µg/mL•day, and mean maximum concentration (C_{max}) was 212 µg/mL in RMS (600 mg infusion) and 141 µg/mL in PPMS (300 mg infusions). Terminal half-life was 26 days.

Absorption

Ocrelizumab is administered intravenously. There have been no clinical studies performed with other routes of administration.

Distribution

The population PK estimate of the central volume of distribution was 2.78 L. Peripheral volume and inter-compartment clearance were estimated at 2.68 L and 0.294 L/day.

Metabolism

The metabolism of ocrelizumab has not been directly studied, as antibodies are cleared principally by catabolism.

Excretion

Constant clearance was estimated at 0.17 L/day, and initial time-dependent clearance at 0.0489 L/day which declined with a half-life of 33 weeks. The terminal elimination half-life was 26 days.

Pharmacokinetics in special populations

Elderly Patients: No studies have been conducted to investigate the PK of ocrelizumab in patients ≥ 65 years.

Paediatric Patients: No studies have been conducted to investigate the PK of ocrelizumab in children and adolescents (< 18 years of age).

Renal impairment: No formal PK study has been conducted. Patients with mild renal impairment were included in clinical trials and no change in the PK of ocrelizumab was observed in those patients.

Hepatic impairment: No formal PK study has been conducted. Patients with mild hepatic impairment were included in clinical trials and no change in the PK of ocrelizumab was observed in those patients.

CLINICAL TRIALS

Relapsing Forms of MS (RMS)

The efficacy and safety of OCREVUS were evaluated in two randomised, double-blind, double-dummy, active comparator-controlled clinical trials with identical design in patients with RMS. Study design and baseline characteristics of the study population are summarised in Table 1.

Demographic and baseline characteristics were well balanced across the two treatment groups. Patients receiving OCREVUS (Group A) were given 600 mg every 6 months (Dose 1 - two x 300 mg IV infusions, administered two weeks apart), and subsequent doses were administered as a single 600 mg IV infusion. Patients in Group B were administered interferon beta-1a (Rebif®) 44 mcg subcutaneous (s.c.) injection three times per week.

Key clinical and magnetic resonance imaging (MRI) efficacy results are presented in Table 2 and Figure 1.

Table 1 Study design and demographic characteristics for studies WA21092 and WA21093 (RMS)

	Study 1		**Study 2**	
Study name	**WA21092 (OPERA I) (n=821)**		**WA21093 (OPERA II) (n=835)**	
Study Design				
Population	• Patients with relapsing forms of MS			
Disease history at screening	• At least two relapses within the prior two years or one relapse within the prior year • EDSS between 0 and 5.5, inclusive			
Study duration	• Two years (96 weeks)			
Treatment groups	• Group A: OCREVUS 600 mg • Group B: interferon beta-1a (Rebif®), 44 mcg s.c. (IFN)			
Baseline Characteristics	OCREVUS 600 mg (n=410)	IFN 44 mcg (n=411)	OCREVUS 600 mg (n=417)	IFN 44 mcg (n=418)
Mean age (years)	37.1	36.9	37.2	37.4
Gender distribution (% male/% female)	34.1 / 65.9	33.8 / 66.2	35.0 / 65.0	33.0 / 67.0
Mean/Median duration since onset of MS symptoms (years)	6.74 / 4.88	6.25 / 4.62	6.72 / 5.16	6.68 / 5.07
Mean/Median disease duration since diagnosis (years)	3.82 / 1.53	3.71 / 1.57	4.15 / 2.10	4.13 / 1.84
Mean EDSS	2.82	2.71	2.73	2.79
Mean number of relapses in the last	1.31	1.33	1.32	1.34

year				
Mean Gd-enhancing T1 lesion count	1.69	1.87	1.82	1.95
Mean T2 lesion count	51.04	51.06	49.26	51.01

Table 2 Key clinical and MRI endpoints from studies WA21092 and WA21093

	Study 1: WA21092 (OPERA I)		**Study 2: WA21093 (OPERA II)**	
	OCREVUS 600 mg (n=410)	**IFN 44 mcg (n=411)**	**OCREVUS 600 mg (n=417)**	**IFN 44 mcg (n=418)**
Clinical Endpoints				
Primary efficacy endpoint Annualised Relapse Rate	0.156	0.292	0.155	0.290
Relative Reduction	46% (p < 0.0001)		47% (p < 0.0001)	
Proportion of patients with 12-week Confirmed Disability Progression[3]	9.8% OCREVUS vs 15.2% IFN			
Risk Reduction (Pooled Analysis[1])	40% (p=0.0006)			
Risk Reduction (Individual Studies[2])	43% (p=0.0139)		37% (p=0.0169)	
Proportion of patients with 24-week Confirmed Disability Progression[3]	7.6% OCREVUS vs 12.0% IFN			
Risk Reduction (Pooled Analysis[1])	40% (p=0.0025)			
Risk Reduction (Individual Studies[2])	43% (p=0.0278)		37% (p=0.0370)	
Proportion of patients with at least 12-week Confirmed Disability Improvement[4] (Pooled)	20.7% OCREVUS vs 15.6% IFN			
Relative Increase (Pooled Analysis[1])	33% (p=0.0194)			
Relative Increase (Individual Studies[2])	61% (p=0.0106)		14% (p=0.4019)	
Mean change from baseline in Multiple Sclerosis Functional Composite (MSFC)	0.213	0.174	0.276	0.169
Difference	0.039 (p=0.3261)		0.107 (p=0.0040)	
Proportion of patients with No Evidence of Disease Activity (NEDA)[5]	48%	29%	48%	25%
Relative Increase[2]	64% (p<0.0001)		89% (p<0.0001)	
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI scan	0.016	0.286	0.021	0.416
Relative Reduction	94% (p<0.0001)		95% (p<0.0001)	

Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan	0.323	1.413	0.325	1.904
Relative Reduction	77% (p<0.0001)		83% (p<0.0001)	
Mean number of new T1-hypo-intense lesions (chronic black holes) per MRI scan	0.420	0.982	0.449	1.255
Relative reduction	57% (p<0.0001)		64% (p<0.0001)	
Percentage change in brain volume from week 24 to week 96	-0.572	-0.741	-0.638	-0.750
Relative reduction in brain volume loss	22.8% (p=0.0042)[6]		14.9% (p=0.0900)	
Quality of Life				
Mean change from baseline in SF-36 Physical Component Summary	0.036	-0.657	0.326	-0.833
Difference	0.693 (p=0.2193)		1.159 (p=0.0404)[6]	

[1] Data prospectively pooled from Study 1 & 2

[2] Non-confirmatory p-value; analysis not part of the pre-specified testing hierarchy

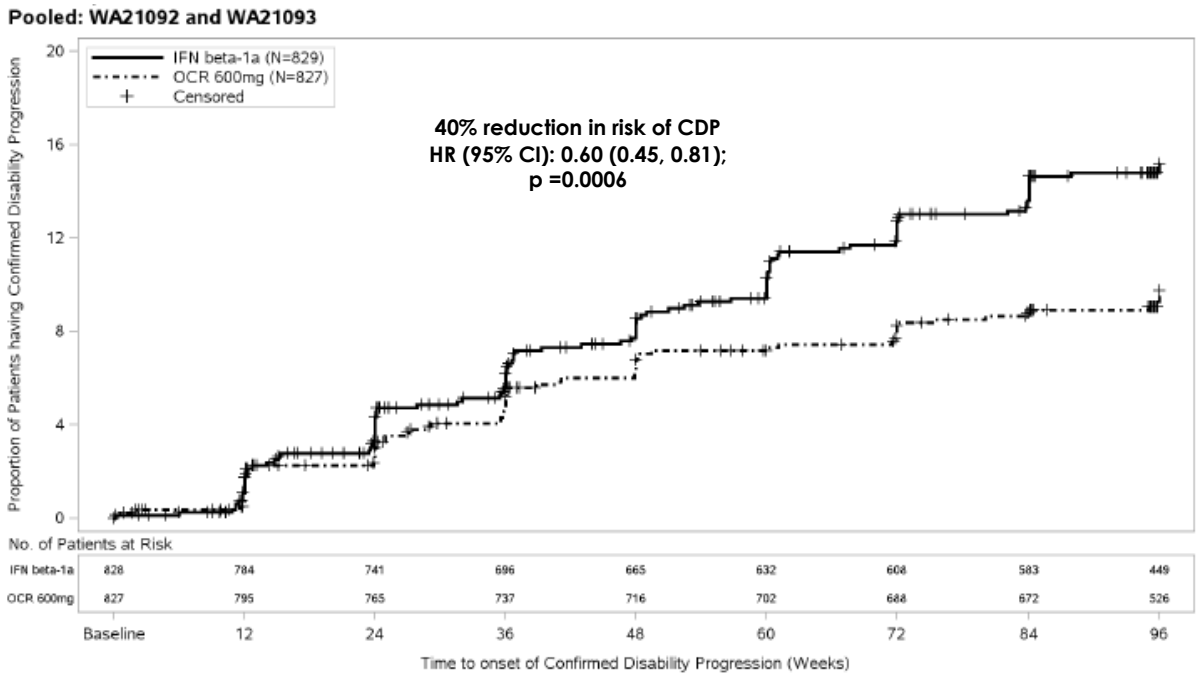
[3] Defined as an increase of ≥ 1.0 point from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline EDSS score of 5.5 or less, or ≥ 0.5 when the baseline score is > 5.5; Kaplan-Meier estimates at Week 96

[4] Defined as decrease of ≥ 1.0 point from the baseline EDSS score for patients with baseline EDSS score of ≥ 2 and ≤ 5.5, or ≥ 0.5 when the baseline score is > 5.5. Patients with baseline score < 2 were not included in analysis

[5] NEDA defined as absence of protocol defined relapses, Confirmed Disability Progression and any MRI activity (either Gd-enhancing T1 lesions, or new or enlarging T2 lesions) during the whole 96 week treatment period. Exploratory result based on complete ITT population

[6] Non-confirmatory p-value; hierarchical testing procedure terminated before reaching endpoint

Figure 1 Kaplan-Meier plot of time to onset of confirmed disability progression sustained for at least 12 weeks with the initial event of neurological worsening occurring during the double-blind treatment period (pooled ITT population)*



*Pre-specified pooled analysis of OPERA I & II

Results of the pre-specified pooled analyses of time to CDP sustained for at least 12 weeks (40% risk reduction for OCREVUS compared to interferon beta-1a, p=0.0006) were highly consistent with the results sustained for at least 24 weeks (40% risk reduction for OCREVUS compared to interferon beta-1a, p=0.0025).

Primary Progressive MS (PPMS)

The efficacy and safety of OCREVUS were evaluated in a randomised, double-blind, placebo-controlled clinical trial in patients with PPMS (Study WA25046). Study design and baseline characteristics of the study population are presented in Table 3. Demographic and baseline characteristics were well balanced across the two treatment groups.

Throughout the treatment period patients receiving OCREVUS (Group A) were given 600 mg every 6 months (as two x 300 mg IV infusions, administered two weeks apart) (see DOSAGE AND ADMINISTRATION for OCREVUS dosing instructions). Patients in Group B were administered placebo. The two x 300 mg infusions in PPMS demonstrated consistent PK/PD profiles to the 600 mg infusions in RMS.

Table 3 Study design and baseline characteristics for study WA25046

Study name	**WA25046 (ORATORIO) (n=732)**
Study Design	
Population	• Patients with primary progressive MS
Disease history at screening	• Age 18 – 55 years

	• EDSS between 3.0 and 6.5	
Study duration	• Event-driven (minimum 120 weeks and 253 confirmed disability progression events) • Median follow-up time – OCREVUS 3.0 years, placebo 2.8 years	
Treatment groups	• Group A: OCREVUS 600 mg • Group B: placebo, 2:1 randomisation	
Baseline Characteristics	OCREVUS 600 mg (n=488)	Placebo (n=244)
Mean age (years)	44.7	44.4
Gender distribution (% male/% female)	51.4 / 48.6	49.2 / 50.8
Mean/Median duration since onset of MS symptoms (years)	6.7 / 6.0	6.1 / 5.5
Mean/Median disease duration since diagnosis (years)	2.9 / 1.6	2.8 / 1.3
Mean EDSS	4.7	4.7
Number of Gd-enhancing T1 lesions (%) 0 1 ≥ 2	 72.5 12.8 14.7	 75.3 11.9 12.8

Key clinical and MRI efficacy results are presented in Table 4 and Figure 2.

Table 4 Key clinical and MRI endpoints from study WA25046 (PPMS)

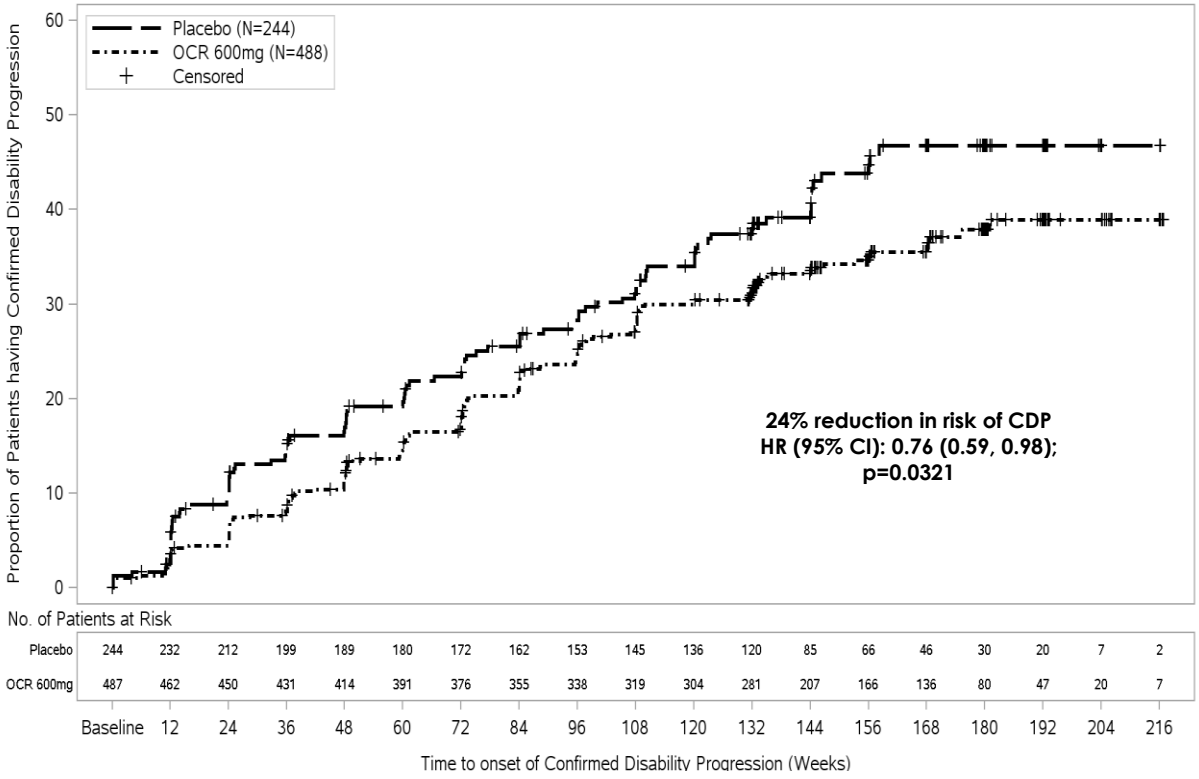
	Study 3: WA25046 (ORATORIO)	
	OCREVUS 600 mg (n=488)	**Placebo (n=244)**
Clinical Endpoints		
Primary efficacy endpoint Proportion of patients with 12 weeks Confirmed Disability Progression[1]	30.2%	34.0%
Risk Reduction	24% (p=0.0321)	
Time for 30% of patients to reach 12 weeks Confirmed Disability Progression (weeks)[2]	120.0	100.1
Proportion of patients with 24 weeks Confirmed Disability Progression[1]	28.3%	32.7%
Risk Reduction	25% (p=0.0365)	
Time for 30% of patients to reach 24 weeks Confirmed Disability Progression (weeks)[2]	134.4	108.1

Percentage change in timed 25-foot walk from baseline to week 120	38.9	55.1
Relative reduction in progression rate of walking time	29.4% (p=0.0404)	
MRI Endpoints		
Percentage change in T2 hyperintense lesion volume, from baseline to week 120	-3.4	7.4
	p<0.0001	
Percentage change brain volume from week 24 to week 120	-0.902	-1.093
Relative reduction in rate of brain volume loss	17.5% (p=0.0206)	
Quality of Life		
Mean change from baseline in SF-36 Physical Component Summary	-0.731	-1.108
Difference	0.377 (p=0.6034)	

[1]Defined as an increase of ≥ 1.0 point from the baseline EDSS score for patients with baseline score of ≤ 5.5, or ≥ 0.5 when the baseline score is > 5.5; Kaplan-Meier estimates at week 120

[2] As the proportion of patients experiencing a CDP event remained below 50% until the end of the controlled treatment period in study WA25046, median times are not estimable

Figure 2 Kaplan-Meier plot of time to onset of confirmed disability progression sustained for at least 12 weeks with the initial event of neurological worsening occurring during the double-blind treatment period (ITT population)*



*All patients in this analysis had a minimum of 120 weeks of follow-up. The primary analysis is based on all events accurred

A post-hoc analysis suggested that patients who are 50 years of age or below, or patients who have inflammation determined by MRI (Gd enchancing or T2 lesion) may receive a greater treatment benefit than patients who are over 50 years of age or patients who do not have inflammation by MRI.

Immunogenicity

Patients in the MS trials (WA21092, WA21093 and WA25046) were tested at multiple time points (baseline and every 6 months post treatment for the duration of the trial) for anti-drug antibodies (ADAs). Out of 1311 patients treated with ocrelizumab, 12 (~1%) tested positive for treatment-emergent ADAs, of which two patients tested positive for neutralising antibodies. The impact of treatment-emergent ADAs on safety and efficacy cannot be assessed given the low incidence of ADA associated with OCREVUS.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore comparison of the incidence of antibodies to OCREVUS with the incidence of antibodies to other products may be misleading.

INDICATIONS

OCREVUS is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and to reduce the frequency of relapse.

OCREVUS is indicated for the treatment of patients with primary progressive multiple sclerosis (PPMS) to delay the progression of physical disability.

CONTRAINDICATIONS

OCREVUS is contraindicated in patients with a known hypersensitivity to ocrelizumab or any of the excipients.

PRECAUTIONS

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded or stated in the patient medical record.

Infusion Related Reactions (IRRs)

OCREVUS is associated with IRRs, which may be related to cytokine release and/or other chemical mediators.

Symptoms of IRRs may occur during any infusion, but have been more frequently reported during the first infusion. IRRs can occur within 24 hours of the infusion. These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea and tachycardia (see ADVERSE EFFECTS). Patients treated with OCREVUS should

be observed for at least one hour after the completion of the infusion for any symptom of IRR. Physicians should alert patients that IRRs can occur within 24 hours of infusion.

A hypersensitivity reaction could also occur (acute allergic reaction to drug). IRRs may be clinically indistinguishable from Type 1 (IgE-mediated) acute hypersensitivity reactions (see *Hypersensitivity Reactions*).

For premedication to reduce the frequency and severity of IRRs see DOSAGE AND ADMINISTRATION.

Managing IRRs
For patients experiencing life-threatening, severe or mild to moderate IRR symptoms see DOSAGE AND ADMINISTRATION - *Infusion Adjustments during Treatment*.

Patients who experience severe pulmonary symptoms, such as bronchospasm or asthma exacerbation, must have their infusion interrupted immediately and permanently. After administering symptomatic treatment, monitor the patient until the pulmonary symptoms have resolved because initial improvement of clinical symptoms could be followed by deterioration.

Hypotension as a symptom of IRR may occur during OCREVUS infusions. Therefore withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each OCREVUS infusion. Patients with a history of congestive heart failure (New York Heart Association III & IV) were not studied in the controlled clinical trials.

Hypersensitivity Reactions

No hypersensitivity reactions to OCREVUS were reported in the controlled clinical trials.

Symptoms of a hypersensitivity reaction may be difficult to distinguish from IRRs. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensivity reaction. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to OCREVUS must not be treated (see CONTRAINDICATIONS).

Infections

Delay OCREVUS administration in patients with an active infection until the infection is resolved.

Progressive Multifocal Leukoencephalopathy (PML)
No cases of PML were identified in the OCREVUS clinical trials. John Cunningham (JC) virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies, and is associated with risk factors (e.g. patient population, polytherapy with immunosuppressants). However a risk of PML cannot be ruled out.

Physicians should be vigilant for any new or worsening neurological symptoms or signs suggestive of PML as these can be similar to an MS relapse. Physicians treating patients should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Physicians should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). If such symptoms occur, further administration of OCREVUS should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. Once PML has been excluded, the administration of OCREVUS may resume.

If a diagnosis of PML is confirmed OCREVUS must be permanently discontinued. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

Hepatitis B reactivation
There were no reports of Hepatitis B reactivation in MS patients treated with OCREVUS. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has been reported in patients treated with anti-CD20 antibodies.

HBV screening should be performed in all patients before initiation of treatment with OCREVUS as per institutional guidelines. Patients with active HBV (i.e. an active infection confirmed by positive results for Hepatitis B surface antigen (HBsAg) and anti-HB testing) should not be treated with OCREVUS. Patients with positive serology (i.e. negative for HBsAg and positive for HB core antibody (HBcAb+)) and carriers of HBV (positive for surface antigen (HBsAg+)) should consult liver disease experts before start of treatment and should be monitored and managed according to current clinical practice.

Treatment with immunosuppressants before, during or after OCREVUS

In other auto-immune conditions, use of OCREVUS concomitantly with immunosuppressive medications (e.g. chronic corticosteroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) resulted in an increase of serious infections, including opportunistic infections. Infections included and were not limited to atypical pneumonia and pneumocystis jirovecii pneumonia, varicella pneumonia, tuberculosis, histoplasmosis. In rare cases, some of these infections were fatal. Risk factors for serious infections included higher doses of OCREVUS than recommended in MS, other comorbidities, chronic use of immunosuppressants/corticosteroids, and patients from Asia.

OCREVUS should not be co-administered with other disease-modifying MS therapies. It is not recommended to use other immunosuppressives concomitantly with OCREVUS except corticosteroids for symptomatic treatment of relapses.

When initiating OCREVUS after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS, the potential for overlapping pharmacodynamic effects should be taken into consideration (see PHARMACOLOGY – *Pharmacodynamics*). Exercise caution when prescribing OCREVUS taking into consideration the pharmacodynamics of other disease-modifying MS therapies.

Vaccinations

The safety of immunisation with live or live-attenuated viral vaccines following OCREVUS therapy has not been studied and vaccination with live or live-attentuated viral vaccines is not recommended during treatment and until B-cell repletion (see PHARMACOLOGY – *Pharmacodynamics*).

After treatment with OCREVUS over 2 years, the proportion of patients with positive antibody titres against *S.pneumoniae*, mumps, rubella and varicella were generally similar to the proportions at baseline.

No data are available on the effects of vaccination in patients receiving OCREVUS. Physicians should review the immunisation status of patients being considered for treatment with OCREVUS. Patients should complete vaccinations at least 6 weeks prior to initiation of OCREVUS.

Malignancy

Immunomodulatory drugs may increase the risk of malignancy. In controlled trials, malignancies, including breast cancer, occurred more frequently in OCREVUS-treated patients although the incidence was within the background rate expected for an MS population. However, a possible increased risk of malignancy cannot be excluded. Patients should follow standard cancer screening guidelines.

Use in renal impairment

The safety and efficacy of OCREVUS in patients with renal impairment have not been formally studied. Patients with mild renal impairment were included in clinical trials. OCREVUS is a monoclonal antibody and cleared via catabolism rather than renal excretion, and a change in dose is not expected to be required for patients with renal impairment (see PHARMACOLOGY – Pharmacokinetics in Special Populations).

Use in hepatic impairment

The safety and efficacy of OCREVUS in patients with hepatic impairment have not been formally studied. Patients with mild hepatic impairment were included in clinical trials. OCREVUS is a monoclonal antibody and cleared via catabolism rather than hepatic metabolism, and a change in dose is not expected to be required for patients with hepatic impairment (see PHARMACOLOGY – Pharmacokinetics in Special Populations).

Effects on fertility

Preclinical data reveal no special hazards for humans based on studies of male and female fertility in cynomolgus monkeys. No impact on male or female fertility as assessed by fertility indices was detected in male and female cynomolgus monkeys in which OCREVUS was administered intravenously at weekly doses of up to 100 mg/kg. Exposure (based on serum AUC) in these studies was up to at least 150 times that expected in patients at the recommended clinical dose.

Use in pregnancy – Category C

OCREVUS should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the foetus. OCREVUS is a humanised monoclonal antibody and immunoglobulins are known to cross the placental barrier. Women of child bearing potential should use effective contraception while receiving OCREVUS and for 6 months after the last infusion (see PHARMACOLOGY - Excretion).

B-cell levels in human neonates following maternal exposure to OCREVUS have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient peripheral B-cell depletion and lymphocytopenia have

been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy.

It is not known whether OCREVUS can cause harm to the foetus when administered to pregnant women or whether it affects reproductive capacity. In an embryo-foetal developmental study in cynomolgus monkeys, there was no evidence of maternal toxicity, teratogenicity or embryotoxicity following weekly intravenous ocrelizumab administration at doses up to 100 mg/kg (at least 200 times the anticipated exposure, based on serum AUC, than in patients at the recommended clinical dose). IgG molecules are known to cross the placental barrier and ocrelizumab causes depletion of B-cells in the foetuses of treated cynomolgus monkeys.

In a pre- and post-natal development study in cynomolgus monkeys, weekly intravenous administration of ocrelizumab at 20 and 100 mg/kg (associated with respective exposures at least 40 and 175 times the clinical exposure, based on serum AUC) was associated with glomerulopathy (7/24 neonates), and lymphoplasmacytic inflammation in the kidney (2/24 neonates). Testicular weights of the neonates were significantly reduced in the 100 mg/kg group compared with controls, although relationship to treatment is uncertain. There were two cases of moribundity (2/24) at 100 mg/kg, one attributed to weakness due to premature birth accompanied by opportunistic infection and the other to an infective meningoencephalitis involving the cerebellum of the offspring from a maternal dam with an active infection (mastitis). The course of both neonatal infections could have potentially been impacted by B-cell depletion. Newborn offspring of maternal animals exposed to OCREVUS were noted to have depleted B-cell populations during the post-natal phase.

Use in lactation

As human IgG is excreted in human milk and the potential for OCREVUS absorption leading to B-cell depletion is unknown, women should be advised to discontinue breast-feeding during OCREVUS therapy. Animal studies have shown excretion of OCREVUS in breast milk. Measurable levels of ocrelizumab were detected in the milk of monkeys (approximately 0.2% of steady state trough serum levels) during the lactation period.

It is unknown whether OCREVUS is excreted in human breast milk or has any effect on the breast-fed child and on milk production.

Paediatric use

The safety and efficacy of OCREVUS in children and adolescents (< 18 years of age) have not been studied.

Use in the elderly

The safety and efficacy of OCREVUS in patients > 55 years of age have not been established.

Genotoxicity

Genotoxicity studies have not been conducted with OCREVUS. As ocrelizumab is a monoclonal antibody it would not be expected to have genotoxic potential.

Carcinogenicity

Carcinogenicity studies with OCREVUS have not been conducted.

Effect on laboratory tests

See ADVERSE EFFECTS.

Ability to Drive and Use Machines

No studies on the effects of OCREVUS on the ability to drive and to use machines have been performed. The pharmacological activity and adverse events reported to date do not indicate such an effect is likely.

Other

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, acute and repeated dose toxicity.

INTERACTIONS WITH OTHER MEDICINES

No formal drug interaction studies have been performed as no drug interactions are expected via CYP and other metabolising enzymes or transporters.

ADVERSE EFFECTS

The safety of OCREVUS has been established in 1311 patients across MS clinical studies, which includes 825 patients in active-controlled RMS clinical trials and 486 patients in a placebo-controlled PPMS trial. Table 5 summarises the adverse drug reactions (ADRs) that have been reported in association with the use of OCREVUS in clinical trials. The most frequently reported ADRs were IRRs and respiratory tract infections.

RMS

The ADRs described in this section were identified based on data from two identical active-controlled studies (WA21092 and WA21093) evaluating the efficacy and safety of OCREVUS in adults with RMS. In the two studies, patients (n=825) were given OCREVUS 600 mg, every 6 months (with the first dose administered as two 300 mg IV infusions separated by two weeks and all subsequent doses as a single, 600 mg infusion), or interferon beta-1a (IFN) 44 mcg (n=826) s.c. three times per week. The controlled period of the study was 96 weeks (four doses of OCREVUS).

PPMS

The ADRs described in this section were identified based on data from a placebo-controlled study (WA25046) evaluating the efficacy and safety of OCREVUS in adults with PPMS. Patients were given OCREVUS 600 mg (n=486) or placebo (n=239) every 6 months (administered as two 300 mg infusions separated by two weeks during the entire study).

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000) and very rare (< 1/10,000). Adverse reactions are presented in order of decreasing frequency.

Table 5 Summary of ADRs associated with OCREVUS (RMS or PPMS) with an incidence of ≥ 2% and higher than the comparator[1]

ADR (MedDRA)	RMS Pooled WA21092 & WA21093		PPMS WA25046[2]		Frequency category for OCREVUS
	OCREVUS (n=825)	Interferon beta-1a (n=826)	OCREVUS (n=486)	Placebo (n=239)	
Injury, Poisoning and Procedural Complications					
Infusion-related reactions[3]	283 (34.3%)	82 (9.9%)	195 (40.1%)	61 (25.5%)	Very common
Infections and Infestations					
Upper respiratory tract infection	125 (15.2%)	88 (10.7%)	59 (12.1%)	14 (5.9%)	Very common
Nasopharyngitis	123 (14.9%)	84 (10.2%)	117 (24.1%)	67 (28.0%)	Very common
Sinusitis	46 (5.6%)	45 (5.4%)	19 (3.9%)	7 (2.9%)	Common
Bronchitis	42 (5.1%)	29 (3.5%)	31 (6.4%)	15 (6.3%)	Common
Influenza	38 (4.6%)	39 (4.7%)	57 (11.7%)	20 (8.4%)	Very common
Gastroenteritis	25 (3.0%)	19 (2.3%)	22 (4.5%)	12 (5.0%)	Common
Oral herpes	25 (3.0%)	18 (2.2%)	13 (2.7%)	2 (0.8%)	Common
Respiratory tract infection	19 (2.3%)	17 (2.1%)	13 (2.7%)	2 (0.8%)	Common
Viral infection	18 (2.2%)	23 (2.8%)	15 (3.1%)	4 (1.7%)	Common
Herpes zoster	17 (2.1%)	8 (1.0%)	8 (1.6%)	4 (1.7%)	Common
Conjunctivitis	9 (1.1%)	5 (0.6%)	10 (2.1%)	1 (0.4%)	Common
Cellulitis	7 (0.8%)	5 (0.6%)	11 (2.3%)	1 (0.4%)	Common
Respiratory, Thoracic and Mediastinal Disorders					
Cough	25 (3.0%)	12 (1.5%)	34 (7.0%)	8 (3.3%)	Common
Catarrh	0	0	10 (2.1%)	2 (0.8%)	Common

[1] Interferon beta-1a 44 mcg s.c. or placebo
[2] PPMS patients were randomised 2:1 (OCREVUS:placebo)
[3] Symptoms reported as IRRs within 24 hours of infusion are described below under *Infusion Related Reactions*

Infusion Related Reactions

Across the RMS and PPMS trials, symptoms associated with IRRs included, but are not limited to, pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, nausea and tachycardia. In the controlled clinical trials there were no fatal IRRs.

In the active-controlled RMS clinical trials, IRRs were the most common adverse event in patients treated with OCREVUS 600 mg with an overall incidence of 34.3% compared with an incidence of 9.9% in the interferon beta-1a treatment group (placebo infusion). The incidence of IRRs was highest during Dose 1, infusion 1 (27.5%) and decreased over time to

<10% at Dose 4. The majority of IRRs in both treatment groups were mild to moderate (see PRECAUTIONS - *Infusion Related Reactions*).

In the placebo-controlled PPMS clinical trial, the incidence of IRRs was highest during Dose 1, infusion 1 (27.4%) and decreased with subsequent doses to < 10% at Dose 4. A greater proportion of patients in each group experienced IRRs with the first infusion of each dose compared with the second infusion of that dose. The majority of IRRs were mild to moderate (see PRECAUTIONS - *Infusion Related Reactions*).

Due to overall more infusions with the two x 300 mg regimen in the PPMS clinical trial, the total number of IRRs were higher. Therefore, after Dose 1 it is recommended to administer OCREVUS in a single 600 mg infusion in patients with RMS or PPMS (see Table 6) to reduce the total number of infusions (and concurrent exposure to prophylactic methylprednisolone) and IRRs (see PRECAUTIONS - *Infusion Related Reactions* and DOSAGE AND ADMINISTRATION).

Infection

There was no increase in serious infections associated with OCREVUS treatment. In RMS patients the rate of serious infections was lower than for interferon beta-1a, and in PPMS patients the rate was similar to placebo.

In the active-controlled RMS and placebo-controlled PPMS clinical trials, respiratory tract infections and herpes infections (both predominantly mild to moderate) were more frequently reported in the OCREVUS treatment arm.

Respiratory Tract Infections

The proportion of respiratory tract infections was higher in the OCREVUS treated patients compared to interferon and placebo. The infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections (including nasopharyngitis) and bronchitis (see Table 5).

Herpes

In the active-controlled RMS clinical trials, herpes infections were reported more frequently in OCREVUS treated patients than interferon beta-1a treated patients including herpes zoster (2.1% vs 1.0%), herpes simplex (0.7% vs 0.1%) and oral herpes (3.0% vs 2.2%), genital herpes (0.1% vs 0%), herpes virus infection (0.1% vs 0%). Infections were predominantly mild to moderate in severity and patients recovered with treatment by standard therapies. There were no reports of disseminated herpes.

In the placebo-controlled PPMS clinical trial, a higher proportion of patients with oral herpes (2.7% vs 0.8%) were observed in the OCREVUS treatment arm.

Serious Infections from clinical trials in Autoimmune Conditions other than MS

OCREVUS in combination with concomitant immunosuppressive medications (e.g. chronic steroids, non-biologic and biologic disease-modifying antirheumatic drugs (DMARDs), mycophenolate mofetil, cyclophosphamide and azathioprine) has been studied in other autoimmune conditions.

The majority of available data is from studies in patients with rheumatoid arthritis (RA), where an imbalance in serious infections was observed including, but not limited to, atypical pneumonia and pneumocystis jirovecii pneumonia, varicella pneumonia, tuberculosis, histoplasmosis in the OCREVUS-immunosuppressant group. In rare cases some of these infections were fatal. Serious infections were reported more frequently in the 1000 mg dose group compared to the 400 mg dose group or immunosuppressant-placebo group.

Risk factors for serious infections in these trials included other comorbidities, chronic use of immunosuppressants/steroids, and patients from Asia.

Laboratory Abnormalities

Immunoglobulins

Treatment with OCREVUS resulted in a decrease in total immunoglobulins over the controlled period of the studies, mainly driven by reduction in IgM, with no apparent association with serious infections.

In the active-controlled RMS clinical trials, the proportion of patients at baseline reporting IgG, IgA and IgM < lower limit of normal (LLN) in the OCREVUS treatment arm was 0.5%, 1.5% and 0.1%, respectively. Following treatment, the proportion of OCREVUS-treated patients reporting IgG, IgA and IgM < LLN at 96 weeks was 1.5%, 2.4% and 16.5%, respectively.

In the placebo-controlled PPMS clinical trial, the proportion of patients at baseline reporting IgG, IgA and IgM < LLN in the OCREVUS treatment arm was 0.0%, 0.2% and 0.2%, respectively. Following treatment, the proportion of OCREVUS-treated patients reporting IgG, IgA and IgM < LLN at 120 weeks was 1.1%, 0.5% and 15.5%, respectively.

Neutrophils

In the active-controlled treatment period of the RMS clinical trials, decreased neutrophils were observed in 14.7% of OCREVUS patients as compared to 40.9% of patients treated with interferon beta-1a. In the placebo-controlled PPMS clinical trial, the proportion of OCREVUS patients presenting decreased neutrophils was slightly higher (12.9%) than placebo patients (10.0%).

In the majority of cases decreased neutrophils were transient (only observed once for a given patient treated with OCREVUS) and were Grade 1 and 2 in severity.

Overall, approximately 1% of the patients in the OCREVUS group had Grade 3 or 4 neutropenia. These were not temporally associated with an infection.

DOSAGE AND ADMINISTRATION

General

OCREVUS is administered as an IV infusion through a dedicated line under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious IRRs. OCREVUS infusions should not be administered as an intravenous push or bolus. Use isotonic 0.9% sodium chloride solution as the infusion vehicle. In the event an IV infusion cannot be completed the same day, the remaining liquid in the infusion bag must be discarded (see *Instructions for dilution* and PRESENTATION AND STORAGE CONDITIONS).

Observe the patient for at least one hour after the completion of the infusion (see PRECAUTIONS – *Infusion Related Reactions*). After the initial dose IRRs are not increased in severity or frequency when OCREVUS is given as a single 600 mg dose compared with 2 x 300 mg doses separated by 2 weeks (see ADVERSE EFFECTS - *Infusion Related Reactions*.

Premedication for Infusion Related Reactions (IRR)

Premedicate with 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes prior to each OCREVUS infusion (see *PRECAUTIONS – Infusion Related Reactions*) and with an antihistaminic drug approximately 30-60 minutes before each infusion of OCREVUS to further reduce the frequency and severity of IRRs.

The addition of an antipyretic (e.g. paracetamol) may also be considered approximately 30-60 minutes before each infusion of OCREVUS.

Dosing

OCREVUS is administered by IV infusion as a 600 mg dose every 6 months.

Initial Dose
The initial 600 mg dose is administered as two separate IV infusions; one 300 mg infusion, followed by a second 300 mg infusion two weeks later (see Table 6).

Subsequent Doses
Subsequent doses of OCREVUS thereafter are administered as a single 600 mg IV infusion every 6 months (see Table 6). (A minimum interval of 5 months should be maintained between each dose of OCREVUS.)

Table 6 Dose and Schedule of OCREVUS

		Quantity of OCREVUS to be administered*	**Infusion Instructions**
Initial Dose (600 mg) divided into 2 infusions	Infusion 1	300 mg in 250 mL	• Initiate the infusion at a rate of 30 mL/hr • Thereafter the rate can be increased in 30 mL/hr increments every 30 minutes to a maximum of 180 mL/hr • Each infusion should be given over approximately 2.5 hrs
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent Doses (600 mg)** once every 6 months	Single infusion	600 mg in 500 mL	• Initiate the infusion at a rate of 40 mL/hr • Thereafter the rate can be increased in 40 mL/hr increments every 30 minutes to a maximum of 200 mL/hr • Each infusion should be given over approximately 3.5 hrs

* Solutions of OCREVUS for IV infusion are prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride, to a final drug concentration of approximately 1.2 mg/mL (see *Dosage and administration – Instructions for dilution*)
** The first single infusion should be administered 6 months after Infusion 1 of the Initial dose

Delayed or missed doses

If a planned infusion of OCREVUS is missed, it should be administered as soon as possible; do not wait until the next planned dose. The treatment interval for OCREVUS should be maintained between doses.

Infusion Adjustments during Treatment

No dose reductions of OCREVUS are recommended.

In case of IRRs during any infusion, see the following adjustments below. Additional information on IRRs can be found under PRECAUTIONS – *Infusion Related Reactions*.

Life-threatening IRRs

Immediately stop OCREVUS if there are signs of a life-threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. The patient should receive appropriate supportive treatment. Permanently discontinue OCREVUS in these patients.

Severe IRRs

If a patient experiences a severe IRR or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately and the patient should receive symptomatic treatment. The infusion should be restarted only after all symptoms have resolved. The initial infusion rate at restart should be half the infusion rate at the time of onset of the reaction.

Mild to Moderate IRRs

If a patient experiences a mild to moderate IRR (e.g. headache), 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 tolerated, the infusion rate may then be increased according to the patient's initial infusion schedule.

See PRECAUTIONS - *Infusion Related Reactions* for a full description of the symptoms associated with IRRs.

Dose modifications in Special Populations

Children: The safety and efficacy of OCREVUS in children and adolescents below 18 years of age have not been established.

Elderly: The safety and efficacy of OCREVUS in patients > 55 years of age have not been established.

Renal Impairment: The safety and efficacy of OCREVUS in patients with renal impairment have not been formally studied. A change in dose is not expected to be required for patients with renal impairment (see PHARMACOLOGY - Pharmacokinetics in special populations).

Hepatic Impairment: The safety and efficacy of OCREVUS in patients with hepatic impairment have not been formally studied. A change in dose is not expected to be required for patients with hepatic impairment (see PHARMACOLOGY - Pharmacokinetics in special populations).

Instructions for dilution

OCREVUS should be prepared by a healthcare professional using aseptic technique.

OCREVUS may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not use the solution if discoloured or if the solution contains discrete foreign particulate matter.

OCREVUS must be diluted before administration. Solutions of OCREVUS for IV administration are prepared by dilution into an infusion bag containing 0.9% sodium chloride (300 mg/250 mL or 600 mg/500 mL), to a final drug concentration of approximately 1.2 mg/mL.

The diluted infusion solution must be administered using an infusion set with a 0.2 or 0.22 micron in-line filter.

Prior to the start of the IV infusion, the content of the infusion bag must be at room temperature to avoid an infusion reaction to the administration of the solution at low temperatures.

Incompatibilities

No incompatibilities between OCREVUS and polyvinyl chloride or polyolefine bags, and IV administration sets have been observed. Do not use diluents other than 0.9% sodium chloride to dilute OCREVUS since use has not been tested.

OVERDOSAGE

There is limited clinical trial experience with doses higher than the approved IV dose of OCREVUS. The highest dose tested to date in MS patients is 2000 mg, administered as two 1000 mg IV infusions separated by two weeks (Phase II dose finding study in RRMS). The ADRs were consistent with the safety profile for OCREVUS in the pivotal clinical studies.

There is no specific antidote in the event of an overdose. Interrupt the infusion immediately and observe the patient for IRRs (see PRECAUTIONS – *Infusion Related Reactions*).

Treatment of overdose should consist of general supportive measures.

Contact the Poison Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

OCREVUS is a clear or slightly opalescent, and colourless to pale brown solution supplied as a single-use formulation containing 30 mg/mL ocrelizumab in 20 mM sodium acetate, 106 mM trehalose dihydrate, acetic acid – glacial (2.5 mg as buffer), 0.02% (w/v) polysorbate 20 and water for injections, at pH 5.3.

OCREVUS is a concentrate for solution for infusion supplied at a volume of 10 mL in a 15 mL glass vial.

Storage conditions
Store vial in a refrigerator at 2℃ to 8℃. Keep vial in the outer carton in order to protect from light. Do not freeze. Do not shake. Do not use after the expiry date (EXP) shown on the pack.

Shelf-life of reconstituted solution
OCREVUS does not contain any anti-microbial preservative; therefore, care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue.

To reduce microbiological hazard, the prepared infusion solution should be used immediately. If storage is necessary, the prepared infusion can be held at 2°C - 8°C for up to 24 hours and subsequently 8 hours at room temperature.

In the event an IV infusion cannot be completed the same day, the remaining solution should be discarded.

Disposal of unused/expired medicines
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

The following should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:

- Needles and syringes should never be reused
- Place all used needles and syringes into a sharps container (puncture-proof disposable container)

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
4–10 Inman Road
Dee Why NSW 2099
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Customer enquiries: 1800 233 950

POISON SCHEDULE OF THE MEDICINE

Schedule 4. Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

13 July 2017