

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ocrevus 300 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg of ocrelizumab in 10 mL at a concentration of 30 mg/mL. The final drug concentration after dilution is approximately 1.2 mg/mL.

Ocrelizumab is a recombinant humanised anti-CD20 monoclonal antibody produced in Chinese Hamster Ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, and colourless to pale brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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 (see section 5.1).

Ocrevus is indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity (see section 5.1).

4.2 Posology and method of administration

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

Premedication for infusion-related reactions

The following two premedications must be administered prior to each Ocrevus infusion to reduce the frequency and severity of IRRs (see Infusion-related reactions in section 4.4 for additional steps to reduce IRRs):

- 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each Ocrevus infusion;
- antihistamine approximately 30-60 minutes prior to each Ocrevus infusion;

In addition, premedication with an antipyretic (e.g paracetamol) may also be considered approximately 30-60 minutes prior to each Ocrevus infusion.

Posology:

Initial Dose

The initial 600 mg dose is administered as two separate intravenous infusions; first as a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion (Table 1).

Subsequent Doses

Subsequent doses of Ocrevus thereafter are administered as a single 600 mg intravenous infusion every 6 months (Table 1). The first subsequent dose of 600 mg should be administered six months after the first infusion of the initial dose. A minimum interval of 5 months should be maintained between each dose of Ocrevus.

Infusion Adjustments in case of IRRs

In case of IRRs during any infusion, see the following adjustments. Additional information on IRRs can be found in section 4.4.

Life-threatening IRRs

If there are signs of a life threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome, the infusion must be stopped immediately and the patient should receive appropriate treatment. Ocrevus must be permanently discontinued in these patients (see section 4.3).

Severe IRRs

If a patient experiences a severe IRR (such as dyspnea) 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. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

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 rate. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

Dose Modifications during Treatment

The above examples of dose interruption and slowing (for mild/moderate and severe IRRs) will result in a change in the infusion rate and increase the total duration of the infusion, but not the total dose. No dose reductions of Ocrevus are recommended.

Delayed or Missed Doses

If an infusion of Ocrevus is missed, it should be administered as soon as possible; do not wait until the next planned dose. The treatment interval of 6 months (with a minimum of 5 months) for Ocrevus should be maintained between doses (see Table 1).

Special Populations

Adults over 55 years old and elderly population

Based on the limited data available (see section 5.1 and section 5.2), no posology adjustment is needed in patients over 55 years of age. Patients enrolled in the ongoing clinical trials continue to be dosed with 600 mg ocrelizumab every six months after they become 55 and older.

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. There is no experience in patients with moderate and severe renal impairment. Ocrevus is a monoclonal antibody and cleared via catabolism (i.e. breakdown into peptides and amino acids), and a change in dose is not expected to be required for patients with renal impairment (see section 5.2).

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. There is no experience in patients with moderate and severe hepatic impairment. 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 5.2).

Paediatric population

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

Method of Administration

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

Table 1: Dose and Schedule of Ocrevus

		Amount of Ocrevus to be administered	Infusion instructions
Initial Dose (600 mg) divided into 2 infusions	Infusion 1	300 mg in 250 mL	<ul style="list-style-type: none"> • Initiate the infusion at a rate of 30 mL/hour for 30 minutes • The rate can be increased in 30 mL/hour increments every 30 minutes to a maximum of 180 mL/hour. • Each infusion should be given over approximately 2.5 hours
	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	<ul style="list-style-type: none"> • Initiate the infusion at a rate of 40 mL/hour for 30 minutes • The rate can be increased in 40 mL/hour increments every 30 minutes to a maximum of 200 mL/hour • Each infusion should be given over approximately 3.5 hours

Solutions of Ocrevus for intravenous infusion are prepared by dilution of the medicinal product into an infusion bag containing 0.9% sodium chloride, to a final concentration of approximately 1.2 mg/mL. For instructions on dilution of the medicinal product before administration see section 6.6.

Patients should be monitored during the infusion and for at least one hour after the completion of the infusion (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Current active infection (see section 4.4)
- Patients in a severely immunocompromised state (see section 4.4).

- Known active malignancies (see section 4.4)

4.4 Special warnings and precautions for use

Traceability

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

Infusion-Related Reactions (IRRs)

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 section 4.8).

Before the infusion:

- Management of severe reactions: Appropriate resources for the management of severe reactions such as serious IRR, hypersensitivity reactions and/or anaphylactic reactions should be available.
- 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.
- Premedication: Patients must receive premedication to reduce the frequency and severity of IRRs (see section 4.2.).

During the infusion:

- The following measures need to be taken for patients who experience severe pulmonary symptoms, such as bronchospasm or asthma exacerbation:
 - their infusion must be interrupted immediately and permanently
 - symptomatic treatment must be administered
 - the patient must be monitored until the pulmonary symptoms have resolved because initial improvement of clinical symptoms could be followed by deterioration
- Hypersensitivity may be difficult to distinguish from an IRR in terms of symptoms. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently (see ‘Hypersensitivity Reactions’ below).

After the infusion:

- 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 an IRR can occur within 24 hours of infusion.

For guidance regarding posology for patients experiencing IRR symptoms see section 4.2.

Hypersensitivity Reactions

A hypersensitivity reaction could also occur (acute allergic reaction to medicinal product). Type 1 acute hypersensitivity reactions (IgE-mediated) may be clinically indistinguishable from IRR 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. Patients with known IgE mediated hypersensitivity to ocrelizumab must not be treated (see section 4.3).

Infection

Ocrevus administration must be delayed in patients with an active infection until the infection is resolved.

It is recommended to verify the patient's immune status before dosing since severely immunocompromised patients (e.g. with lymphopenia, neutropenia, hypogammaglobulinemia) should not be treated (see sections 4.3 and 4.8).

The overall proportion of patients experiencing a serious infection was similar to comparators (see section 4.8). The frequency of grade 4 (life-threatening) and grade 5 (fatal) infections was low in all treatment groups, but in PPMS it was higher with Ocrevus compared with placebo for life-threatening (1.6% vs 0.4%) and fatal (0.6% vs 0%) infections. All life-threatening infections resolved without discontinuing ocrelizumab.

In PPMS, patients with swallowing difficulties are at a higher risk of aspiration pneumonia. Ocrevus treatment may further increase the risk of severe pneumonia in these patients. Physicians should take prompt action for patients presenting with pneumonia.

Progressive multifocal leukoencephalopathy (PML)

A risk of PML cannot be ruled-out since John Cunningham (JC) virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies and other MS therapies, and associated with risk factors (e.g. patient population, polytherapy with immunosuppressants).

Physicians should be vigilant for the early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms, as these can be similar to MS disease.

If PML is suspected, dosing with Ocrevus must be withheld. Evaluation including Magnetic Resonance Imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebro-spinal fluid (CSF) testing for John Cunningham (JC) Viral Deoxyribonucleic acid (DNA) and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued 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 other anti-CD20 antibodies.

HBV screening should be performed in all patients before initiation of treatment with Ocrevus as per local guidelines. Patients with active HBV (i.e. an active infection confirmed by positive results for HBsAg and anti HB testing) should not be treated with 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.

Malignancies

An increased number of malignancies (including breast cancers) have been observed in clinical trials in patients treated with ocrelizumab, compared to control groups. However, the incidence was within the background rate expected for an MS population. Individual benefit risk should be considered in patients with known risk factors for malignancies and in patients who are being actively monitored for recurrence of malignancy. Patients with a known active malignancy should not be treated with Ocrevus (see section 4.3). Patients should follow standard breast cancer screening per local guidelines. Please see section 4.2 for populations not studied.

In the controlled period of the clinical trials, the incidence of non-melanoma skin cancers was low and there was no imbalance between treatment groups. An increase in incidence was observed between years 3 and 4 of treatment due to basal cell carcinoma, which was not observed in subsequent years. The incidence remains within the background rate expected for an MS population.

Treatment of severely immunocompromised patients

Patients in a severely immunocompromised state must not be treated until the condition resolves (see section 4.3.).

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. An exploratory analysis identified the following factors associated with risk of serious infections: higher doses of Ocrevus than recommended in MS, other comorbidities, and chronic use of immunosuppressants/corticosteroids.

It is not recommended to use other immunosuppressives concomitantly with Ocrevus except corticosteroids for symptomatic treatment of relapses. Knowledge is limited as to whether concomitant steroid use for symptomatic treatment of relapses is associated with an increased risk of infections in clinical practice. In the ocrelizumab MS pivotal studies the administration of corticosteroids for the treatment of relapse was not associated with an increased risk of serious infection.

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

Vaccinations

The safety of immunisation 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 not until B-cell repletion (in clinical trials, the median time for B-cell repletion was 72 weeks). See section 5.1.

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 who require vaccination should complete their immunisation at least 6 weeks prior to initiation of Ocrevus.

See section 4.5 for further information about vaccinations.

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

Due to the potential depletion of B cells in infants of mothers who have been exposed to Ocrevus during pregnancy, infants should be monitored for B-cell depletion and vaccinations with live and live attenuated vaccines should be postponed until the infant's B-cell count has recovered. The safety and timing of vaccination should be discussed with the infant's physician (see section 4.6).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed, as no drug interactions are expected via cytochrome P450 enzymes, other metabolising enzymes or transporters.

Vaccinations

The safety of immunisation with live or live-attenuated viral vaccines, following Ocrevus therapy has not been studied.

No data are available on the effects of vaccination in patients receiving Ocrevus. See section 4.4.

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

Immunosuppressants

It is not recommended to use other immunosuppressives concomitantly with Ocrevus except corticosteroids for symptomatic treatment of relapses.

See section 4.4 ‘Treatment of severely immunocompromised patients’ for information about the use of immunosuppressants before, during or after Ocrevus treatment.

4.6 Fertility, pregnancy and lactation

Women of child bearing potential

Women of child bearing potential should use contraception while receiving Ocrevus and for 12 months after the last infusion of Ocrevus (see below and section 5.1 and 5.2).

Pregnancy

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

There is a limited amount of data from the use of Ocrevus in pregnant women. No B cell count data have been collected in infants exposed to ocrelizumab and the potential duration of B-cell depletion in infants is unknown (see section 4.4).

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

Animal studies (embryo-foetal toxicity) do not indicate teratogenic effects. B-cell depletion in utero was detected. Reproductive toxicity was observed in pre and post natal development studies (see section 5.3).

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

Breast-feeding

It is unknown whether ocrelizumab/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of ocrelizumab in milk (for details see section 5.3). A risk to the newborns/infants cannot be excluded. Women should be advised to discontinue breast-feeding during Ocrevus therapy.

Fertility

Preclinical data reveal no special hazards for humans based on studies of male and female fertility in cynomologous monkeys.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most important and frequently reported adverse drug reactions (ADRs) were IRRs and infections. See section 4.4 and section 4.8 (subsection 'Description of selected adverse reactions') for further details.

Tabulated list of adverse reactions

The overall safety profile of Ocrevus in Multiple Sclerosis is based on data from patients from pivotal clinical trials in MS (RMS and PPMS).

The table 2 summarises the ADRs that have been reported in association with the use of Ocrevus in 1311 patients (3054 patient years) during the controlled treatment periods of MS clinical trials.

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$). Within each System Organ Class, the adverse reactions are presented in order of decreasing frequency.

Table 2 ADRs Reported with Ocrevus (in RMS or PPMS)

MedDRA System Organ Class (SOC)	Very Common	Common
Infections and infestations	Upper respiratory tract infection, nasopharyngitis, influenza	Sinusitis, bronchitis, oral herpes, gastroenteritis, respiratory tract infection, viral infection, herpes zoster, conjunctivitis, cellulitis
Respiratory, thoracic and mediastinal disorders		Cough, catarrh
Investigations	Blood immunoglobulin M decreased	Blood immunoglobulin G decreased
Blood and lymphatic system disorders		Neutropenia
Injury, poisoning and procedural complications	Infusion-related reactions ¹	

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

Description of selected adverse reactions

Infusion-related reactions

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, tachycardia. In controlled trials there were no fatal IRRs.

In active-controlled (RMS) clinical trials, IRR was the most common adverse event in patients treated with Ocrevus 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 the 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. 21.7% and 10.1% of Ocrevus treated patients experienced mild and moderate IRRs respectively, 2.4% experienced severe IRRs and 0.1% experienced lifethreatening IRRs. See section 4.4.

In the placebo-controlled (PPMS) clinical trial, IRR was the most common adverse event in patients treated with Ocrevus with an overall incidence of 40.1% compared with an incidence of 25.5% in the placebo group. 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. 26.7% and 11.9% of Ocrevus treated patients experienced mild and moderate IRRs respectively, 1.4% experienced severe IRRs. There were no life-threatening IRRs. See section 4.4.

Infection

In the active-controlled studies in RMS, infections occurred in 58.5% of patients receiving Ocrevus vs 52.5% of patients receiving interferon beta 1a. Serious infections occurred in 1.3% of patients receiving Ocrevus vs 2.9% of patients receiving interferon beta 1a. In the placebo-controlled study in PPMS, infections occurred in 72.2% of patients receiving Ocrevus vs 69.9% of patients receiving placebo. Serious infections occurred in 6.2% of patients receiving Ocrevus vs 6.7% of patients receiving placebo. An increase in the rate of serious infections was observed in RMS between Years 2 and 3, but not in subsequent years. No increase was observed in PPMS.

Respiratory Tract Infections

The proportion of respiratory tract infections was higher in Ocrevus treated patients compared to interferon beta-1-a and placebo.

In the RMS clinical trials, 39.9% of Ocrevus treated patients and 33.2% interferon beta-1-a treated patients experienced an upper respiratory tract infection and 7.5% of Ocrevus treated patients and 5.2% of interferon beta-1-a treated patients experienced a lower respiratory tract infection.

In the PPMS clinical trial, 48.8% of Ocrevus treated patients and 42.7% of patients who received placebo experienced an upper respiratory tract infection, and 9.9% of Ocrevus treated patients and 9.2% of patients who received placebo experienced a lower respiratory tract infection.

The respiratory tract infections reported in patients treated with Ocrevus were predominately mild to moderate (80 – 90 %).

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in Ocrevus-treated patients than in interferon-beta-1a treated patients including herpes zoster (2.1% vs 1.0%), herpes simplex, (0.7 % vs 0.1 %) oral herpes (3.0% vs 2.2%), genital herpes (0.1% vs 0%) and herpes virus infection (0.1% vs 0%). Infections were predominantly mild to moderate in severity and patients recovered with treatment by standard therapies.

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.

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. There may be an association between a sustained decrease in IgG, IgM or IgA and serious infections, however due to limited exposure and number of patients, definitive conclusions cannot be drawn.

In the active-controlled (RMS) studies, the proportion of patients reporting at baseline 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 reporting at baseline 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.

Lymphocytes

In RMS, a decrease in lymphocyte < LLN was observed in 20.7% of Ocrevus patients compared with 32.6% of patients treated with interferon beta-1a. In PPMS, a decrease in lymphocytes < LLN was observed in 26.3% of Ocrevus treated patients vs 11.7% of placebo-treated patients.

The majority of these decreases reported in Ocrevus treated patients were Grade 1 (<LLN - 800 cells/mm³) and 2 (between 500 and 800 cells/mm³) in severity. Approximately 1% of the patients in the Ocrevus group had a Grade 3 lymphopenia (between 200 and 500 cells/mm³). None of the patients was reported with Grade 4 lymphopenia (< 200 cells/mm³).

An increased rate of serious infections was observed during episodes of confirmed total lymphocytes counts decrease in ocrelizumab treated patients. The number of serious infections was too low to draw definitive conclusions.

Neutrophils

In the active-controlled (RMS) treatment period, a decrease in neutrophils < LNN was observed in 14.7% of Ocrevus patients compared with 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 higher (12.9 %) than placebo patients (10.0 %); among these a higher percentage of patients (4.3%) in the Ocrevus group had Grade 2 or above neutropenia vs 1.3% in the placebo group; approximately 1% of the patients in the Ocrevus group had Grade 4 neutropenia vs 0% in the placebo group.

The majority of the neutrophil decreases were transient (only observed once for a given patient treated with Ocrevus) and were Grade 1 (<1500 cells/mm³) and 2 (between 1000 and 1500 cells/mm³) in severity. One patient with grade 3 (between 500 and 1000 cells/mm³) and one patient with grade 4 (< 500 cells/mm³) neutropenia required specific treatment with granulocyte-colony stimulating factor, and remained on ocrelizumab after the episode.

Other

One patient, who received 2000 mg of Ocrevus, died of systemic inflammatory response syndrome (SIRS) of unknown etiology, following a magnetic resonance imaging (MRI) examination 12 weeks

after the last infusion; an anaphylactoid reaction to the MRI gadolinium-contrast agent could have contributed to the SIRS.

Reporting of suspected adverse reactions

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

4.9 Overdose

There is limited clinical trial experience 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 intravenous 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.

Please refer to section 4.8 for information about the Systemic Inflammatory Response Syndrome (SIRS) that occurred in a patient treated with Ocrevus 2000 mg.

There is no specific antidote in the event of an overdose; interrupt the infusion immediately and observe the patient for IRRs (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressants group, ATC code: L04AA36.

Mechanism of Action

Ocrelizumab is a recombinant humanised 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 is 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 preexisting 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.

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 study 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). 90% of all patients had their B-cells repleted to LLN or baseline by approximately two and a half years after the last infusion.

Clinical efficacy and safety

Relapsing forms of MS

Efficacy and safety of Ocrevus were evaluated in two randomised, double-blind, double-dummy, active comparator-controlled clinical trials (WA21092 and WA21093), with identical design, in patients with relapsing forms of MS (in accordance with McDonald criteria 2010) and evidence of disease activity (as defined by clinical or imaging features) within the previous two years. Study design and baseline characteristics of the study population are summarised in Table 3.

Demographic and baseline characteristics were well balanced across the two treatment groups. Patients receiving Ocrevus (Group A) were given 600 mg every 6 months (Dose 1 as 2 x 300 mg intravenous infusions, administered 2 weeks apart, and subsequent doses were administered as a single 600 mg intravenous infusion). Patients in Group B were administered Interferon beta-1a (Rebif) 44 mcg via subcutaneous injection 3 times per week.

Table 3 Study Design, Demographic and Baseline 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 years or one relapse within the prior year; EDSS* between 0 and 5.5, inclusive			
Study duration	2 years			
Treatment groups	Group A: Ocrevus 600 mg Group B: interferon beta-1a 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
Age range (years) at inclusion	18 - 56	18 - 55	18 - 55	18 - 55
Gender distribution (% male/% female)	34.1/65.9	33.8/66.2	35.0/65.0	33.0/67.0
Mean/Median disease duration since diagnosis (years)	3.82/1.53	3.71/1.57	4.15/2.10	4.13/1.84
Patients naive to previous DMT (%)**	73.4	71.0	72.7	74.9
Mean number of relapses in the last year	1.31	1.33	1.32	1.34
Proportion of patients with Gd enhancing T1 lesions	42.5	38.1	39.0	41.4
Mean EDSS*	2.82	2.71	2.73	2.79

* Expanded Disability Status Scale

** Patients who had not been treated with any MS medication in the 2 years prior to randomization.

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

The results of these studies show that Ocrevus significantly suppressed relapses, sub-clinical disease activity measured by MRI, and disease progression compared with interferon beta-1a 44mcg subcutaneous.

Table 4 Key Clinical and MRI Endpoints from Studies WA21092 and WA21093 (RMS)

Endpoints	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				
Annualised Relapse Rate (ARR) (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) ⁷			
Risk Reduction (Individual Studies ²)	43 % (p=0.0139) ⁷		37 % (p=0.0169) ⁷	
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) ⁷			
Risk Reduction (Individual Studies ²)	43 % (p=0.0278) ⁷		37 % (p=0.0370) ⁷	
Proportion of patients with at least 12 weeks Confirmed Disability Improvement ⁴	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)	
Proportion of patients Relapse free at 96 weeks ²	80.4%	66.7%	78.9%	64.3%
	(p<0.0001)		(p<0.0001)	
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)	
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)	

¹ Data prospectively pooled from Study 1 and 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

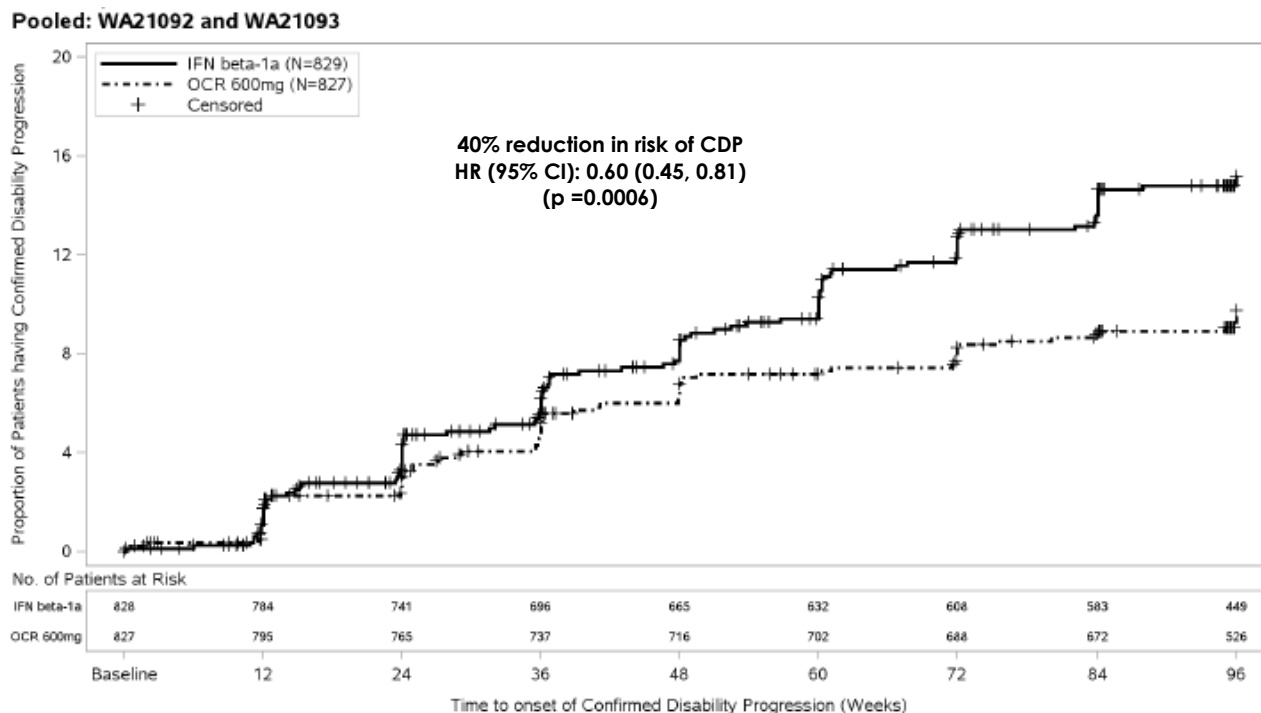
⁴ Defined as decrease of ≥ 1.0 point from the baseline EDSS score for patients with baseline EDSS score ≥ 2 and ≤ 5.5 , or ≥ 0.5 when the baseline score is > 5.5 . Patients with baseline score < 2 were not included in analysis.

⁵ NEDA defined as absence of protocol defined relapses, 12-week 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.

⁷ Log-rank test

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 WA21092 and WA21093 ITT Population)*



*Pre-specified pooled analysis of WA21092 and WA21093

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).

The studies enrolled patients with active disease. These included both active treatment naive and previously treated inadequate responders, as defined by clinical or imaging features. Analysis of patient populations with differing baseline levels of disease activity, including active and highly active disease, showed that the efficacy of Ocrevus on ARR and 12 week CDP was consistent with the overall population.

Primary Progressive MS

Efficacy and safety of Ocrevus were also evaluated in a randomised, double-blind, placebo-controlled clinical trial in patients with primary progressive MS (Study WA25046) who were early in their disease course according to the main inclusion criteria, i.e. ages 18-55 years, inclusive; EDSS at screening from 3.0 to 6.5 points; disease duration from the onset of MS symptoms less than 10 years in patients with an EDSS at screening ≤ 5.0 or less than 15 years in patients with an EDSS at screening > 5.0 . With regard to disease activity, features characteristic of inflammatory activity, even in progressive MS, can be imaging-related, (i.e. T1 Gd-enhancing lesions and/or active [new or enlarging] T2 lesions). MRI evidence should be used to confirm inflammatory activity in all patients. Patients over 55 years of age were not studied. 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. Cranial MRI showed imaging features characteristic of inflammatory activity either by T1 Gd enhancing lesions or T2 lesions.

During the Phase 3 PPMS study, patients received 600 mg Ocrevus every 6 months 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 were 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 4.8 and 5.2), but due to overall more infusions with the 2 x 300 mg regimen, the total number of IRRs were higher. Therefore, after Dose 1 it is recommended to administer Ocrevus in a 600 mg single infusion (see section 4.2) to reduce the total number of infusions (with concurrent exposure to prophylactic methylprednisolone and an antihistamine) and the related infusion reactions).

Table 5 Study design, demographics 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 (<i>Minimum 120 weeks and 253 confirmed disability progression events</i>) (<i>Median follow-up time: Ocrevus 3.0 years, Placebo 2.8 years</i>)	
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 randomisation	
Baseline characteristics	Ocrevus 600 mg (n=488)	Placebo (n=244)
Mean age (years)	44.7	44.4
Age range (years) at inclusion	20 - 56	18 - 56
Gender distribution (% male/% female)	51.4/48.6	49.2/50.8
Mean/Median disease duration since PPMS diagnosis (years)	2.9/1.6	2.8/1.3
Mean EDSS	4.7	4.7

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

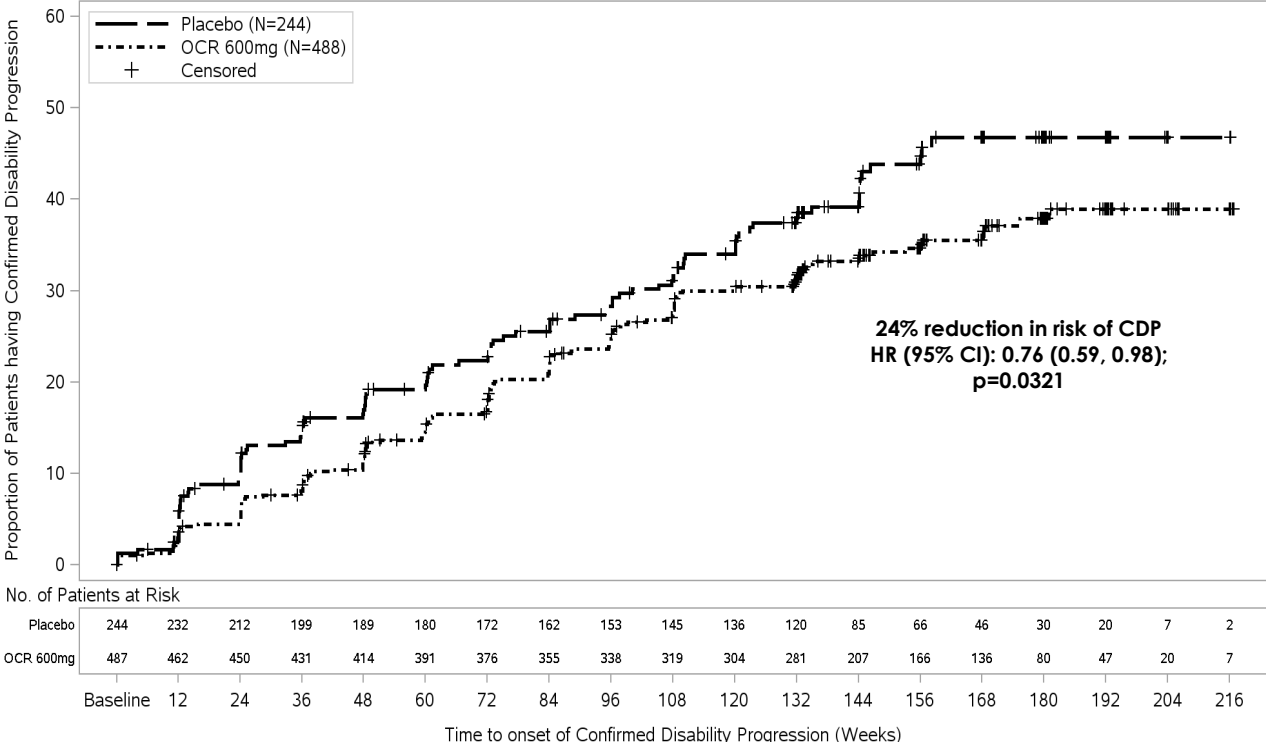
The results of this study show that Ocrevus significantly delays disease progression and reduces deterioration in walking speed compared with placebo.

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

	Study 3	
	WA25046 (Oratorio)	
Endpoints	Ocrevus 600 mg (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)	

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 (WA25046 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.

Pre-specified non-powered subgroup analysis of the the primary endpoint suggests that patients who are younger or those with T1 Gd-enhancing lesions at baseline receive a greater treatment benefit than patients who are older or without T1 Gd-enhancing lesions (≤ 45 years: HR 0.64 [0.45, 0.92], >45 years: HR 0.88 [0.62, 1.26]; with T1 Gd-enhancing lesions at baseline: HR 0.65 [0.40-1.06], without T1 Gd-enhancing lesions at baseline: HR 0.84 [0.62-1.13]).

Moreover, post-hoc analyses suggested that younger patients with T1 Gd-enhancing lesions at baseline have the better treatment effect (≤ 45 years: HR 0.52 [0.27-1.00]; ≤ 46 years [median age of the WA25046 study]; HR 0.48 [0.25-0.92]; <51 years: HR 0.53 [0.31-0.89]).

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 anti-drug antibodies (ADAs). Out of 1311 patients treated with Ocrevus, 12 (~1%) tested positive for treatment-emergent ADAs, of which 2 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.

Paediatric population

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

5.2 Pharmacokinetic properties

The pharmacokinetics of ocrelizumab 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. The overall exposure (AUC over the 24 weeks dosing interval) 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 the curve (AUC_τ) after the 4th dose of 600 mg ocrelizumab 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).

Absorption

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

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.

Biotransformation

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

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 of ocrelizumab was 26 days.

Pharmacokinetics in Special Populations

Paediatrics

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

Elderly

There are no dedicated PK studies of ocrelizumab in patients ≥55 years due to limited clinical experience (see section 4.2).

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. There is no PK information available in patients with moderate or severe renal impairment.

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. There is no PK information available in patients with moderate or severe hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and embryo-foetal development. Neither carcinogenicity nor mutagenicity studies have been conducted with ocrelizumab.

In a pre- and post-natal development study in cynomolgus monkeys, administration of ocrelizumab from gestation day 20 to approximately 5 weeks postpartum was associated with glomerulopathy, lymphoid follicle formation in bone marrow, lymphoplasmacytic renal inflammation, and decreased testicular weight in offspring. The maternal doses administered in this study resulted in maximum mean serum concentrations (C_{max}) that were 4.5- and 21-fold above those anticipated in the clinical setting.

There were two cases of moribundity attributed to weakness due to premature birth accompanied by opportunistic infection and the other to an infective meningoencephalitis involving the cerebellum of the neonate 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 ocrelizumab were noted to have depleted B cell populations during the post natal phase. Measurable levels of ocrelizumab were detected in milk (approximated 0.2% of steady state trough serum levels) during the lactation period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Acetate Trihydrate
Glacial Acetic Acid
Trehalose Dihydrate
Polysorbate 20
Water for Injection

6.2 Incompatibilities

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

Do not use diluents other than the one detailed in section 6.6 to dilute Ocrevus since its use has not been tested.

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

6.3 Shelf life

Unopened vial

18 months

Diluted solution for intravenous infusion

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and subsequently for 8 hours at room temperature.

From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and

would normally not be longer than 24 hours at 2-8°C and subsequently for 8 hours at room temperature, unless dilution is undertaken in controlled and validated aseptic conditions.

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

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep the vials in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL concentrate in a glass vial. Pack size of 1 or 2 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for dilution

Ocrevus should be prepared by a healthcare professional using aseptic technique. Do not shake the vial.

The product is intended for single use only.

Do not use the solution if discoloured or if the solution contains foreign particulate matter (see section 3. for a description of the solution).

Ocrevus medicinal product must be diluted before administration. Solutions of Ocrevus for intravenous administration are prepared by dilution of the drug product into an infusion bag containing isotonic 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 intravenous infusion, the content of the infusion bag must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Disposal

Disposal of unused/expired medicines

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

7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1231/001

EU/1/17/1231/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

<{DD month YYYY}>

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

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

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

Name and address of the manufacturer of the biological active substance

Genentech Inc.
1000 New Horizons Way
Vacaville
CA 95688
United States

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Whylen
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

• **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ocrevus 300 mg concentrate for solution for infusion
ocrelizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 300 mg ocrelizumab in 10 ml (30 mg/ml).

3. LIST OF EXCIPIENTS

Sodium Acetate Trihydrate
Glacial Acetic Acid
Trehalose Dihydrate
Polysorbate 20
Water for injection

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
300 mg/10 ml
1 vial
2 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

Do not freeze

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

Keep the vials in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Roche Registration GmbH

Emil-Barell-Strasse 1

79639 Grenzach-Wyhlen

Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1231/001 1-vial pack

EU/1/17/1231/002 2-vials pack

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

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

Ocrevus 300 mg concentrate for solution for infusion
ocrelizumab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg/10 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ocrevus 300 mg concentrate for solution for infusion

Ocrelizumab

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

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

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

What is in this leaflet

1. What Ocrevus is and what it is used for
2. What you need to know before you are given Ocrevus
3. How Ocrevus is given
4. Possible side effects
5. How to store Ocrevus
6. Contents of the pack and other information

1. What Ocrevus is and what it is used for

What Ocrevus is

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

What Ocrevus is used for

Ocrevus is used to treat adults with:

- Relapsing forms of multiple sclerosis (RMS)
- Early primary progressive multiple sclerosis (PPMS)

What is Multiple Sclerosis

Multiple Sclerosis (MS) affects the central nervous system, especially the nerves in the brain and spinal cord. In MS, the immune system (the body’s defence system) works incorrectly and attacks a protective layer (called myelin sheath) around nerve cells and causes inflammation. Breakdown of the myelin sheath stops the nerves working properly.

Symptoms of MS depend on which part of the central nervous system is affected and can include problems with walking and balance, weakness, numbness, double vision and blurring, poor coordination and bladder problems.

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

- **In primary progressive MS.** the symptoms generally continue to worsen from the start of the disease.

How does Ocrevus work?

Ocrevus attaches to specific B cells, which are a type of white blood cells that are part of the immune system and play a role in MS. Ocrevus targets and removes those specific B cells. This reduces inflammation and attacks on the myelin sheath, reduces the chance of having a relapse and slows the progression of your disease.

- **In Relapsing forms of MS (RMS),** Ocrevus helps to significantly reduce the number of attacks (relapses) and significantly slow down the progression of the disease. Ocrevus also significantly increases the chance of a patient having no evidence of disease activity (brain lesions, relapses and worsening of disability).
- **In Primary Progressive MS (PPMS),** Ocrevus helps to slow down the progression of the disease and reduce deterioration in walking speed.

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

You must not be given Ocrevus:

- if you are allergic to ocrelizumab or any of the other ingredients of this medicine (listed in section 6).
- if you currently have an infection
- if you have been told that you have severe problems with your immune system
- if you have cancer

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

Warnings and precautions

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

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

Effect on the immune system :

- **Diseases that affect your immune system:** if you have another disease which affects the immune system. You may not be able to receive Ocrevus.
- **Medicines that affect your immune system :** if you have ever taken, are taking or are planning to take medicines that affect the immune system – such as chemotherapy, immunosuppressants or other medicines used to treat MS. Your doctor may decide to delay your treatment with Ocrevus or may ask you to stop such medicines before starting treatment with Ocrevus. See under ‘Other medicines and Ocrevus’, below for more information.

Infusion-related reactions

- Infusion-related reactions are the most common side effect of Ocrevus treatment.
- **Tell your doctor or nurse straight away if you have any infusion-related reaction** (see section 4 for a list of infusion-related reactions). Infusion-related reactions can happen during the infusion or up to 24 hours after the infusion.
- To reduce the risk of infusion-related reaction, your doctor will give you other medicines before each infusion of Ocrevus (see section 3) and you will be closely monitored during the infusion and for at least one hour after the infusion has been given.

Infections

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

Vaccinations

- Tell your doctor if you have recently been given any vaccine or might be given a vaccine in the near future.
- While you are being treated with Ocrevus, you should not be given live or live attenuated vaccines (for example BCG for tuberculosis or vaccines against yellow fever). It is not known how Ocrevus may affect your response to other types of vaccines.
- Your doctor will check if you need any vaccinations before you start treatment with Ocrevus. Any vaccinations should be given at least 6 weeks before you start treatment with Ocrevus.

Children and adolescents

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

Other medicines and Ocrevus

Tell your doctor if you are taking, have recently taken or might take any other medicines.

In particular tell your doctor if:

- you have ever taken, are taking or are planning to take **medicines that affect the immune system** – such as chemotherapy, immunosuppressants or other medicines used to treat MS. The effect on the immune system of these medicines with Ocrevus could be too strong. Your doctor may decide to delay your treatment with Ocrevus or may ask you to stop such medicines before starting treatment with Ocrevus.
- you are taking **medicines for high blood pressure**. This is because Ocrevus may lower blood pressure. Your doctor may ask you to stop taking your blood pressure medicines for 12 hours before each Ocrevus infusion.

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

Pregnancy

- Tell your doctor before being given Ocrevus if you are pregnant, think that you might be pregnant or are planning to have a baby. This is because Ocrevus may cross the placenta and affect your baby.
- Do not use Ocrevus if you are pregnant unless you have discussed this with your doctor. Your doctor will consider the benefit of you taking Ocrevus against the risk to your baby.

Contraception for women

If you are able to become pregnant (conceive), you must use contraception:

- during treatment with Ocrevus and
- for 12 months after your last infusion of Ocrevus.

Breast-feeding

Do not breast-feed while you are being treated with Ocrevus. This is because Ocrevus may pass into breast milk.

Driving and using machines

It is not known whether Ocrevus can affect your being able to drive or use tools or machines.

Your doctor will tell you whether your MS may affect your ability to drive or use tools and machines safely.

Ocrevus contains sodium

This medicine contains less than 1 mmol **sodium** (23 mg) per dose, i.e., it is essentially sodium-free.

3. How Ocrevus is given

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

Medicines you will have before you are given Ocrevus

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

You will receive a corticosteroid and an anti-histamine before each infusion and you may also receive medicines to reduce fever.

How Ocrevus is given

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

How much and how often you will be given Ocrevus

You will be given a total dose of 600 mg of Ocrevus every 6 months.

- The first 600 mg dose of Ocrevus will be given as 2 separate infusions (300 mg each), given 2 weeks apart. Each infusion will last about 2 hours 30 minutes.
- The next 600 mg doses of Ocrevus will be given as a single infusion. Each infusion will last about 3 hours 30 minutes.

If you miss an infusion of Ocrevus

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

If you stop Ocrevus treatment

- It is important to continue your treatment for as long as you and your doctor decide that it is helping you.
- Some side effects can be related to having low B cells. After you stop Ocrevus treatment, you may still experience side effects until your B-cells return to normal. Your blood B-cells will gradually increase to normal levels. This can take from six months to two and a half years, or up to several years in rare cases.
- Before you start any other medicines, tell your doctor when you had your last Ocrevus infusion.

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

4. Possible side effects

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

The following side effects have been reported with Ocrevus:

Infusion-related reactions

- Infusion-related reactions are the most common side effect of Ocrevus treatment (very common: may affect more than 1 in 10 people). In most cases these are mild reactions but some serious reactions can happen.
- **Tell your doctor or nurse straight away if you experience any signs or symptoms of an infusion-related reaction during the infusion or up to 24 hours after the infusion.** Symptoms can include, but are not limited to:
 - itchy skin

- rash
 - hives
 - redness of the skin
 - throat irritation or pain
 - shortness of breath
 - swelling of the throat
 - flushing
 - low blood pressure
 - fever
 - feeling tired
 - headache
 - feeling dizzy
 - feeling sick (nausea)
 - fast heart beat.
- If you have an infusion-related reaction, you will be given medicines to treat it and the infusion may need to be slowed down or stopped. When the reaction has stopped, the infusion may be continued. If the infusion-related reaction is life-threatening, your doctor will permanently stop your treatment with Ocrevus.

Infections

- You might get infections more easily with Ocrevus. The following infections have been seen in patients treated with Ocrevus in MS:
 - **Very common:** may affect more than 1 in 10 people
 - upper respiratory tract infection
 - flu.
 - **Common:** may affect up to 1 in 10 people
 - sinus infection
 - bronchitis (bronchial tube inflammation)
 - herpes infection (cold sore or shingles).
 - infection of the stomach and bowel (gastroenteritis)
 - respiratory tract infection
 - viral infection
 - skin infection (cellulitis)

Some of them might be serious

- **Tell your doctor or nurse straight away if you notice any of these signs of infection:**
 - fever or chills
 - cough which does not go away
 - herpes (such as cold sore, shingles and genital sores).

Other side effects

Very common: may affect more than 1 in 10 people

- decrease in specific proteins in the blood (immunoglobulins) which help protect against infection

Common: may affect up to 1 in 10 people

- cough
- a build-up of thick mucus in the nose, throat or chest.
- low levels of a type of white blood cell (neutropenia)

Reporting of side effects

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

5. How to store Ocrevus

Ocrevus will be stored by the healthcare professionals at the hospital or clinic under the following conditions:

- This medicine is to be kept out of the sight and reach of children.
- This medicine is not to be used after the expiry date which is stated on the outer carton and the vial label after 'EXP'. The expiry date refers to the last day of that month.
- This medicine is to be stored in a refrigerator (2°C - 8°C). It is not to be frozen. The vials are to be kept in the outer carton to protect them from light.

Ocrevus must be diluted before it is given to you. Dilution will be done by a healthcare professional. It is recommended that the product is used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the healthcare professional and would normally not be longer than 24 hours at 2°C - 8°C and subsequently 8 hours at room temperature.

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

6. Contents of the pack and other information

What Ocrevus contains

- The active substance is ocrelizumab. Each vial contains 300 mg of ocrelizumab in 10 mL at a concentration of 30mg/mL.
- The other ingredients are sodium acetate trihydrate, glacial acetic acid, trehalose dihydrate, polysorbate 20 and water for injection.

What Ocrevus looks like and contents of the pack

- Ocrevus is a clear to slightly opalescent, and colourless to pale brown solution.
- It is supplied as a concentrate for solution for infusion.
- This medicine is available in packs containing 1 or 2 vials (vials of 10 mL concentrate). Not all pack sizes may be marketed.

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Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

Read the SmPC for additional information.

Posology

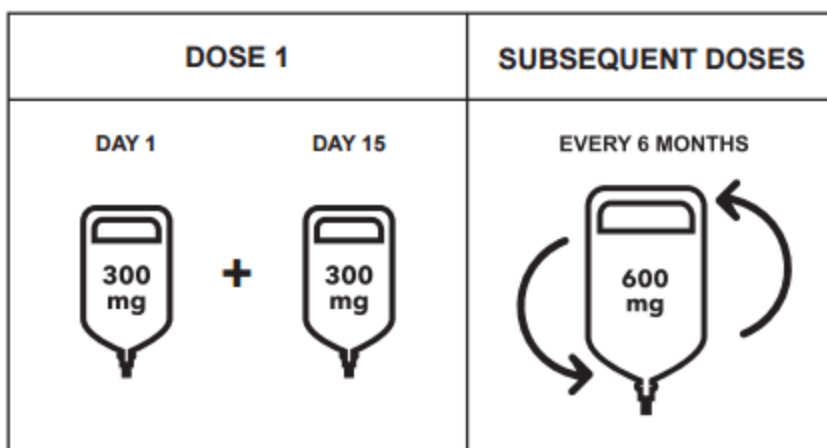
- Initial Dose

The initial 600 mg dose is administered as two separate intravenous 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 intravenous infusion every 6 months (Table 1). The first subsequent dose of 600 mg should be administered six months after the first infusion of the initial dose. A minimum interval of 5 months should be maintained between each dose of Ocrevus.

Figure 1: Dose and Schedule of Ocrevus



Management of IRRs before the infusion

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

- Premedication for IRRs

The two following premedications must be administered prior to each Ocrevus infusion to reduce the frequency and severity of IRRs:

- 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each Ocrevus infusion;
- antihistamine approximately 30-60 minutes prior to each Ocrevus infusion;

In addition, premedication with an antipyretic (e.g. paracetamol) may also be considered approximately 30-60 minutes prior to each Ocrevus infusion.

- 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.

Instructions for dilution

- Ocrevus should be prepared by a healthcare professional using aseptic technique. Do not shake the vial.

- The product 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 discoloured or if the solution contains foreign particulate matter.
- Ocrevus medicinal product must be diluted before administration. Solutions of Ocrevus for intravenous administration are prepared by dilution of the drug product into an infusion bag containing isotonic 0.9% sodium chloride (300mg/250mL or 600mg/500mL), 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 intravenous infusion, the content of the infusion bag must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Method of administration

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

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	<ul style="list-style-type: none"> • Initiate the infusion at a rate of 30 mL/hour for 30 minutes • The rate can be increased in 30 mL/hour increments every 30 minutes to a maximum of 180 mL/hour. • Each infusion should be given over approximately 2.5 hours.
	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	<ul style="list-style-type: none"> • Initiate the infusion at a rate of 40 mL/hour for 30 minutes • The rate can be increased in 40 mL/hour increments every 30 minutes to a maximum of 200 mL/hour • Each infusion should be given over approximately 3.5 hours.

Management of IRRs during and after the infusion

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

During the infusion

- **Infusion Adjustments in case of IRRs**

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

Life-threatening IRRs

If there are signs of a life threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome the infusion must be stopped immediately and the patient should receive appropriate treatment. Ocrevus must be permanently discontinued in these patients (see section 4.3).

Severe IRRs

If a patient experiences a severe IRR (such as dyspnea) 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. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

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 rate. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

- 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.
- Hypersensitivity may be difficult to distinguish from an IRR in terms of symptoms. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently.

After the infusion

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

Shelf life

Unopened vial

18 months

Diluted solution for intravenous infusion

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C and subsequently 8 hours at room temperature.
- From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C and subsequently 8 hours at room temperature, unless dilution undertaken in controlled and validated aseptic conditions.
- In the event an intravenous infusion cannot be completed the same day, the remaining solution should be discarded.