Summary Report of Benefit-Risk Assessment

OCREVUS CONCENTRATE FOR SOLUTION FOR INFUSION 300MG/10ML

NEW DRUG APPLICATION

Active Ingredient(s)	Ocrelizumab
Product Registrant	Roche Singapore Pte. Ltd.
Product Registration Number	SIN16871P
Application Route	Abridged evaluation
Date of Approval	28 September 2023

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A INTRODUCTION

Ocrevus is indicated for the treatment of:

- Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features, to reduce the frequency of clinical relapses and delay the progression of physical disability.
- Adult patients with early primary progressive multiple sclerosis (PPMS) with imaging features characteristic of inflammatory activity to delay progression of physical disability.

The active substance, ocrelizumab, is a recombinant, humanised immunoglobulin (Ig) G1 monoclonal antibody (mAb) that selectively targets CD20-expressing B cells. The mechanisms through which ocrelizumab exerts its therapeutic clinical effects in multiple sclerosis (MS) are not fully elucidated but are presumed to involve immunomodulation through the reduction in the number and function of B cells. Binding of ocrelizumab to CD20 on target cells induces immune effector mechanisms such as antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis to selectively and effectively deplete CD20 B cells.

Ocrevus is available as concentrate for solution for infusion containing 300 mg/10 ml of ocrelizumab. Other ingredients in the concentrate for solution are sodium acetate trihydrate, glacial acetic acid, α,α-trehalose dihydrate, polysorbate 20 and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, ocrelizumab, is manufactured at Genentech Inc, Vacaville, United States. The drug product, Ocrevus Concentrate for Solution for Infusion 300 mg/10 ml, is manufactured at Roche Diagnostics GmbH, Mannheim, Germany and F. Hoffmann-La Roche Ltd, Kaiseraugst, Switzerland.

Drug substance:

Adequate controls have been presented for the cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities has been appropriately performed. Potential and actual impurities are adequately controlled.

The drug substance specifications were established in accordance with ICH Q6B guideline and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The drug substance is stored in steam-sanitised stainless steel or hastelloy freeze/thaw (F/T) vessels. The stability data presented was adequate to support the storage of drug substance at ≤ -20°C with a shelf life of 36 months.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

All manufacturing sites are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline. Information on the reference standards used for identity, assay and impurities testing was presented.

The container closure system is a 15 ml colourless type 1 glass vial with fluororesin-laminated rubber stopper and aluminium seal containing 10 ml of product. The stability data presented was adequate to support the storage of drug product at 2-8°C with a shelf life of 24 months. The shelf life after dilution is 24 hours at 2-8°C and 8 hours at 25°C and is supported with appropriate data.

C ASSESSMENT OF CLINICAL EFFICACY

RMS

The clinical efficacy of ocrelizumab for the treatment of patients with RMS was primarily supported by two randomised, double-blind, parallel-group, active-controlled, 96-week Phase III studies, WA21092 and WA21093. Both studies enrolled patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS), who experienced at least either two documented clinical attacks within 2 years or one clinical attack within one year prior to screening.

Patients were randomised in a 1:1 ratio to either receive an intravenous (IV) infusion of 600 mg of ocrelizumab every 24 weeks, with the first dose given as two separate IV infusions of 300 mg ocrelizumab two weeks apart, or the active comparator interferon beta-1a (IFN), which was administered by subcutaneous (SC) injection three times weekly in accordance with local labelling recommendations. Interferon beta-1a is considered an appropriate comparator as it is approved for the treatment of RMS.

The primary efficacy endpoint was protocol-defined annualised relapse rate (ARR) at 96 weeks. Secondary efficacy endpoints included time to onset of Confirmed Disability Progression (CDP) for at least 12 weeks and 24 weeks, proportion of patients who have Confirmed Disability Improvement (CDI) for at least 12 weeks, mean change from baseline in Multiple Sclerosis Functional Composite (MSFC) at Week 96, the total number of T1 Gd-enhancing lesions as detected by brain MRI at Weeks 24, 48, and 96, new and/or enlarging T2 hyperintense lesions per MRI scan, new T1 hypointense lesions per MRI scan, mean percentage change from Week 24 in brain volume at Week 96, and proportion of patients with No Evidence of Disease Activity (NEDA) at Week 96.The statistical methods employed, and the hierarchical testing procedure were appropriate for the endpoints studied.

A total of 821 and 835 patients were randomised into WA21092 and WA21093, respectively, and comprised mainly subjects with active disease (96% - 98%) characterised by least one prior relapse in the one year before randomisation and/or had on-going evidence of neuro-inflammatory activity as characterised by the presence of T1 gadolinium (Gd)-enhancing lesions at baseline. The demographics and baseline characteristics were balanced between the two treatment arms and across the two studies. The majority of patients were female (65% - 67%), White (88% - 92%), with a median age of 37-38 years (range 18-56 years in WA21092 and 18-55 years in WA21093) and had similar disease histories and magnetic resonance imaging (MRI) disease characteristics.

Treatment with ocrelizumab achieved a statistically significant and clinically relevant reduction in annualised relapse rate (ARR) as compared to interferon beta-1a at 96 weeks (46.5% [p<0.001] in pooled analysis). The proportion of patients who had 12-week confirmed disability progression (CDP) at 96 weeks was statistically significantly lower in the ocrelizumab arm (9.75%) as compared to the IFN arm (15.18%) (HR 0.60; 95% CI 0.45, 0.81; p=0.0006), and consistent results were observed for the 24-week CDP endpoint. In terms of 12-week confirmed disability improvement (CDI), a greater proportion of patients achieved an improvement in the ocrelizumab arm (20.70%) as compared to the IFN arm (15.64%) at 96 weeks (HR 1.33; 95% CI 1.05, 1.68; p=0.0194). Other key secondary endpoints pertaining to disease activity and brain MRI corroborated the primary endpoint.

Summary of Primary and Secondary Efficacy Endpoints at Week 96 (Studies WA21092, WA21093; ITT Population)

Study	**WA21092**		**WA21093**		**Pooled**	
Treatment	**IFN SC (N=411)**	**OCR 600mg (N=410)**	**IFN SC (N=418)**	**OCR 600mg (N=417)**	**IFN SC (N=829)**	**OCR 600mg (N=827)**
Primary efficacy endpoint						
ARR at 96 weeks						
Rate	0.292	0.156	0.290	0.155	**0.291**	**0.156**
Rate ratio (95% CI)	0.536 (0.400, 0.719)		0.532 (0.397, 0.714)		**0.535 (0.435, 0.659)**	
p-value	<0.0001		<0.0001		**<0.0001**	
Secondary efficacy endpoints - Disability						
12-week CDP						
% Patients at 96 wks	12.97	8.31	17.54	11.14	**15.18**	**9.75**
HR (95% CI)	0.57 (0.37, 0.90)		0.63 (0.42, 0.92)		**0.60 (0.45, 0.81)**	
p-value	0.0139		0.0169		**0.0006**	
24-week CDP						
% Patients at 96 wks	10.57	6.51	13.63	8.60	**12.03**	**7.58**
HR (95% CI)	0.57 (0.34, 0.95)		0.63 (0.40, 0.98)		**0.60 (0.43, 0.84)**	
p-value	0.0278		0.0370		**0.0025**	
12-week CDI						
% Patients improved	12.42	20.00	18.83	21.38	**15.64**	**20.70**
Relative Inc (95% CI)	1.61 (1.11, 2.33)		1.14 (0.84, 1.56)		**1.33 (1.05, 1.68)**	
p-value	0.0106		0.4019		**0.0194**	
MSFC						
Adj. mean change	0.174	0.213	0.169	0.276	**0.171**	**0.248**
Mean diff (95% CI)	0.039 (-0.039, 0.116)		0.107 (0.034, 0.180)		**0.077 (0.025, 0.129)**	
p-value	0.3261		0.0040		**0.0038**	
Secondary efficacy endpoints – Disease activity						
NEDA						
% Patients with NEDA	27.1	47.4	24.1	43.9	**25.7**	**45.7**

Relative Inc (95% CI) p-value	1.74 (1.39, 2.17) <0.0001*		1.81 (1.41, 2.32) <0.0001*		**1.77 (1.50, 2.09) p<0.0001**	
Secondary efficacy endpoints – Brain MRI						
T1 Gd-enhancing lesions Mean no. lesions/scan	0.286	0.016	0.416	0.021	**0.356**	**0.020**
Rate ratio (95% CI) p-value	0.058 (0.032, 0.104) <0.0001		0.051 (0.029, 0.089) <0.0001		**0.055 (0.037, 0.082) <0.0001**	
New and/or enlarging T2 hyperintense lesions Mean no. lesions/scan	1.413	0.323	1.904	0.325	**1.684**	**0.331**
Rate ratio (95% CI) p-value	0.229 (0.174, 0.300) <0.0001		0.171 (0.130, 0.225) <0.0001		**0.196 (0.162, 0.238) <0.0001**	
New T1 hypointense lesions Mean no. lesions/scan	0.982	0.420	1.255	0.449	**1.140**	**0.437**
Rate ratio (95% CI) p-value	0.428 (0.328, 0.557) <0.0001		0.357 (0.272, 0.470) <0.0001		**0.384 (0.317, 0.464) <0.0001**	
Brain volume Mean % change	-0.741	-0.572	-0.750	-0.638	**-0.744**	**-0.604**
Mean diff (95% CI) p-value % Relative reduction	0.168 (0.053, 0.283) 0.0042* 22.807 (8.186, 35.043)		0.112 (-0.018, 0.241) 0.0900 14.933 (-2.011, 30.174)		**0.140 (0.054, 0.226) 0.0015 18.817 (7.501, 28.338)**	

* Non-confirmatory p-value; hierarchical testing procedure terminated before reaching endpoint.

Subgroup analyses showed a greater improvement compared to interferon beta-1a in ARR in patients with ≥ 1 baseline presence of Gd-enhancing lesions (RR 0.363; 95% CI 0.262, 0.503; p<0.0001) vs those without baseline presence of Gd-enhancing lesions (RR 0.735; 95% CI 0.562, 0.963; p=0.0251), which suggests that the improvement in the disability demonstrated in the secondary endpoints could potentially be driven by the improvement on the neuro-inflammatory activity, which is aligned with the mechanism of action of ocrelizumab and could potentially limit the efficacy on neurodegenerative disability independent of inflammatory responses.

Uncertainty remains with regard to the clinical efficacy of ocrelizumab in SPMS as the two pivotal studies enrolled patients with RRMS and SPMS but did not provide a pre-defined breakdown of these two categories of patients. Nonetheless, a retrospective identification of SPMS patients in both pivotal studies based on non-pre-specified definitions estimated that the proportion of SPMS patients ranged from 1.9% to 10.2%. A post-hoc subgroup analysis conducted on these patients putatively identified as SPMS provided some evidence of a treatment benefit on relapse-independent disability progression with ocrelizumab. Given that relapses in RRMS and SPMS share the same underlying inflammatory pathophysiology, it is biologically plausible that the efficacy observed with the anti-inflammatory effect of ocrelizumab in RRMS will provide clinical benefit to SPMS patients with evidence of neuroinflammation. Hence, the broad indication for RMS that encompasses both RRMS and SPMS is considered acceptable.

Overall, the clinical efficacy of ocrelizumab in RMS patients can be considered adequately demonstrated across both clinical studies WA21092 and WA21093, with a statistically significant and clinically relevant reduction in relapse rates and supported by the secondary efficacy endpoints to show a clinical benefit on clinical progression and MRI lesion outcomes.

PPMS

The clinical efficacy of ocrelizumab in the treatment of patients with PPMS was primarily supported by study WA25046, a randomised, double-blind, parallel-group, placebo-controlled Phase III study. Patients were randomly assigned in a 2:1 ratio to receive either ocrelizumab 600 mg arm or placebo arm. Each dose of ocrelizumab/placebo was administered as two IV infusions of 300 mg given 14 days apart every 24 weeks. A placebo-controlled study is considered acceptable as there is currently no approved treatment for PPMS.

The primary efficacy endpoint was time to onset of CDP for at least 12 weeks during the double-blind treatment period. Secondary efficacy endpoints included time to onset of CDP for at least 24 weeks, change in Timed 25-Foot Walk (T25-FW) from baseline to Week 120, change from baseline in total volume of T2 lesions at Week 120, percent change in total brain volume from Week 24 to Week 120, and change from baseline in SF-36 PCS at Week 120. The statistical methods employed, and the hierarchical testing procedure were appropriate for the endpoints studied.

A total of 732 subjects were randomised in the study: 488 patients in the ocrelizumab arm and 244 pts in the placebo arm. Of these, 725 subjects received at least one dose of ocrelizumab or placebo. The demographic characteristics of the intent-to-treat (ITT) population were well balanced between groups. The majority of patients were White (>90% in both groups), with a median age of 46 years (range 18-56 years) and approximately half of the patients were male in both groups (51% in the ocrelizumab group and 49% in the placebo group). The baseline disease characteristics were representative of PPMS and notably different from the RMS population of WA21092 and WA21093, which is expected given the epidemiological differences between RMS and PPMS (lesser females [50% in PPMS vs 66% in RMS], older patients [approximately 10 years older for PPMS], higher EDSS score as compared to RMS [mean EDSS 4.7 vs 2.8], and half as many T1 Gd-enhancing lesions as compared to RMS).

The study met its primary efficacy endpoint to demonstrate a statistically significant, albeit clinically modest improvement in 12-week CDP (HR 0.76; 95% CI 0.59, 0.98; p=0.0321) as compared to placebo. Results of key secondary endpoints, including 24-week CDP and brain MRI endpoints, supported the primary endpoint, suggesting consistency of efficacy of ocrelizumab when compared with placebo. However, the T25FW observed by Week 120 showed that performance on the timed 25-foot walk worsened by 38.9% with ocrelizumab versus 55.1% with placebo (p=0.04). While statistical significance was shown, the absolute difference was 16.2%, which was less than the minimal clinical important difference of 20%, a value that represents a clinically meaningful change in walking performance in MS and used by clinical trials as a benchmark for improvement in walking performance.

Summary of Primary and Secondary Efficacy Endpoints at Week 120 (Study WA25046; ITT Population)

	Placebo (N=244)	**OCR 600 mg (N=488)**
Primary Endpoint		
12-Week CDP Proportion of patients with events at 120 weeks (Kaplan Meier estimate)	N=244 0.340	N=487 0.302
Hazard ratio (95% CI)	**0.76 (0.59, 0.98)**	
p-value (Log-rank)	0.0321	
Secondary Endpoints		
Disability		

24-Week CDP Proportion of patients with events at 120 weeks (Kaplan Meier estimate) Hazard ratio (95% CI) p-value (Log-rank)	N=244 0.327 **0.75 (0.58, 0.98)** 0.0365	N=487 0.283
Change in Timed 25-Foot Walk Relative Ratio to Baseline at Week 120 (MMRM) Adjusted Geometric Mean (%change) % Relative reduction (95% CI) p-value (ranked ANCOVA)	N=174 55.097 **29.337 (-1.618, 51.456)** 0.0404	N=397 38.933
Brain MRI		
T2 Lesion Volume Relative Ratio to Baseline at Week 120 (MMRM) Adjusted Geometric Mean (%change) p-value (ranked ANCOVA)	N=183 7.426 <0.0001	N=400 -3.366
Percent Change from Week 24 to Week 120 in Total Brain Volume (MMRM) Adjusted Mean (% change) % Relative reduction (95% CI) p-value	N=150 -1.093 17.475 (3.206, 29.251) 0.0206	N=325 -0.902
Quality of Life		
Change from Baseline in SF-36 PCS Score (MMRM) Adjusted Mean Difference in Adjusted Means (95% CI) p-value	N=128 -1.108 **0.377 (-1.048, 1.802)** 0.6034	N=292 -0.731

CDP - confirmed disability progression, SF-36 PCS - Short Form 36 Physical Component Summary.

Subgroup analyses showed that there was a greater reduction compared to placebo in 12-week CDP in younger patients ≤ 45 years of age (HR 0.64; 95% CI 0.45, 0.92; p=0.0170) vs patients > 45 years of age (HR 0.88; 95% CI 0.62, 1.26; p=0.4937), as well as in patients with ≥ 1 baseline presence of Gd-enhancing lesions (HR 0.65; 95% CI 0.40, 1.06; p=0.0826) vs those without baseline presence of Gd-enhancing lesions (HR 0.84; 95% CI 0.62, 1.13; 0=0.2441), which suggest that the clinical benefit of ocrelizumab is more evident in early PPMS with imaging features characteristic of inflammatory activity. This was corroborated by the subgroup analyses of the 24-week CDP, where a greater reduction compared to placebo in 24-week CDP was similarly observed in younger patients ≤ 45 years of age (HR 0.61; 95% CI 0.42, 0.90; p=0.0114) vs patients > 45 years of age (HR 0.92; 95% CI 0.63, 1.34; p=0.6478).

Taken together, the clinical efficacy of ocrelizumab in early PPMS patients with imaging features characteristic of inflammatory activity can be considered adequately demonstrated with a statistically significant, albeit clinically modest improvement in 12-week CDP as compared to placebo, as well as the subgroup analyses which suggested a greater treatment benefit in younger patients with evidence of active disease.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of ocrelizumab in RMS and PPMS was based primarily on safety data derived from 2,376 patients enrolled across two pivotal Phase III studies in RMS (WA21092 and WA21093) and one pivotal Phase III study in PPMS (WA25046). At least 1,140 MS

patients have been exposed to the proposed dose of 600 mg ocrelizumab for more than 95 weeks.

Overview of safety profile

	Phase III RMS Controlled Treatment Population		Phase III PPMS Controlled Treatment Population	
	IFN Beta-1a (N=826)	**OCR 600mg (N=825)**	**Placebo (N=239)**	**OCR 600mg (N=486)**
Any AE	688 (83.3%)	687 (83.3%)	215 (90.0%)	462 (95.1%)
Serious AE	72 (8.7%)	57 (6.9%)	53 (22.2%)	99 (20.4%)
AE leading to death	2 (0.2%)	1 (0.1%)	1 (0.4%)	4 (0.8%)
AE leading to withdrawal from treatment	51 (6.2%)	29 (3.5%)	8 (3.3%)	20 (4.1%)
Infusion related reaction (IRR)	80 (9.7%)	283 (34.3%)	61 (25.5%)	194 (39.9%)
Serious IRR	1 (0.1%)	1 (0.1%)	0	5 (1.0%)
IRRs leading to withdrawal	0	11 (1.3%)	1 (0.4%)	2 (0.4%)
Infection (SOC)	433 (52.4%)	482 (58.4%)	162 (67.8%)	339 (69.8%)
Serious infection (SOC)	24 (2.9%)	11 (1.3%)	20 (8.4%)	34 (7.0%)
Malignancies	2 (0.2%)	4 (0.5%)	2 (0.8%)	11 (2.3%)

The commonly reported AEs associated with ocrelizumab in RMS patients included infusion related reaction (IRR) (34.3% in ocrelizumab arm vs 9.7% in IFN arm), upper respiratory tract infection (15.2% in ocrelizumab arm vs 10.5% in IFN arm), and nasopharyngitis (14.8% in ocrelizumab arm vs 10.2% in IFN arm). In terms of serious AEs, the rates estimated per 100 patient-years (PY) were numerically lower in the ocrelizumab arm (5.39 per 100 PY) as compared to the IFN arm (6.29 per 100 PY), with the more commonly reported serious AEs being infections and infestations (1.3% in ocrelizumab arm vs 2.9% in IFN arm), nervous system disorders (1.0% in ocrelizumab arm vs 1.3% in IFN arm) and injury, poisoning and procedural complications (0.7% in ocrelizumab arm vs 1.2% in IFN arm). AEs leading to treatment discontinuations and deaths were similarly lower in the ocrelizumab arm (discontinuations: 3.5% in ocrelizumab arm vs 6.2% in IFN arm; deaths: 1 patient in ocrelizumab arm vs 2 patients in IFN arm).

The commonly reported AEs associated with ocrelizumab in PPMS patients were similar to RMS patients and included IRR (39.9% in ocrelizumab arm vs 25.5% in placebo arm), upper respiratory tract infections (10.9% in ocrelizumab arm vs 5.9% in placebo arm), and nasopharyngitis (22.6% in ocrelizumab arm vs 27.2% in placebo arm). In terms of serious AEs, the rates estimated per 100 PY were comparable across ocrelizumab and placebo arms (10.2 vs 11.7 per 100 PY), with the more commonly reported serious AEs being infections and infestations (6.2% in ocrelizumab arm vs 5.9% in placebo arm), nervous system disorders (3.7% in ocrelizumab arm vs 3.8% in placebo arm) and injury, poisoning and procedural complications (3.9% in ocrelizumab arm vs 4.6% in placebo arm). AEs leading to treatment discontinuations were also comparable across ocrelizumab and placebo arms (4.1% in ocrelizumab arm vs 3.3% in placebo arm), while deaths reported were higher in the ocrelizumab arm (4 patients in ocrelizumab arm vs 1 patients in placebo arm).

The types of AEs reported with ocrelizumab were generally in line with the known safety profile of B-cell depleting monoclonal antibodies. The overall incidence of AEs in the pivotal clinical studies was similar in both arms, except for IRR which was substantially higher in the

ocrelizumab arms but was expected based on the route of administration of ocrelizumab. Nonetheless, most of these reported AEs were grade 1 to 2 in severity and few led to withdrawal of study treatment.

Key AEs of special interests (AESIs) reported with ocrelizumab were representative of its mechanism of action and included IRRs, infections and malignancies. These risks have been adequately described as warnings and precautions in the package insert. In general, the safety profile of ocrelizumab in RMS and PPMS was manageable and no major safety concerns were raised.

E ASSESSMENT OF BENEFIT-RISK PROFILE

RMS

RMS is a chronic, immune-mediated disease of the central nervous system that could lead to long-term severe disability. There is currently no available curative therapy for RMS. Patients with RMS are currently managed with disease-modifying therapies (DMTs) with the objective of shortening the duration and severity of symptoms of acute relapses and delaying accumulation of disability. There remains an unmet medical need given the significant morbidity associated with the disease, and newer therapeutic options with mechanism of action which is different from other DMTs may potentially offer alternatives to patients.

In the two pivotal Phase III studies (WA21092 and WA21093) in RMS patients, treatment with ocrelizumab achieved a statistically significant and clinically relevant reduction in ARR (pooled analysis rate ratio 0.535; 95% CI: 0.435, 0.659; $p<0.001$) at 96 weeks as compared with a valid comparator, interferon beta-1a. Treatment with ocrelizumab was also able to delay the progression of disability, as evidenced by the 12-week CDP, 24-week CDP and 12-week CDI endpoints that were in favour of ocrelizumab. However, subgroup analyses suggested that the improvement in the disability demonstrated in the secondary endpoints could potentially be driven by the improvement on the neuro-inflammatory activity and limited the efficacy on neurodegenerative disability independent of inflammatory responses. Also, there was indirect evidence in terms of a post-hoc analysis conducted on a retrospective identification of SPMS patients and a biological extrapolation of ocrelizumab's anti-inflammatory effect from RMS to SPMS based on the same underlying inflammatory pathophysiology to suggest a likely clinical benefit in both RMS and SPMS patients. Nonetheless, the overall evidence was adequate to support an indication for the treatment of adult patients with RMS with active disease.

The safety profile of ocrelizumab was similar to other B-cell depleting monoclonal antibodies and was generally manageable across the clinical studies. Important risks of ocrelizumab were representative of its mechanism of action and included IRRs, infections and malignancies. These risks have been adequately addressed in the local package insert via the provision of relevant warnings and precautions, ADRs, as well as dose adjustments in the event of toxicities.

Taken together, the benefit-risk profile of ocrelizumab for the treatment of adult patients with RMS with active disease defined by clinical or imaging features, to reduce the frequency of clinical relapses and delay the progression of physical disability was considered favourable.

PPMS

Primary progressive multiple sclerosis (PPMS) affects about 10 percent of patients with MS and is characterised by slow accumulation of neurological disability without acute attacks of neurological dysfunction. The debilitating nature of the disease and the lack of an approved therapy for the treatment of PPMS presents a significant unmet medical need for this group of patients.

The pivotal Phase III study (WA25046) in PPMS patients demonstrated that treatment with ocrelizumab achieved a statistically significant, albeit clinically modest improvement in 12-week CDP (HR 0.76; 95% CI 0.59, 0.98; p=0.0321) as compared to placebo at 120 weeks. The results of the key secondary endpoints in terms of 24-week CDP and the MRI endpoints were consistent with the primary endpoint. However, ocrelizumab was not able to result in a clinically relevant improvement in walking speed, as shown by a 16% absolute difference in the performance on T25-FW between ocrelizumab and placebo which was lower than the minimal clinical important difference of 20%. Subgroup analyses also suggested a better treatment effect of ocrelizumab in younger patients with presence of T1 Gd enhancing lesions, which implied that ocrelizumab is likely to exert a greater anti-inflammatory effect which is characteristic of earlier stages of PPMS. Nonetheless, the extent of improvement observed in WA25046 was considered clinically meaningful given the unmet medical need in PPMS.

The safety profile of ocrelizumab in PPMS patients was acceptable and manageable and shown to be consistent with the safety profile demonstrated in patients with RMS. No new safety concerns were identified from the clinical study in PPMS patients.

Overall, the benefit-risk profile of ocrelizumab for the treatment of adult patients with PPMS with imaging features characteristic of inflammatory activity to delay progression of physical disability was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Ocrevus was deemed favourable and approval of the product registration was granted on 28 September 2023 for the treatment of:

- Adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features, to reduce the frequency of clinical relapses and delay the progression of physical disability.
- Adult patients with early primary progressive multiple sclerosis (PPMS) with imaging features characteristic of inflammatory activity to delay progression of physical disability.

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INJ-OCR-2023 09

Ocrevus®

Ocrelizumab

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Recombinant humanized anti-CD20 monoclonal antibody.

ATC Code: L04AA36

1.2 TYPE OF DOSAGE FORM

Concentrate for solution for infusion

1.3 ROUTE OF ADMINISTRATION

Intravenous (IV) Infusion

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: ocrelizumab

Excipients: sodium acetate trihydrate, glacial acetic acid, α,α-trehalose dihydrate, polysorbate 20, water for injection

Ocrevus is a clear or slightly opalescent, and colorless to pale brown solution supplied as a single-use formulation containing 30 mg/mL ocrelizumab in 20 mM sodium acetate, 106 mM trehalose dihydrate and 0.02% (w/v) polysorbate 20 at pH 5.3. The drug product is supplied at a volume of 10.0 mL in a 15 mL glass vial.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Ocrevus is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features, to reduce the frequency of clinical relapses and delay the progression of physical disability.

Ocrevus is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) with imaging features characteristic of inflammatory activity to delay progression of physical disability.

2.2 DOSAGE AND ADMINISTRATION

General

Substitution by any other biological medicinal product approved in the indication requires the consent of the prescribing physician.

Premedication for infusion-related reactions

Premedicate with 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes prior to each Ocrevus infusion (see section *2.4 Warnings and Precautions*) and with an antihistaminic drug (e.g. diphenhydramine) approximately 30-60 minutes before each infusion of Ocrevus to reduce the frequency and severity of infusion-related reactions.

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

Administration of Ocrevus

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 section *4.1 Storage and 4.2 Special Instructions for Use, Handling and Disposal*).

Observe the patient for at least one hour after the completion of the infusion (see section *2.4.1 Warnings and Precautions, General, Infusion-Related Reactions*).

Initial Dose

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

The initial 600 mg dose is administered as two separate IV infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion.

Subsequent Doses

Subsequent doses of Ocrevus thereafter are administered as a single 600 mg IV infusion every 6 months (see Table 1).

If patients did not experience a serious infusion-related reaction (IRR) with any previous Ocrevus infusion, a shorter (2-hour) infusion can be administered for subsequent doses (see Table 1, Option 2) (see sections *2.6.1 Undesirable Effects*, *Clinical Trials* and *3.1.2 Clinical/Efficacy Studies*).

A minimum interval of 5 months should be maintained between each dose of Ocrevus.

Table 1 Dose and Schedule of Ocrevus

		Amount of Ocrevus to be administered*	Infusion instruction
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 hr
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent Doses**	Option 1	600mg 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 hr
		OR	
	Option 2 Infusion of approximately 2 hours duration	600mg in 500 mL	• Initiate the infusion at a rate of 100 mL/hr for the first 15 minutes • Increase the infusion rate to 200 mL/hr for the next 15 minutes • Increase the infusion rate to 250 mL/hr for the next 30 minutes • Increase the infusion rate to 300 mL/hr for the remaining 60 minutes • Each infusion should be given over approximately 2 hr

* 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.

** First single infusion should be administered 6 months after Infusion 1 of 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 infusion-related reactions (IRRs) during any infusion, see the following adjustments. Additional information on IRRs can be found in section 2.4.1 Warnings and Precautions, General, Infusion-Related Reactions.

Life-threatening IRRs

Immediately stop Ocrevus if there are signs of a life-threatening or disabling infusion-related reaction 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 infusion-related reaction 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 of the infusion rate at the time of onset of the reaction.

Mild to Moderate IRRs

If a patient experiences a mild to moderate infusion-related reaction (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 section 2.4.1 Warnings and Precautions, General, Infusion-Related Reactions for full description of symptoms associated with IRRs.

2.2.1 Special Dosage Instructions

Pediatric Use

The safety and efficacy of Ocrevus in children and adolescents (<18 years) has not been studied.

Geriatric Use

The safety and efficacy of Ocrevus in patients ≥55 years of age has not been studied.

Renal Impairment

The safety and efficacy of Ocrevus in patients with renal impairment has not been formally studied. A change in dose is not expected to be required for patients with renal impairment (see section *2.5.6 Use in Special Populations, Renal Impairment and 3.2.5 Pharmacokinetics in Special Populations, Renal Impairment*).

Hepatic Impairment

The safety and efficacy of Ocrevus in patients with hepatic impairment has not been formally studied. A change in dose is not expected to be required for patients with hepatic impairment (see section *2.5.7 Use in Special Populations, Hepatic Impairment and 3.2.5 Pharmacokinetics in Special Populations, Hepatic Impairment*).

2.3 CONTRAINDICATIONS

- Hypersensitivity to ocrelizumab or to any of the excipients.
- Severe active infection until resolution (see Section *2.4 Warnings and Precautions*).
- Patients with severely immunocompromised state (see Section *2.4 Warnings and Precautions*).

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

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 file.

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 (see section *2.6 Undesirable Effects*). These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia, and anaphylaxis (see section *2.6 Undesirable 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 section 2.2 Dosage and Administration.

Managing infusion-related reactions:

For patients experiencing life-threatening, severe or mild to moderate IRR symptoms see section 2.2 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.

Hypersensitivity Reactions

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

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. 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 hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab must not be treated (see section *2.3 Contraindications*).

Infections

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

Progressive multifocal leukoencephalopathy (PML)

John Cunningham (JC) virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies, including Ocrevus, and mostly associated with risk factors (e.g. patient population, polytherapy with immunosuppressants). The reporting rate with Ocrevus has been approximately 1 case per 100,000 patients.

Since a risk of PML cannot be ruled out, physicians should be vigilant for 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 an MS relapse.

If PML is suspected, withhold dosing with Ocrevus. Evaluation of PML, including MRI scan preferably with contrast (compared with pre-treatment MRI), confirmatory CSF testing for JC Viral DNA and repeat neurological assessments, should be considered.

If PML is confirmed, discontinue treatment permanently.

Hepatitis B reactivation

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 local guidelines. Patients with active Hepatitis B virus (HBV), (i.e. an active infection confirmed by positive results for 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+]; carriers of HBV [positive for surface antigen, HBsAg+]) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Treatment with immunosuppressants before, during or after Ocrevus

When initiating Ocrevus after an immunosuppressive therapy or initiating an immunosuppressive therapy after Ocrevus, the potential for overlapping pharmacodynamics effects should be taken into consideration (see section *3.1.1 Mechanism of Action, Pharmacodynamic effects*). Exercise caution when prescribing Ocrevus taking into consideration the pharmacodynamics of other disease modifying MS therapies. Ocrevus has not been studied in combination with other disease modifying MS therapies.

Vaccinations

The safety of immunization with live or live-attenuated vaccines, following Ocrevus therapy has not been studied and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion (see section *3.1.1 Mechanism of Action, Pharmacodynamic effects*).

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

In a randomized open-label study, RMS patients treated with Ocrevus were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet hemocyanin neoantigen, and seasonal influenza vaccines. It is still recommended to vaccinate patients treated with Ocrevus with seasonal influenza vaccines that are inactivated.

Physicians should review the immunization status of patients before starting treatment with Ocrevus. Patients who require vaccination should complete their immunizations at least 6 weeks prior to initiation of Ocrevus.

Exposure in utero to ocrelizumab and vaccination of neonates and infants with live or live-attenuated vaccines

Due to the potential depletion of B-cells in neonates and infants of mothers who have been exposed to Ocrevus during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cell levels have recovered; therefore, measuring CD19-positive B-cell level, in neonates and infants, prior to vaccination is recommended.

It is recommended that all vaccinations other than live or live-attenuated should follow the local immunization schedule and measurement of vaccine-induced response titers should be considered to check whether individuals can mount a protective immune response because the efficacy of the vaccination may be decreased.

Malignancies

An increased risk of malignancy with Ocrevus may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in Ocrevus-treated patients. Breast cancer occurred in 6 of 781 females treated with Ocrevus and none of 668 females treated with REBIF or placebo. Patients should follow standard breast cancer screening guidelines.

2.4.2 Drug Abuse and Dependence

No studies on drug abuse and dependence have been conducted.

2.4.3 Ability to Drive and Use Machines

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

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential

Fertility

(see section *3.3.3 Impairment of Fertility*).

Contraception

Women of childbearing potential should use contraception while receiving Ocrevus and for 6 months after the last infusion of Ocrevus (see section *3.2.4 Pharmacokinetic Properties, Elimination*).

2.5.2 Pregnancy

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

Ocrevus should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. 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. See section 3.3.4 Nonclinical Safety, Reproductive Toxicity.

Postponing vaccination with live or live-attenuated vaccines should be considered for neonates and infants born to mothers who have been exposed to Ocrevus in utero. B-cell levels in neonates and infants following maternal exposure to Ocrevus have not been studied in clinical trials and the potential duration of B-cell depletion in neonates and infants is unknown (see section *2.4 Warnings and Precautions, 2.4.1 General, Vaccinations*).

Labor and Delivery

The safe use of Ocrevus during labor and delivery has not been established.

2.5.3 Lactation

It is unknown whether Ocrevus is excreted in human breast milk or has any effect on the breastfed child and on milk production. Animal studies have shown excretion of ocrelizumab in breast milk (see section 3.3.4 *Nonclinical Safety, Reproductive Toxicity*). Because human IgG is excreted in human milk, and the potential for ocrelizumab absorption leading to B-cell depletion is unknown, women should be advised to discontinue breastfeeding during Ocrevus therapy.

2.5.4 Pediatric Use

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

2.5.5 Geriatric Use

The safety and efficacy of Ocrevus in patients ≥55 years of age has not been studied.

2.5.6 Renal Impairment

The safety and efficacy of Ocrevus in patients with renal impairment has 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 section *3.2.5 Pharmacokinetics in Special Populations, Renal Impairment*).

2.5.7 Hepatic Impairment

The safety and efficacy of Ocrevus in patients with hepatic impairment has 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 section *3.2.5 Pharmacokinetics in Special Populations, Hepatic Impairment*).

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

The safety of Ocrevus has been evaluated 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) study. Table 2 summarizes 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.

Relapsing forms of MS

The ADRs described in this section were identified based on data from two identical active-controlled studies WA21092 and WA21093 to evaluate the efficacy and safety of Ocrevus in adults with relapsing forms of MS (RMS). In the two studies, patients were given Ocrevus 600 mg (n=825), every 6 months (with the first dose administered as two 300 mg IV infusions separated by 2 weeks and all subsequent doses as a single, 600 mg infusion), or interferon beta-1a (IFN) 44 mcg (n=826) subcutaneous 3 times per week. The controlled period of the study was 96 weeks (4 doses of Ocrevus).

Primary Progressive MS

The ADRs described in this section were identified based on data from a placebo-controlled study WA25046 to evaluate the efficacy and safety of Ocrevus in adults with primary progressive MS (PPMS). Patients were given Ocrevus 600 mg (n=486) or placebo (n=239) every 6 months (administered as two 300 mg infusions separated by 2 weeks during the entire study).

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) and very rare (< 1/10,000). Adverse reactions are presented in order of decreasing frequency.

Table 2 Summary of ADRs associated with Ocrevus (in 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 reaction [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 randomized 2:1 (Ocrevus:placebo).
[3] Symptoms reported as IRRs within 24 hours of infusion are described below in "Infusion-related reactions"

Description of selected adverse drug reactions from clinical trials

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 edema, nausea, tachycardia. In the controlled clinical trials there were no fatal IRRs.

In 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 section *2.4 Warnings and Precautions, 2.4.1 General, 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 section *2.4.1 Warnings and Precautions, General, Infusion- Related Reactions*).

Alternative Shorter Infusion of Subsequent Doses

In a study (MA30143 Shorter Infusion Substudy) designed to characterize the safety profile of shorter (2-hour) Ocrevus infusions in patients with Relapsing-Remitting Multiple Sclerosis, the incidence, intensity, and types of symptoms of IRRs were consistent with those of infusions administered over 3.5 hours (see section *3.1.2 Clinical/Efficacy Studies*).

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 the 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 predominately mild to moderate and consisted mostly of upper respiratory tract infections (including nasopharyngitis) and bronchitis (see Table 2).

Herpes

In 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, 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.

In the active-controlled (RMS) studies, 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) study, 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.

The pooled data of the Ocrevus pivotal clinical studies (RMS and PPMS) and their open-label extensions (up to approximately 7 years of exposure) have shown an apparent association between decreased levels of immunoglobulins and serious infections (SI), and was most apparent for IgG (0.5% of patients had a SI during a period with IgG < LLN). The type, severity, latency, duration, and outcome of SIs observed during episodes of immunoglobulins below LLN were consistent with the overall SIs observed in patients treated with OCR.

Neutrophils

In the active-controlled (RMS) treatment period, 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%).
The majority of the 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 and was not temporally associated with an infection.

2.6.2 Post-marketing Experience

Not applicable.

2.7 OVERDOSE

There is limited clinical trial experience with doses higher than the approved intravenous dose of Ocrevus. The highest dose tested to date in MS patients is 2000 mg, administered as two 1000 mg IV infusions separated by 2 weeks (Phase II dose finding study in RRMS). The adverse drug reactions 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 infusion-related reactions (see section *2.4 Warnings and Precautions, 2.4.1 General, Infusion-Related Reactions*).

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 Mechanism of Action

Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-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 precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in 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, ocrelizumab selectively depletes CD20-expressing B-cells through antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. The capacity of B-cell reconstitution and pre-existing humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

Pharmacodynamic effects

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 recognition of CD20 by the assay (see section *3.1.1 Mechanism of Action*).

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 PPMS and 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 (returned 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.

3.1.2 Clinical / Efficacy Studies

Relapsing forms of MS

Efficacy and safety of Ocrevus were evaluated in two randomized, double-blind, double-dummy, active comparator-controlled clinical trials with identical design, in patients with relapsing forms of MS (in accordance with McDonald criteria 2010). Study design and baseline characteristics of the study population are summarized in Table 3.

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 as 2 x 300 mg IV infusions, administered 2 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 via subcutaneous (s.c.) injection 3 times per week.

Key clinical and MRI efficacy results are presented in Table 4 and Figure 1.

Table 3 Study Design and Demographic Characteristics

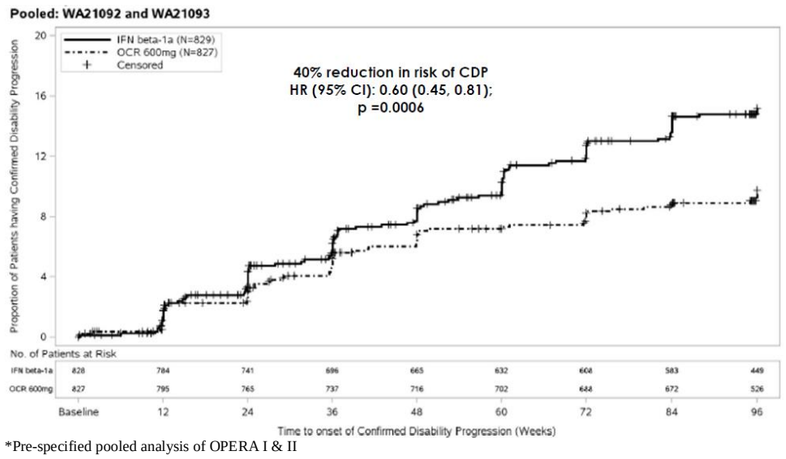
	Study 1		Study 2	
Study name	WA21092 (OPERA I) (n=821)		WA21093 (OPERA II) (n=835)	
Study design				
Study population	Patients with relapsing forms of MS			
Disease history at screening	At least two relapses within the prior two yaers or one relapse within the prior year; EDSS between 0 and 5.5, inclusive			
Study duration	2 years (96 weeks)			
Treatment groups	Group A: Ocrevus 600 mg Group B: interferon beta-1A (Rebif®), 44 mcg s.c. (IFN)			
Baseline characteristics	Ocrevus 600mg (n=410)	IFN 44 mcg (n=411)	Ocrevus 600mg (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 number of relapses in the last year	1.31	1.33	1.32	1.34
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
Mean EDSS	2.82	2.71	2.73	2.79

Table 4 Key Clinical and MRI Endpoints from Studies WA21092 and WA21093

Endpoints	Study 1: WA21092 (OPERA I)		Study 2: WA21093 (OPERA II)	
	Ocrevus 600mg (n=410)	IFN 44 mcg (n=411)	Ocrevus 600mg (n=417)	IFN 44 mcg (n=418)
Clinical Endpoints				
Annualized Relapse Rate (primary endpoint)	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-weeks 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 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 ≥ 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 (CDP), and any MRI activity (either Gd-enhancing T1 lesions, or new or enlarging T2 lesions) during the whole 96-week treatment. 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).

Shorter Infusion Substudy
The safety of the shorter (2-hour) Ocrevus infusion was evaluated in a prospective, multicenter, randomized, double-blind, controlled, parallel arm substudy to Study MA30143 (Ensemble) in patients with Relapsing-Remitting Multiple Sclerosis that were naïve to other disease modifying treatments. The first dose of Ocrevus was administered as two 300 mg infusions (600 mg total) separated by 14 days. Patients were randomized from their second dose or onwards (Dose 2 to 6) in a 1:1 ratio to either the conventional infusion group with Ocrevus infused over approximately 3.5 hours every 24 weeks, or the shorter infusion group with Ocrevus infused over approximately 2 hours every 24 weeks. The randomization was stratified by region and the dose at which patients were first randomized.

The primary endpoint was the proportion of patients with IRRs occurring during or within 24 hours following the first randomized infusion of Ocrevus. The primary analysis was performed when 580 patients were randomized. The proportion of patients with IRRs occurring during or within 24 hours following the first randomized infusion was 24.6% in the shorter infusion group compared to 23.1% in the conventional infusion group. The stratified group difference was similar. Overall, in all randomized doses, the majority of the IRRs were mild or moderate and only two IRRs were severe in intensity, with one severe IRR in each group. There were no life-threatening, fatal, or serious IRRs.

Primary Progressive MS
Efficacy and safety of Ocrevus were also evaluated in a randomized, double-blind, placebo-controlled clinical trial in patients with primary progressive MS (Study WA25046). Study design and baseline characteristics of the study population are presented in Table 5.

Demographic and baseline characteristics were well balanced across the two treatment groups.

Patients receiving Ocrevus (Group A) were given 600 mg every 6 months (as 2 x 300 mg IV infusions, administered 2 weeks apart. Patients in Group B were administered placebo. During the Phase 3 PPMS study, patients received the 600 mg dose as two 300 mg infusions, given two weeks apart throughout the treatment period. The 600 mg infusions in RMS and the 2 x 300 mg infusions in PPMS demonstrated consistent PK/PD profiles. IRR profiles per infusion are also similar, independent of whether the 600 mg dose was administered as a single 600 mg infusion or as two 300 mg infusions separated by two weeks (see sections 2.6 and 3.2), but due to overall more infusions with the 2 x 300 mg regimen, the total number of IRRs are higher. Therefore, after Dose 1 it is recommended to administer Ocrevus in a 600 mg single infusion (see Table 1) to reduce the total number of infusions, (with concurrent exposure to prophylactic methylprednisolone) and the related infusion reactions.

Table 5 Study design and baseline characteristics for Study WA25046

Study Name	Study WA25046 ORATORIO (n=732)	
Study design		
Study population	Patients with primary progressive form of MS	
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*	
Disease history at screening	Age 18-55 years, EDSS of 3.0 to 6.5	
Treatment groups	Group A: Ocrevus 600 mg Group B: Placebo, in 2:1 randomization	
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 PPMS 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

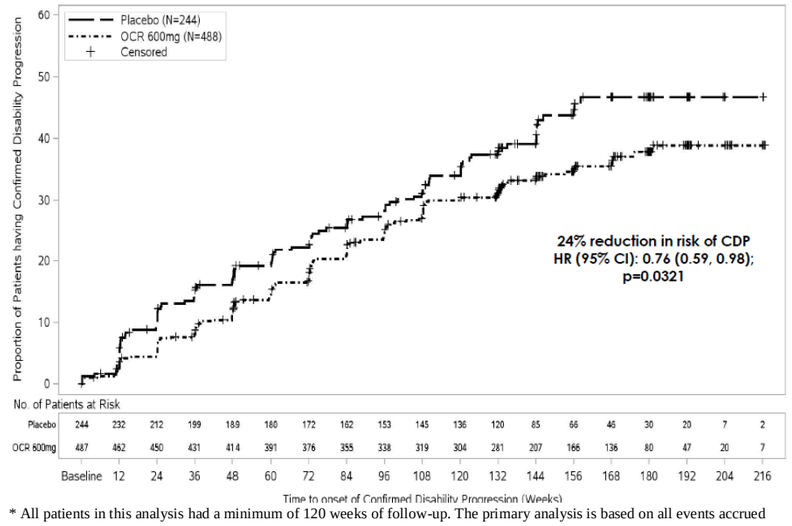
Key clinical and MRI efficacy results are presented in Table 6 and Figure 2.

Table 6 Key Clinical and MRI Endpoints from Study WA25046 (PPMS)

Endpoints	Study 3 WA25046 (Oratorio)	
	Ocrevus 600mg (n=488)	Placebo (n-244)
Clinical Endpoints		
Primary efficacy endpoint Proportion of patients with 12 weeks - Confirmed Disability Progression[1] (primary endpoint)	30.2%	34.0%
Risk reduction	24% (p=0.0321)	
Proportion of patients with 24 weeks – Confirmed Disability Progression[1]	28.3%	32.7%
Risk reduction	25% (p=0.0365)	
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 in 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 less, or ≥ 0.5 when the baseline score is > 5.5, Kaplan-Meier estimates at Week 120

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 accrued

Post-hoc analyses were performed in the Extended Controlled Period (ECP), which includes double-blinded treatment and approximately 9 additional months of controlled follow-up before continuing into the Open-Label Extension (OLE) or until withdrawal from study treatment. The proportion of patients with 24 week Confirmed Disability Progression of EDSS≥7.0 (24W-CDP of EDSS≥7.0, time to wheelchair) was 9.1% in the placebo group compared to 4.8% in the Ocrevus group at Week 144, resulting in a 47% risk reduction of the time to wheelchair (HR 0.53, [0.31, 0.92]) during the ECP. These results were exploratory in nature and included data after unblinding.

3.1.3 Immunogenicity

Patients in 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 antidrug antibodies (ADAs). Out of 1311 patients treated with ocrelizumab, 12 (~1%) tested positive for treatment-emergent ADAs, of which 2 patients tested positive for neutralizing 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.

3.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics of Ocrevus in the MS studies were described by a two compartment model with time-dependent clearance, and with 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 (AUC over the 24 week dosing intervals) was identical in the 2 x 300 mg in PPMS and 1 x 600 mg in RMS studies, as expected given an identical dose was administered. Area under curve (AUCτ) after the 4th dose of 600 mg Ocrevus was 3510 µg/mL•day, and mean maximum concentration (Cmax) was 212 µg/mL in RMS (600 mg infusion) and 141 µg/mL in PPMS (300 mg infusions). Terminal half-life was 26 days.

3.2.1 Absorption
Ocrevus is administered as an IV infusion. There have been no studies performed with other routes of administration.

3.2.2 Distribution
The population pharmacokinetics 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.

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

3.2.4 Elimination
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.

3.2.5 Pharmacokinetics in Special Populations
Pediatric Population
No studies have been conducted to investigate the pharmacokinetics of Ocrevus in children and adolescents (<18 years of age).

Geriatric Population
No studies have been conducted to investigate the pharmacokinetics of Ocrevus in patients ≥55 years.

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

Hepatic impairment
No formal pharmacokinetic study has been conducted. Patients with mild hepatic impairment were included in clinical trials, and no change in the pharmacokinetics was observed in those patients.

3.3 NONCLINICAL SAFETY
3.3.1 Carcinogenicity
No carcinogenicity studies have been performed as no appropriate animal or in vitro models are available to assess the carcinogenic potential of Ocrevus.

3.3.2 Genotoxicity
No studies have been performed to assess the mutagenic potential of Ocrevus. As an antibody, Ocrevus is not expected to interact directly with DNA or other chromosomal material.

3.3.3 Impairment of Fertility
Nonclinical data reveal no special hazards for humans based on studies of male and female fertility in cynomolgus monkeys.

3.3.4 Reproductive Toxicity
It is not known whether Ocrevus can cause harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. In an embryo-fetal developmental study in cynomolgus monkeys, there was no evidence of maternal toxicity, teratogenicity, or embryotoxicity following Ocrevus administration at 75/100 mg/kg (loading dose/study dose). As IgG molecules are known to cross the placental barrier Ocrevus causes depletion of B-cells in the fetuses of treated cynomolgus monkeys.

In a pre- and post-natal development study in cynomolgus monkeys, administration of Ocrevus (15/20 and 75/100 mg/kg loading/study doses, which correspond to human equivalent doses of approximately 3000 mg (approximately 5 x clinical dose) and 15000 mg (approximately 25 x clinical dose), respectively) was associated with glomerulopathy (7/24 animals), lymphoid follicle formation in bone marrow (9/24 animals), and lymphoplasmacytic inflammation in the kidney (2/24 animals). Testicular weights of the neonates were significantly reduced in the 75/100 mg/kg group compared with controls. There were two cases of moribundity on study (2/24), 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. Measurable levels of Ocrevus were detected in milk (approximated 0.2% of steady state trough serum levels) during the lactation period (see section *2.5.3 Lactation*).

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

4. PHARMACEUTICAL PARTICULARS
4.1 STORAGE
Vials
Store vials at 2-8°C.

Keep the vial in the outer carton to protect from light.

Do not freeze. Do not shake.

Shelf life
As registered locally.

This medicine should not be used after the expiry date (EXP) shown on the pack.

Shelf-life of the solution for intravenous infusion
The prepared infusion solution should be used immediately. If not used immediately, it can be stored up to 24 hours at 2 - 8ºC and 8 hours at room temperature (up to 25ºC).

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

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL
Ocrevus should be prepared by a healthcare professional using aseptic technique. A sterile needle and syringe should be used to prepare the diluted infusion solution.

The product contains no preservative and is intended for single use only.

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

Ocrevus drug product must be diluted before administration. Solutions of Ocrevus for IV administration are prepared by dilution of the drug product 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 should be at room temperature.

Incompatibilities
No incompatibilities between Ocrevus and polyvinyl chloride (PVC) or polyolefin (PO) bags and IV administration sets have been observed.

Do not use other diluents to dilute Ocrevus since its use has not been tested.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

The following points 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).

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

4.3 PACKS
One pack contains one vial (Type 1 glass vial with butyl rubber stopper, aluminium seal and flip-off cap).

Medicine: keep out of reach of children

Current at September 2023

F. Hoffmann-La Roche Ltd, Basel, Switzerland