ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 medicinal product concentration after dilution is approximately 1.2 mg/mL.

Ocrelizumab is a humanised 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

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 ocrelizumab infusion to reduce the frequency and severity of IRRs (see section 4.4 for additional steps to reduce IRRs):

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

In addition, premedication with an antipyretic (e.g., paracetamol) may also be considered approximately 30-60 minutes prior to each 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 (see Table 1).

Subsequent doses

Subsequent doses of ocrelizumab thereafter are administered as a single 600 mg intravenous infusion every 6 months (see 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 ocrelizumab.

Infusion adjustments in case of IRRs

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

Severe IRRs

If a patient experiences a severe IRR (such as dyspnoea) 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 are recommended.

Delayed or missed doses

If an infusion 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) should be maintained between doses (see Table 1).

Special populations

Adults over 55 years old

Based on the limited data available (see sections 5.1 and 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 older than 55 years old.

Renal impairment

The safety and efficacy of ocrelizumab 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. Ocrelizumab is a monoclonal antibody and

cleared via catabolism (i.e. breakdown into peptides and amino acids), and a dose adjustment is not expected to be required for patients with renal impairment (see section 5.2).

Hepatic impairment

The safety and efficacy of ocrelizumab 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. Ocrelizumab is a monoclonal antibody and cleared via catabolism (rather than hepatic metabolism), and a dose adjustment is not expected to be required for patients with hepatic impairment (see section 5.2).

Paediatric population

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

Method of administration

Ocrevus 300 mg concentrate for solution for infusion is not intended for subcutaneous administration and should be administered via an intravenous infusion only.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed.

Patients may start treatment using intravenous or subcutaneous ocrelizumab.

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

If patients did not experience a serious infusion-related reaction (IRR) with any previous ocrelizumab infusion, a shorter (2-hour) infusion can be administered for subsequent doses (see Table 1, Option 2).

Table 1: Dose and schedule

<table>
<tr><th colspan="2"></th><th>Amount of ocrelizumab to be administered</th><th>Infusion instructions</th></tr>
<tr><td rowspan="2">Initial dose
(600 mg)
divided into 2 infusions</td><td>Infusion 1</td><td>300 mg in 250 mL</td><td rowspan="2">• 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</td></tr>
<tr><td>Infusion 2
(2 weeks later)</td><td>300 mg in 250 mL</td></tr>
<tr><td rowspan="3">Subsequent doses
(600 mg)
single infusion
once every 6 months</td><td>Option 1

Infusion of approximately 3.5 hours duration</td><td>600 mg in 500 mL</td><td>• 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</td></tr>
<tr><td colspan="3">OR</td></tr>
<tr><td>Option 2

Infusion of approximately 2 hours duration</td><td>600 mg in 500 mL</td><td>• Initiate the infusion at a rate of 100 mL/hour for the first 15 minutes
• Increase the infusion rate to 200 mL/hour for the next 15 minutes
• Increase the infusion rate to 250 mL/hour for the next 30 minutes</td></tr>
</table>

		Amount of ocrelizumab to be administered	Infusion instructions
			• Increase the infusion rate to 300 mL/hour for the remaining 60 minutes • Each infusion should be given over approximately 2 hours

Solutions for intravenous infusion are prepared by dilution of the concentrate into an infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for infusion, to a final ocrelizumab 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)

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

Symptoms of IRRs may occur during any ocrelizumab infusion, but have been more frequently reported during the first infusion. IRRs can occur within 24 hours of the infusion (see section 4.8). 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, tachycardia and anaphylaxis.

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, hypotension may occur during infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each 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 clinically indistinguishable 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 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 infusion adjustments in case of IRR, 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 administration, although typically would not present during the first administration. For subsequent administrations, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. Patients with known Ig-E mediated hypersensitivity to ocrelizumab or any of the excipients must not be treated (see section 4.3).

Infection

Administration of ocrelizumab 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 (SI) 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 ocrelizumab 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. Treatment with ocrelizumab 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)

John Cunningham virus (JCV) infection resulting in PML has been observed very rarely in patients treated with anti-CD20 antibodies, including ocrelizumab, and mostly associated with risk factors (patient population e.g., lymphopenia, advanced age, polytherapy with immunosuppressants).

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

If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation including Magnetic Resonance Imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebro-spinal fluid (CSF) testing for JCV Deoxyribonucleic acid (DNA) and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently.

Hepatitis B 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 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 ocrelizumab (see section 4.3). 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.

Late neutropenia

Cases of late onset of neutropenia have been reported at least 4 weeks after the latest ocrelizumab infusion (see section 4.8). Although some cases were Grade 3 or 4, the majority of the cases were Grade 1 or 2. In patients with signs and symptoms of infection, measurement of blood neutrophils is recommended.

Malignancies

An increased number of malignancies (including breast cancers) have been observed in the controlled period of the pivotal clinical trials in patients treated with ocrelizumab, compared to control groups. The incidence was within the background rate expected for an MS population. After approximately 10 years of continuous ocrelizumab treatment over the controlled period and Open-Label Extension (OLE) phase of the pivotal clinical trials, the incidence of malignancies remained within the background rate expected for an MS population. Patients with a known active malignancy should not be treated with ocrelizumab (see section 4.3). 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 should follow standard breast cancer screening per local guidelines.

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 ocrelizumab concomitantly with immunosuppressants (e.g., chronic corticosteroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) resulted in an increase of SIs, 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 SIs: higher doses of ocrelizumab than recommended in MS, other comorbidities, and chronic use of immunosuppressants/corticosteroids.

It is not recommended to use other immunosuppressives concomitantly with ocrelizumab 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 SI.

When initiating ocrelizumab after an immunosuppressive therapy or initiating an immunosuppressive therapy after ocrelizumab, the potential for overlapping pharmacodynamic effects should be taken into consideration (see section 5.1). Caution should be exercised when prescribing ocrelizumab taking into consideration the pharmacodynamics of other disease modifying MS therapies.

Vaccinations

The safety of immunisation with live or live-attenuated vaccines, following ocrelizumab 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).

In a randomised open-label study, RMS patients were able to mount humoral responses, although decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide with or without a booster vaccine, keyhole limpet haemocyanin neoantigen, and seasonal influenza vaccines (see section 4.5 and 5.1).

It is recommended to vaccinate patients treated with ocrelizumab with seasonal influenza vaccines that are inactivated.

Physicians should review the immunisation status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete their immunisation at least 6 weeks prior to initiation of treatment.

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 infants of mothers who have been exposed to ocrelizumab 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 levels 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 immunisation schedule and measurement of vaccine-induced response titres should be considered to check whether individuals have mounted a protective immune response because the efficacy of the vaccination may be decreased.

The safety and timing of vaccination should be discussed with the infant's physician (see section 4.6).

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Vaccinations

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

Data are available on the effects of tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet haemocyanin neoantigen, and seasonal influenza vaccines in patients receiving ocrelizumab (see section 4.4 and 5.1).

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

Immunosuppressants

It is not recommended to use other immunosuppressive therapies concomitantly with ocrelizumab except corticosteroids for symptomatic treatment of relapses (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use contraception while receiving ocrelizumab and for 4 months after the last administered dose of ocrelizumab.

Pregnancy

There is a limited amount of data from the use of ocrelizumab in pregnant women. Ocrelizumab is an immunoglobulin G (IgG). IgG is known to cross the placental barrier. Postponing vaccination with live or live-attenuated vaccines should be considered for neonates and infants born to mothers who have been exposed to ocrelizumab *in utero*. No B cell count data have been collected in neonates and infants exposed to ocrelizumab and the potential duration of B-cell depletion in neonates and infants is unknown (see section 4.4).

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell depletion *in utero* was also detected in animal studies.

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

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

Breast-feeding

Human IgGs are known to be excreted in breastmilk the first few days after birth (colostrum period), which decreases to low concentrations soon afterwards.

In a prospective, multicenter, open-label study MN42989 (SOPRANINO), 13 lactating women received ocrelizumab at a median of 2.0 months postpartum (range 0.5-5.0 months). Low concentrations of ocrelizumab were detected in the breastmilk over 60 days following the mother's first postpartum infusion (median relative infant dose of 0.27% [range 0.0-1.8 %]), indicating minimal transfer of ocrelizumab to breastmilk. At 30 days after the mother's first postpartum infusion, ocrelizumab was undetectable in all available serum samples of breastfed infants (n=9), and infant B-cell levels were within normal range in all available blood samples (n=10). No effects of ocrelizumab on health, growth and development were observed in breastfed infants over a follow-up period of 44.6 weeks (range 8.6-62.7 weeks).

While no clinical data on infants potentially exposed to ocrelizumab via breastmilk receiving live or live-attenuated vaccines are available, no risks are expected due to normal B-cell levels and undetectable serum ocrelizumab levels observed in those infants.

In a separate prospective clinical study, low ocrelizumab concentrations in breastmilk (median relative infant dose of 0.1% [range 0.07-0.7%]) over 90 days after the mother's first postpartum infusion were observed in 29 lactating women who received ocrelizumab at a median of 4.3 months postpartum (range 0.1-36 months). Follow-up of 21 infants breastfed for at least 2 weeks showed normal growth and development up to 1 year.

Ocrelizumab can be used during breastfeeding starting a few days after birth.

Fertility

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

In the controlled period of the pivotal clinical trials, the most important and frequently reported adverse reactions were IRRs (34.3%, 40.1% in RMS and PPMS, respectively) and infections (58.5%, 72.2% in RMS and PPMS, respectively) (see section 4.4).

A total of 2,376 patients were included in the controlled period of the pivotal clinical trials; of these patients, 1,852 entered the OLE phase. All patients switched to ocrelizumab treatment during the OLE phase. 1,155 patients completed the OLE phase, resulting in approximately 10 years of continuous ocrelizumab treatment (15,515 patient-years of exposure) across the controlled period and OLE phase. The overall safety profile observed during the controlled period and OLE phase remains consistent with that observed during the controlled period.

Tabulated list of adverse reactions

Adverse reactions reported in the controlled period of the pivotal clinical trials and derived from spontaneous reporting are listed below in Table 2. The adverse reactions are listed by MedDRA system organ class and categories of frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each System Organ Class, the adverse reactions are presented in order of decreasing frequency.

Table 2 Adverse reactions

MedDRA System Organ Class (SOC)	**Very common**	**Common**	**Not Known**
Infections and infestations	Upper respiratory tract infection, nasopharyngitis, influenza	Sinusitis, bronchitis, oral herpes, gastroenteritis, respiratory tract infection, viral infection, herpes zoster, conjunctivitis, cellulitis	
Blood and lymphatic system disorders		Neutropenia	Late onset of Neutropenia[2]
Respiratory, thoracic and mediastinal disorders		Cough, catarrh	
Investigations	Blood immunoglobulin M decreased	Blood immunoglobulin G decreased	
Injury, poisoning and procedural complications	Infusion-related reactions[1]		

[1] See Descriptions of selected adverse reactions.
[2] Observed in the postmarketing setting.

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 addition, symptoms of IRR in the post-marketing setting included anaphylaxis.

In active-controlled (RMS) clinical trials, IRR was the most common adverse reaction in the ocrelizumab treatment group 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 ocrelizumab treated patients experienced mild and moderate IRRs, respectively. 2.4% experienced severe IRRs and 0.1% experienced life-threatening IRRs.

In the placebo-controlled (PPMS) clinical trial, IRR was the most common adverse reaction in the ocrelizumab treatment group 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 ocrelizumab treated patients experienced mild and moderate IRRs respectively, 1.4% experienced severe IRRs. There were no life-threatening IRRs. See section 4.4.

Over the controlled period and OLE phase of the RMS and PPMS clinical trials, patients were given approximately 20 doses of ocrelizumab. Incidence of IRRs decreased to <4% by Dose 4 of the OLE phase in RMS patients and to <5% by Dose 5 of the OLE phase in PPMS patients. With subsequent doses administered during the OLE phase, incidence of IRR remained low. The majority of IRRs were mild during the OLE phase.

Alternative shorter infusion of subsequent doses

In a study (MA30143 Shorter Infusion Substudy) designed to characterise the safety profile of shorter (2-hour) ocrelizumab 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 5.1). The overall number of interventions needed was low in both infusion groups, however, more interventions (slowing down or temporary interruptions) were needed to manage IRRs in the shorter (2-hour) infusion group compared to the 3.5-hour infusion group (8.7% vs. 4.8%, respectively).

Infection

In the active-controlled studies in RMS, infections occurred in 58.5% of patients receiving ocrelizumab vs 52.5% of patients receiving interferon beta 1a. SIs occurred in 1.3% of patients receiving ocrelizumab vs 2.9% of patients receiving interferon beta 1a. In the placebo-controlled study in PPMS, infections occurred in 72.2% of patients receiving ocrelizumab vs 69.9% of patients receiving placebo. SIs occurred in 6.2% of patients receiving ocrelizumab vs 6.7% of patients receiving placebo.

All patients switched to ocrelizumab during the OLE phase in both RMS and PPMS studies. Over the OLE phase in RMS and PPMS patients, the overall risk of SIs did not increase from that observed during the controlled period. As observed during the controlled period, the rate of SIs in PPMS patients remained higher than that observed in RMS patients.

In line with the previous analysis of risk factors for SIs in auto-immune conditions other than MS (see section 4.4), a multivariate analysis of risk factors for SIs was conducted in the approximately 10 years of cumulative exposure data from the controlled period and OLE phase of the pivotal clinical trials. Risk factors for SIs in RMS patients include having at least 1 comorbidity, recent clinical relapse, and Expanded Disability Status Scale (EDSS) $\geq$ 6.0. Risk factors for SIs in PPMS patients include body mass index greater than 25 kg/m^2, having at least 2 comorbidities, EDSS $\geq$ 6.0, and IgM < lower limit of normal (LLN). Comorbidities included, but were not limited to, cardiovascular, renal and urinary tract conditions, previous infections, and depression.

<u>Respiratory tract infections</u>

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

In the RMS clinical trials, 39.9% of ocrelizumab treated patients and 33.2% interferon beta-1-a treated patients experienced an upper respiratory tract infection and 7.5% of ocrelizumab 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 ocrelizumab treated patients and 42.7% of patients who received placebo experienced an upper respiratory tract infection, and 9.9% of ocrelizumab 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 ocrelizumab were predominately mild to moderate (80 – 90 %).

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in ocrelizumab 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%). All infections were mild to moderate in severity, except one Grade 3 event, 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 ocrelizumab treatment arm.

Laboratory abnormalities

Immunoglobulins

Ocrelizumab treatment resulted in a decrease in total immunoglobulins over the controlled period of the pivotal clinical trials, mainly driven by reduction in IgM.

Clinical trial data from the controlled period and OLE phase of the pivotal clinical trials have shown an association between decreased levels of IgG (and less so for IgM or IgA) and increased rate of SIs. 2.1% of RMS patients had a SI during a period with IgG < LLN and in 2.3% of PPMS patients had a SI during a period with IgG < LLN. The difference in rate of SIs between patients with IgG < LLN compared to patients with IgG ≥ LLN did not increase over time. 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 ocrelizumab during the controlled period and OLE phase. Throughout the 10 years of continuous ocrelizumab treatment, mean IgG levels of RMS and PPMS patients remained above LLN.

Lymphocytes

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

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

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

Neutrophils

In the active-controlled (RMS) treatment period, a decrease in neutrophils < LLN was observed in 14.7% of patients treated with ocrelizumab compared with 40.9% of patients treated with interferon beta-1a. In the placebo-controlled (PPMS) clinical trial, the proportion of ocrelizumab patients presenting decreased neutrophils was higher (12.9 %) than placebo patients (10.0 %); among these a

higher percentage of patients (4.3%) in the ocrelizumabgroup had Grade 2 or above neutropenia vs 1.3% in the placebo group; approximately 1% of the patients in the ocrelizumab 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 ocrelizumab) and were Grade 1 (between<LLN and 1500 cells/mm^3) and 2 (between 1000 and 1500 cells/mm^3) in severity. Overall, approximately 1% of the patients in the ocrelizumab group had Grade 3 or 4 neutropenia. One patient with Grade 3 (between 500 and 1000 cells/mm^3) and one patient with Grade 4 (< 500 cells/mm^3) neutropenia required specific treatment with granulocyte-colony stimulating factor, and remained on ocrelizumab after the episode. Neutropenia can occur several months after the administration of ocrelizumab (see section 4.4).

Other

One patient, who received 2000 mg of ocrelizumab, died of systemic inflammatory response syndrome (SIRS) of unknown aetiology, 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 dose of ocrelizumab. 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) and 1200 mg, administered as a subcutaneous injection (Phase Ib dose finding study). The adverse reactions were consistent with the safety profile in the pivotal clinical studies.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, monoclonal antibodies, ATC code: L04AG08.

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 pre-existing humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

Pharmacodynamic effects

Treatment with ocrelizumab 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 ocrelizumab interferes with the recognition of CD20 by the assay.

In the Phase III studies, between each dose of ocrelizumab, up to 5% of patients showed B-cell repletion (>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 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 multiple sclerosis (RMS)

Efficacy and safety of ocrelizumab 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 ocrelizumab (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 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: Ocrelizumab 600 mg Group B: interferon beta-1a 44 mcg S.C. (IFN)			
Baseline characteristics	Ocrelizumab 600 mg (n=410)	IFN 44 mcg (n=411)	Ocrelizumab 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 a disease-modifying therapy (DMT) in the 2 years prior to randomisation.

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

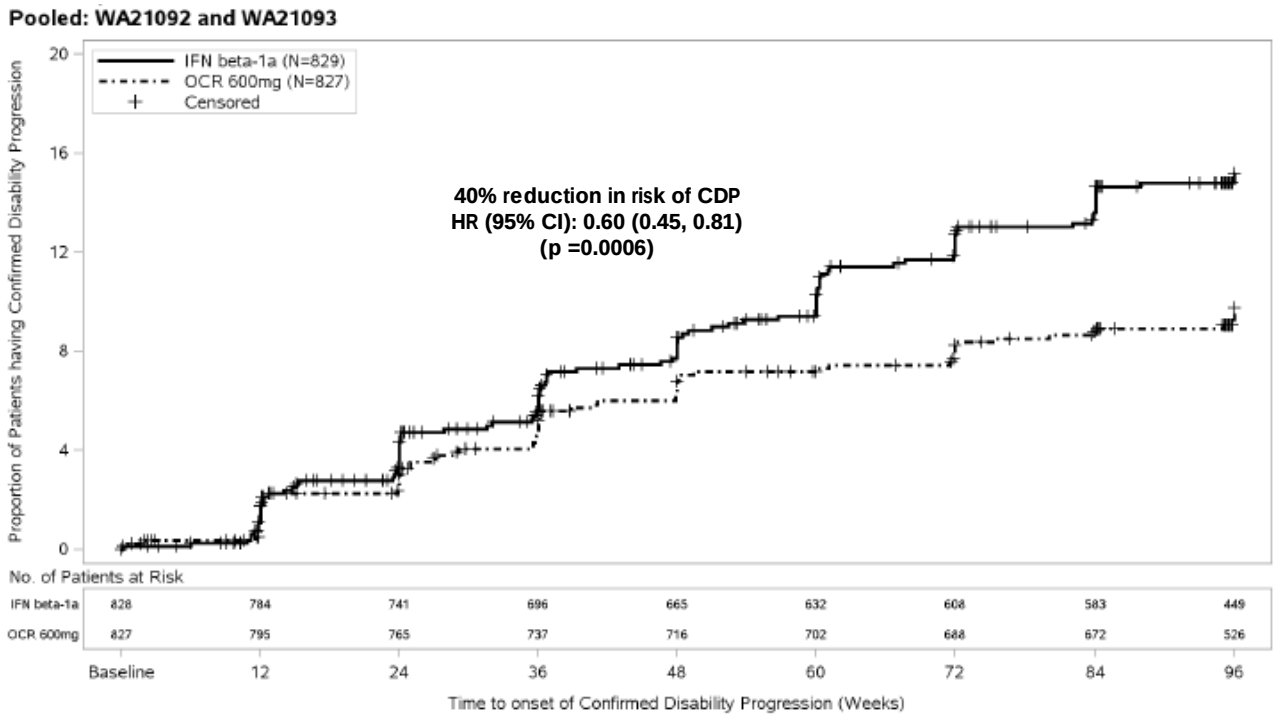
The results of these studies show that ocrelizumab significantly suppressed relapses, sub-clinical disease activity measured by MRI, and disease progression compared with interferon beta-1a 44 mcg subcutaneous.

Table 4 Key clinical and MRI endpoints from Studies WA21092 and WA21093 (RMS)

Endpoints	Study 1: WA21092 (OPERA I)		Study 2: WA21093 (OPERA II)	
	Ocrelizumab 600 mg (n=410)	IFN 44 mcg (n=411)	Ocrelizumab 600 mg (n=417)	IFN 44 mcg (n=418)
Clinical Endpoints				
Annualised Relapse Rate (ARR) (primary endpoint)[8]	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% Ocrelizumab vs 15.2% IFN 40% (p=0.0006)[7]			
Risk Reduction (Pooled Analysis[1]) / Risk Reduction (Individual Studies[2])	43 % (p=0.0139)[7]		37 % (p=0.0169)[7]	
Proportion of patients with 24 week Confirmed Disability Progression (CDP)[3]	7.6% Ocrelizumab vs 12.0% IFN 40% (p=0.0025)[7]			
Risk Reduction (Pooled Analysis[1]) / 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% Ocrelizumab 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] CDP 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 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
[8] Confirmed relapses (accompanied by a clinically relevant change in EDSS).

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 ocrelizumab compared to interferon beta-1a (p=0.0006) were highly consistent with the results sustained for at least 24 weeks (40% risk reduction for ocrelizumab 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 ocrelizumab on ARR and 12 week CDP was consistent with the overall population.

Primary progressive multiple sclerosis (PPMS)

Efficacy and safety of ocrelizumab 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 III PPMS study, patients received 600 mg ocrelizumab 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 ocrelizumab 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 (*Minimum 120 weeks and 253 confirmed disability progression events)* *(Median follow-up time:* Ocrelizumab *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: Ocrelizumab 600 mg Group B: Placebo, in 2:1 randomisation	
Baseline characteristics	Ocrelizumab 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.

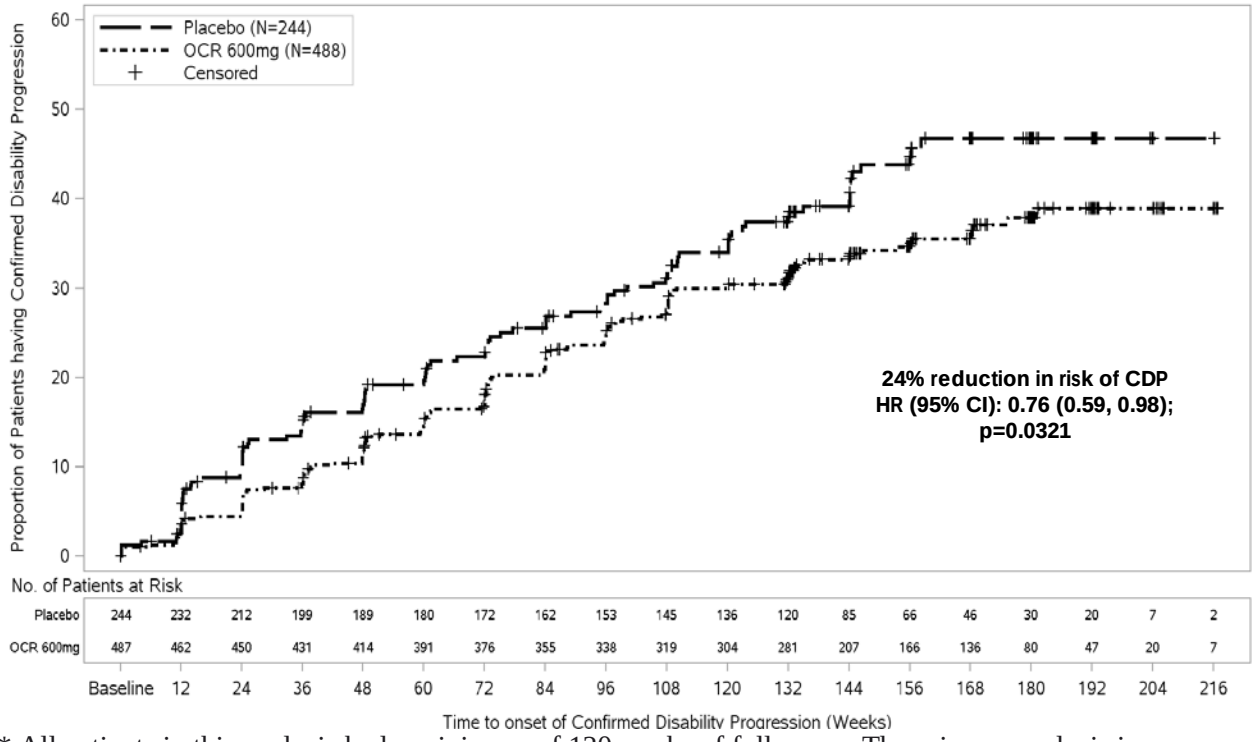
The results of this study show that ocrelizumab significantly delays disease progression and reduces deterioration in walking speed compared with placebo.

Table 6 Key clinical and MRI endpoints from Study WA25046 (PPMS)

	Study 3	
	WA25046 (Oratorio)	
Endpoints	Ocrelizumab 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 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]).

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 ocrelizumab 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. As these results were exploratory in nature and included data after unblinding, the results should be interpreted with caution.

Shorter infusion substudy

The safety of the shorter (2-hour) ocrelizumab infusion was evaluated in a prospective, multicenter, randomised, 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 was administered as two 300 mg infusions (600 mg total) separated by 14 days. Patients were randomised from their second dose onwards (Dose 2 to 6) in a 1:1 ratio to either the conventional infusion group with ocrelizumab infused over approximately 3.5 hours every 24 weeks, or the shorter

infusion group with ocrelizumab infused over approximately 2 hours every 24 weeks. The randomisation was stratified by region and the dose at which patients were first randomised.

The primary endpoint was the proportion of patients with IRRs occurring during or within 24 hours following the first randomised infusion. The primary analysis was performed when 580 patients were randomised. The proportion of patients with IRRs occurring during or within 24 hours following the first randomised infusion was 24.6% in the shorter infusion compared to 23.1% in the conventional infusion group. The stratified group difference was similar. Overall, in all randomised 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.

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 ocrelizumab, 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 ocrelizumab.

Immunisations

In a randomised open-label study in RMS patients (N=102), the percentage of patients with a positive response to tetanus vaccine at 8 weeks after vaccination was 23.9% in the ocrelizumab group compared to 54.5% in the control group (no disease-modifying therapy except interferon-beta). Geometric mean anti-tetanus toxoid specific antibody titres at 8 weeks were 3.74 and 9.81 IU/ml, respectively. Positive response to ≥5 serotypes in 23-PPV at 4 weeks after vaccination was 71.6% in the ocrelizumab group and 100% in the control group. In patients treated with ocrelizumab a booster vaccine (13-PCV) given 4 weeks after 23-PPV did not markedly enhance the response to 12 serotypes in common with 23-PPV. The percentage of patients with seroprotective titres against five influenza strains ranged from 20.0–60.0% and 16.7–43.8% pre-vaccination and at 4 weeks post vaccination from 55.6–80.0% in patients treated with ocrelizumab and 75.0–97.0% in the control group, respectively. See sections 4.4 and 4.5.

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 (AUCτ) 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

Ocrelizumab is administered as an intravenous infusion.

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 ocrelizumab 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.

Special populations

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of ocrelizumab in children and adolescents less than 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 ocrelizumab 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 two pre- and post-natal development studies in cynomolgus monkeys, administration of ocrelizumab from gestation day 20 to at least parturition was associated with glomerulopathy, lymphoid follicle formation in bone marrow, lymphoplasmacytic renal inflammation, and decreased testicular weight in offspring. The maternal doses administered in these studies resulted in maximum mean serum concentrations (C_{max}) that were 4.5- to 21-fold above those anticipated in the clinical setting.

There were five cases of neonatal moribundities, one attributed to weakness due to premature birth accompanied by opportunistic bacterial infection, one due to an infective meningoencephalitis involving the cerebellum of the neonate from a maternal dam with an active bacterial infection (mastitis) and three with evidence of jaundice and hepatic damage, with a viral aetiology suspected,

possibly a polyomavirus. The course of these five confirmed or suspected 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate (E 262)
Glacial acetic acid
Trehalose dihydrate
Polysorbate 20 (E 432)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

2 years

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 vial (colourless Type I glass).
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

The product should be prepared by a healthcare professional using aseptic technique. Do not shake the vial. A sterile needle and syringe should be used to prepare the diluted infusion solution.

The product is intended for single use only.

Do not use the concentrate if discoloured or if the concentrate contains foreign particulate matter (see section 3).

Medicinal product must be diluted before administration. Solutions for intravenous administration are prepared by dilution of the concentrate into an infusion bag containing isotonic sodium chloride 9 mg/mL (0.9%) solution for infusion (300 mg / 250 mL or 600 mg / 500 mL), to a final ocrelizumab concentration of approximately 1.2 mg/mL.

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

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 should be at room temperature.

Disposal

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: 8 January 2018
Date of latest renewal: 21 September 2022

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Ocrevus 920 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 920 mg of ocrelizumab in 23 mL (40 mg/mL).

Ocrelizumab is a humanised 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

Solution for injection.

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

Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions. The first administration should be under clinical observation with appropriate medical support to manage severe reactions such as severe injection reactions, hypersensitivity reactions and/or anaphylactic reactions (see section 4.4).

Premedication for injection reactions

The following two premedications are to be administered shortly before each ocrelizumab injection to reduce the risk of local and systemic injection reactions (IRs):

- 20 mg oral dexamethasone (or equivalent)
- Oral antihistamine (e.g., desloratadine or equivalent)

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

Posology

The recommended dose is 920 mg administered every 6 months.
No division of the initial dose or subsequent doses into separate administrations is required.
A minimum interval of 5 months should be maintained between each dose of ocrelizumab.

Injection or treatment discontinuation in case of IRs

Life-threatening IRs

If there are signs of a life-threatening IR, the injection should be stopped immediately, and the patient should receive appropriate treatment. Treatment must be permanently discontinued in these patients (see section 4.3).

Severe IRs

If a patient experiences a severe IR, the injection should be interrupted immediately, and the patient should receive symptomatic treatment. The injection should be completed only after all symptoms have resolved (see section 4.4).

Delayed or missed doses

If an injection 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) should be maintained between doses.

Special populations

Adults over 55 years old

Based on the limited data available for intravenous ocrelizumab (see sections 5.1 and 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 intravenous ocrelizumab every six months after they become older than 55 years old. The use of subcutaneous ocrelizumab was not studied in patients over 65 years of age.

Renal impairment

The safety and efficacy of ocrelizumab 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. Ocrelizumab is a monoclonal antibody and cleared via catabolism (i.e. breakdown into peptides and amino acids), and a dose adjustment is not expected to be required for patients with renal impairment (see section 5.2).

Hepatic impairment

The safety and efficacy of ocrelizumab 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. Ocrelizumab is a monoclonal antibody and cleared via catabolism (rather than hepatic metabolism), and a dose adjustment is not expected to be required for patients with hepatic impairment (see section 5.2).

Paediatric population

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

Method of administration

Ocrevus 920 mg solution for injection is not intended for intravenous administration and should always be administered as a subcutaneous injection by a healthcare professional.

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient by the correct route, as prescribed.

Patients may start treatment using intravenous or subcutaneous ocrelizumab and patients currently receiving intravenous ocrelizumab may continue treatment with intravenous ocrelizumab or transition to Ocrevus 920 mg solution for injection.

The 920 mg dose should be administered as a subcutaneous injection in the abdomen in approximately 10 minutes. Use of a subcutaneous infusion set (e.g., winged/butterfly) is recommended. Any residual hold-up volume remaining in the subcutaneous infusion set should not be administered to the patient.

The injection site should be the abdomen, except for 5 cm around the navel. Injections should never be given into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars.

Ocrevus solution for injection should always be administered by a healthcare professional. For the initial dose, post-injection monitoring with access to appropriate medical support to manage severe reactions such as IRs, for at least one hour after injection is recommended. For subsequent doses, the need for post-injection monitoring is at the treating physician's discretion (see section 4.4).

For instructions on use and handling of the medicinal product prior to administration, see section 6.6.

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.

Injection reactions (IRs)

Treatment with subcutaneous ocrelizumab is associated with IRs, which may be related to cytokine release and/or other chemical mediators. Physicians should alert patients that IRs can occur during or within 24 hours of administration. Symptoms of IRs have been more frequently reported with the first injection. IRs can be local IRs or systemic IRs. Common symptoms of local IRs at the injection site include erythema, pain, swelling and pruritus. Common symptoms of systemic IRs include headache and nausea (see section 4.8).

Shortly before injection, patients should receive premedication to reduce the risk of IRs (see section 4.2). Patients should be observed for at least one hour after the initial dose of the medicinal product for any symptom of severe IR. Appropriate resources for the management of severe IRs, hypersensitivity reactions and/or anaphylactic reactions should be available for the initial dose of the medicinal product. For subsequent doses, the need for post-injection monitoring is at the treating physician's discretion. IRs can be managed with symptomatic treatment, should they occur.

If there are signs of a life-threatening IR, the injection should be stopped immediately, and the patient should receive appropriate treatment. Ocrelizumab treatment must be permanently discontinued in these patients. If a patient experiences a severe IR, the injection should be interrupted immediately, and the patient should receive symptomatic treatment. The injection should be completed only after all symptoms have resolved.

Intravenous ocrelizumab is associated with infusion-related reactions (IRRs), which may also be related to cytokine release and/or other chemical mediators. IRRs may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia and anaphylaxis. Serious IRRs, some requiring hospitalisation, have been reported with the use of intravenous ocrelizumab.

Hypersensitivity may be clinically indistinguishable from an IR or an IRR in terms of symptoms. If a hypersensitivity reaction is suspected, the injection must be stopped immediately and permanently (see 'Hypersensitivity reactions' below).

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 IR symptoms.

A hypersensitivity reaction may present during any administration, although typically would not present during the first administration. For subsequent administrations, 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 or any of the excipients must not be treated (see section 4.3).

Infection

Administration of ocrelizumab 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 (SI) was similar to comparators (see section 4.8) in studies with intravenous ocrelizumab. 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 intravenous ocrelizumab 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. Treatment with ocrelizumab 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)

John Cunningham virus (JCV) infection resulting in PML has been observed very rarely in patients treated with anti-CD20 antibodies, including ocrelizumab, and mostly associated with risk factors (patient population e.g., lymphopenia, advanced age, polytherapy with immunosuppressants).

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

If PML is suspected, dosing with ocrelizumab must be withheld. Evaluation including Magnetic Resonance Imaging (MRI) scan preferably with contrast (compared with pre-treatment MRI), confirmatory cerebro-spinal fluid (CSF) testing for JCV Deoxyribonucleic acid (DNA) and repeat neurological assessments, should be considered. If PML is confirmed, treatment must be discontinued permanently.

Hepatitis B 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 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 ocrelizumab (see section 4.3). 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.

Late neutropenia

Cases of late onset of neutropenia have been reported at least 4 weeks after the latest intravenous ocrelizumab infusion (see section 4.8). Although some cases were Grade 3 or 4, the majority of the cases were Grade 1 or 2. In patients with signs and symptoms of infection, measurement of blood neutrophils is recommended.

Malignancies

An increased number of malignancies (including breast cancers) have been observed in the controlled period of the pivotal clinical trials in patients treated with intravenous ocrelizumab, compared to control groups. The incidence was within the background rate expected for an MS population. After approximately 10 years of continuous ocrelizumab treatment over the controlled period and Open-Label Extension (OLE) phase of the pivotal clinical trials, the incidence of malignancies remained within the background rate expected for an MS population. Patients with a known active malignancy should not be treated with ocrelizumab (see section 4.3). 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 should follow standard breast cancer screening per local guidelines.

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 ocrelizumab concomitantly with immunosuppressants (e.g., chronic corticosteroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) resulted in an increase of SIs, 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 SIs: higher doses of ocrelizumab than recommended in MS, other comorbidities, and chronic use of immunosuppressants/corticosteroids.

It is not recommended to use other immunosuppressives concomitantly with ocrelizumab 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 intravenous ocrelizumab MS pivotal studies, the administration of corticosteroids for the treatment of relapse was not associated with an increased risk of SI.

When initiating ocrelizumab after an immunosuppressive therapy or initiating an immunosuppressive therapy after ocrelizumab, the potential for overlapping pharmacodynamic effects should be taken into consideration (see section 5.1). Caution should be exercised when prescribing ocrelizumab taking into consideration the pharmacodynamics of other disease modifying MS therapies.

Vaccinations

The safety of immunisation with live or live-attenuated vaccines, following ocrelizumab 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).

In a randomised open-label study, RMS patients treated with intravenous ocrelizumab were able to mount humoral responses, although decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide with or without a booster vaccine, keyhole limpet haemocyanin neoantigen, and seasonal influenza vaccines (see section 4.5 and 5.1).

It is recommended to vaccinate patients treated with ocrelizumab with seasonal influenza vaccines that are inactivated.

Physicians should review the immunisation status of patients being considered for treatment with ocrelizumab. Patients who require vaccination should complete their immunisation at least 6 weeks prior to initiation of ocrelizumab treatment.

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 infants of mothers who have been exposed to ocrelizumab 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 levels 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 immunisation schedule and measurement of vaccine-induced response titres should be considered to check whether individuals have mounted a protective immune response because the efficacy of the vaccination may be decreased.

The safety and timing of vaccination should be discussed with the infant's physician (see section 4.6).

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Vaccinations

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

Data are available on the effects of tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet haemocyanin neoantigen, and seasonal influenza vaccines in patients receiving intravenous ocrelizumab (see section 4.4 and 5.1).

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

Immunosuppressants

It is not recommended to use other immunosuppressive therapies concomitantly with ocrelizumab except corticosteroids for symptomatic treatment of relapses (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use contraception while receiving ocrelizumab and for 4 months after the last administered dose of ocrelizumab.

Pregnancy

There is a limited amount of data from the use of ocrelizumab in pregnant women. Ocrelizumab is an immunoglobulin G (IgG). IgG is known to cross the placental barrier. Postponing vaccination with live or live-attenuated vaccines should be considered for neonates and infants born to mothers who have been exposed to ocrelizumab *in utero*. No B cell count data have been collected in neonates and infants exposed to ocrelizumab and the potential duration of B-cell depletion in neonates and infants is unknown (see section 4.4).

Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. B-cell depletion *in utero* was also detected in animal studies.

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

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

Breast-feeding

Human IgGs are known to be excreted in breastmilk the first few days after birth (colostrum period), which decreases to low concentrations soon afterwards.

In a prospective, multicenter, open-label study MN42989 (SOPRANINO), 13 lactating women received ocrelizumab at a median of 2.0 months postpartum (range 0.5-5.0 months). Low concentrations of ocrelizumab were detected in the breastmilk over 60 days following the mother's first postpartum infusion (median relative infant dose of 0.27% [range 0.0-1.8 %]), indicating minimal transfer of ocrelizumab to breastmilk. At 30 days after the mother's first postpartum infusion, ocrelizumab was undetectable in all available serum samples of breastfed infants (n=9), and infant B-cell levels were within normal range in all available blood samples (n=10). No effects of ocrelizumab on health, growth and development were observed in breastfed infants over a follow-up period of 44.6 weeks (range 8.6-62.7 weeks).

While no clinical data on infants potentially exposed to ocrelizumab via breastmilk receiving live or live-attenuated vaccines are available, no risks are expected due to normal B-cell levels and undetectable serum ocrelizumab levels observed in those infants.

In a separate prospective clinical study, low ocrelizumab concentrations in breastmilk (median relative infant dose of 0.1% [range 0.07-0.7%]) over 90 days after the mother's first postpartum infusion were observed in 29 lactating women who received ocrelizumab at a median of 4.3 months postpartum (range 0.1-36 months). Follow-up of 21 infants breastfed for at least 2 weeks showed normal growth and development up to 1 year.

Ocrelizumab can be used during breastfeeding starting a few days after birth.

Fertility

Preclinical data reveal no special hazards for humans based on studies of male and female fertility in cynomolgus monkeys exposed to ocrelizumab.

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

In the controlled period of the pivotal clinical trials, the most important and frequently reported adverse reactions were IRRs (34.3%, 40.1% in RMS and PPMS, respectively) and infections (58.5%, 72.2% in RMS and PPMS, respectively) (see section 4.4).

A total of 2,376 patients were included in the controlled period of the pivotal clinical trials; of these patients, 1,852 entered the OLE phase. All patients switched to ocrelizumab treatment during the OLE phase. 1,155 patients completed the OLE phase, resulting in approximately 10 years of continuous ocrelizumab treatment (15,515 patient-years of exposure) across the controlled period and OLE phase. The overall safety profile observed during the controlled period and OLE phase remains consistent with that observed during the controlled period.

The safety profile of Ocrevus solution for injection was consistent with the known safety profile of intravenous ocrelizumab below in Table 1 except for the very common adverse reaction of IRs.

Tabulated list of adverse reactions

Adverse reactions reported in the controlled period of the pivotal clinical trials with intravenous ocrelizumab and derived from spontaneous reporting are listed below in Table 1. The adverse reactions are listed by MedDRA system organ class and categories of frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each System Organ Class, the adverse reactions are presented in order of decreasing frequency.

Table 1 Adverse reactions

MedDRA System Organ Class (SOC)	Very common	Common	Not Known
Infections and infestations	Upper respiratory tract infection, nasopharyngitis, influenza	Sinusitis, bronchitis, oral herpes, gastroenteritis, respiratory tract infection, viral infection, herpes zoster, conjunctivitis, cellulitis	
Blood and lymphatic system disorders		Neutropenia	Late onset of Neutropenia[3]
Respiratory, thoracic and mediastinal disorders		Cough, catarrh	
Investigations	Blood immunoglobulin M decreased	Blood immunoglobulin G decreased	
Injury, poisoning and procedural complications	Infusion-related reactions[1], injection reaction[2,3]		

[1] Observed only in the pooled intravenous ocrelizumab dataset

[2] Observed in a study outside of the pooled intravenous ocrelizumab dataset (associated with subcutaneous administration).

[3] Observed in the postmarketing setting .

Description of selected adverse reactions

Injection reactions

Based on the observed symptoms, IRs are categorised into systemic IRs and local IRs.

In OCARINA II, 118 patients (ocrelizumab-naïve) received the first injection of the product. The most common symptoms reported with systemic IRs and local IRs included: headache (2.5%), nausea (1.7%), injection site erythema (29.7%), injection site pain (14.4%), injection site swelling (8.5%), and injection site pruritus (6.8%). IRs occurred in 48.3% of these patients after the first injection. Of the 118 patients, 11.0% and 45.8% of patients experienced at least one event of systemic IR and local IR, respectively. Among the patients with IR, the majority of patients (82.5%) had IRs occur within 24 hours after the end of injection as opposed to during the injection. All IRs were non serious and of mild (71.9%) or moderate (28.1%) severity. The median duration of IR was 3 days for systemic IRs and 4 days for local IRs. All patients recovered from IRs, of which 26.3% required symptomatic treatment.

In OCARINA I, 125 patients received one or more subcutaneous injections of ocrelizumab 1200 mg. Of the 125 patients who received the first injection, 16.0% of patients experienced at least one event of systemic IR and 64.0% of patients experienced at least one event of local IR. Of the 104 patients who

received the second injection, the incidence of systemic IR and local IR decreased to 7.7% and 37.5%, respectively. All IRs were non serious and all except one IR were of mild or moderate severity for the first injection. All IRs were non serious and of mild or moderate severity for the second injection. 21.2% and 17.9% of patients experiencing IR required symptomatic treatment after the first and second injection, respectively.

Intravenous ocrelizumab is associated with infusion-related reactions (IRRs), which may also be related to cytokine release and/or other chemical mediators. IRRs may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia and anaphylaxis. Serious IRRs, some requiring hospitalisation, have been reported with the use of intravenous ocrelizumab.

Infection

In the active-controlled studies in RMS, infections occurred in 58.5% of patients receiving intravenous ocrelizumab vs 52.5% of patients receiving interferon beta 1a. SIs occurred in 1.3% of patients receiving intravenous ocrelizumab vs 2.9% of patients receiving interferon beta 1a. In the placebo-controlled study in PPMS, infections occurred in 72.2% of patients receiving intravenous ocrelizumab vs 69.9% of patients receiving placebo. SIs occurred in 6.2% of patients receiving intravenous ocrelizumab vs 6.7% of patients receiving placebo.

All patients switched to intravenous ocrelizumab during the OLE phase in both RMS and PPMS pivotal intravenous ocrelizumab studies. Over the OLE phase in RMS and PPMS patients, the overall risk of SIs did not increase from that observed during the controlled period. As observed during the controlled period, the rate of SIs in PPMS patients remained higher than that observed in RMS patients.

In line with the previous analysis of risk factors for SIs in auto-immune conditions other than MS (see section 4.4), a multivariate analysis of risk factors for SIs was conducted in the approximately 10 years of cumulative exposure data from the controlled period and OLE phase of the pivotal clinical trials. Risk factors for SIs in RMS patients include having at least 1 comorbidity, recent clinical relapse, and Expanded Disability Status Scale (EDSS) $\geq$ 6.0. Risk factors for SIs in PPMS patients include body mass index greater than 25 kg/m^2, having at least 2 comorbidities, EDSS $\geq$ 6.0, and IgM < lower limit of normal (LLN). Comorbidities included, but were not limited to, cardiovascular, renal and urinary tract conditions, previous infections, and depression.

Respiratory tract infections

The proportion of respiratory tract infections was higher in intravenous ocrelizumab treated patients compared to interferon beta-1-a and placebo.
In the RMS clinical trials, 39.9% of intravenous ocrelizumab treated patients and 33.2% interferon beta-1-a treated patients experienced an upper respiratory tract infection and 7.5% of intravenous ocrelizumab 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 intravenous ocrelizumab treated patients and 42.7% of patients who received placebo experienced an upper respiratory tract infection, and 9.9% of intravenous ocrelizumab 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 intravenous ocrelizumab were predominately mild to moderate (80 – 90 %).

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in intravenous ocrelizumab 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%). All infections were mild to moderate in severity, except one Grade 3 event, 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 intravenous ocrelizumab treatment arm.

Laboratory abnormalities

Immunoglobulins

Ocrelizumab treatment resulted in a decrease in total immunoglobulins over the controlled period of the pivotal clinical intravenous ocrelizumab trials, mainly driven by reduction in IgM.

Clinical trial data from the controlled period and OLE phase of the pivotal clinical trials have shown an association between decreased levels of IgG (and less so for IgM or IgA) and increased rate of SIs. 2.1% of RMS patients had a SI during a period with IgG < LLN and in 2.3% of PPMS patients had a SI during a period with IgG < LLN. The difference in rate of SIs between patients with IgG < LLN compared to patients with IgG ≥ LLN did not increase over time. 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 ocrelizumab during the controlled period and OLE phase. Throughout the 10 years of continuous ocrelizumab treatment, mean IgG levels of RMS and PPMS patients remained above LLN.

Lymphocytes

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

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

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

Neutrophils

In the active-controlled (RMS) treatment period, a decrease in neutrophils < LLN was observed in 14.7% of patients treated with intravenous ocrelizumab compared with 40.9% of patients treated with interferon beta-1a. In the placebo-controlled (PPMS) clinical trial, the proportion of intravenous ocrelizumab patients presenting decreased neutrophils was higher (12.9 %) than placebo patients (10.0 %); among these a higher percentage of patients (4.3%) in the intravenous ocrelizumab group had Grade 2 or above neutropenia vs 1.3% in the placebo group; approximately 1% of the patients in the intravenous ocrelizumab 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 ocrelizumab) and were Grade 1 (between<LLN and 1500 cells/mm^3) and 2 (between 1000 and 1500 cells/mm^3) in severity. Overall, approximately 1% of the patients in the intravenous ocrelizumab group had Grade 3 or 4 neutropenia. One patient with Grade 3 (between 500 and 1000 cells/mm^3) and one patient with Grade 4 (< 500 cells/mm^3) neutropenia required specific treatment with granulocyte-colony stimulating factor, and remained on ocrelizumab after the episode. Neutropenia can occur several months after the administration of ocrelizumab (see section 4.4).

Other

One patient, who received 2000 mg of intravenous ocrelizumab, died of systemic inflammatory response syndrome (SIRS) of unknown aetiology, 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 dose of ocrelizumab. 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) and 1200 mg, administered as a subcutaneous injection (Phase Ib dose finding study). The adverse reactions were consistent with the safety profile in the pivotal clinical studies.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, monoclonal antibodies, ATC code: L04AG08.

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 pre-existing humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

Subcutaneous ocrelizumab contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-formulated active substances when administered subcutaneously.

Pharmacodynamic effects

Treatment with ocrelizumab 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 with intravenous ocrelizumab. For the B-cell counts, CD19 is used, as the presence of ocrelizumab interferes with the recognition of CD20 by the assay.

In the Phase III studies, between each dose of intravenous ocrelizumab, up to 5% of patients showed B-cell repletion (> 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 intravenous 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

Subcutaneous formulation

OCARINA II
Study CN42097 (OCARINA II) was a multi-center, randomised, open-label, parallel arm trial conducted to evaluate the pharmacokinetics, pharmacodynamics, safety, immunogenicity, radiological and clinical effects of subcutaneous ocrelizumab compared with intravenous ocrelizumab in patients with either RMS or PPMS. OCARINA II was designed to demonstrate non-inferiority of treatment with subcutaneous ocrelizumab versus intravenous ocrelizumab based on the primary PK endpoint of area under the concentration time curve (AUC) up to week 12 post-injection/infusion (AUC_{w1-12}).

A total of 236 patients with RMS or PPMS (213 patients with RMS, 23 patients with PPMS) were randomised in a 1:1 ratio to the subcutaneous arm or intravenous arm. During the controlled period (Day 0 to Week 24), patients received either a single 920 mg subcutaneous injection at study Day 1 or two 300 mg intravenous infusions at study Day 1 and 14. After the controlled period, all patients had the opportunity to receive further subcutaneous injections of 920 mg ocrelizumab at Weeks 24 and 48 (Dose 2 and 3, respectively). Patients were excluded if they had previous treatment with anti-CD20 antibodies within the last 24 months, including ocrelizumab.

Patients were aged 18-65 years with an EDSS between 0 to 6.5 at screening. The demographics were similar and baseline characteristics were well balanced across the two treatment groups. The mean age was 39.9 years in the subcutaneous arm and 40.0 years in the intravenous arm. 34.7% of patients were male in the subcutaneous arm and 40.7% of patients were male in the intravenous arm. The mean/median duration since MS diagnosis was 5.70/3.10 years in the subcutaneous arm and 4.78/2.35 years in the intravenous arm.

Non-inferiority of the ocrelizumab exposure after administration of 920 mg subcutaneous ocrelizumab compared to 600 mg intravenous ocrelizumab was demonstrated based on the PK primary endpoint, AUC up to week 12 (AUC_{w1-12}) post-injection (see section 5.2).

Intravenous formulation

Relapsing forms of multiple sclerosis (RMS)

Efficacy and safety of ocrelizumab 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 2.

Demographic and baseline characteristics were well balanced across the two treatment groups. Patients receiving ocrelizumab (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 44 mcg via subcutaneous injection 3 times per week.

Table 2 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: Ocrelizumab 600 mg Group B: interferon beta-1a 44 mcg S.C. (IFN)			
Baseline characteristics	Ocrelizumab 600 mg (n=410)	IFN 44 mcg (n=411)	Ocrelizumab 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 a disease-modifying therapy (DMT) in the 2 years prior to randomisation.

Key clinical and MRI efficacy results are presented in Table 3 and Figure 1.

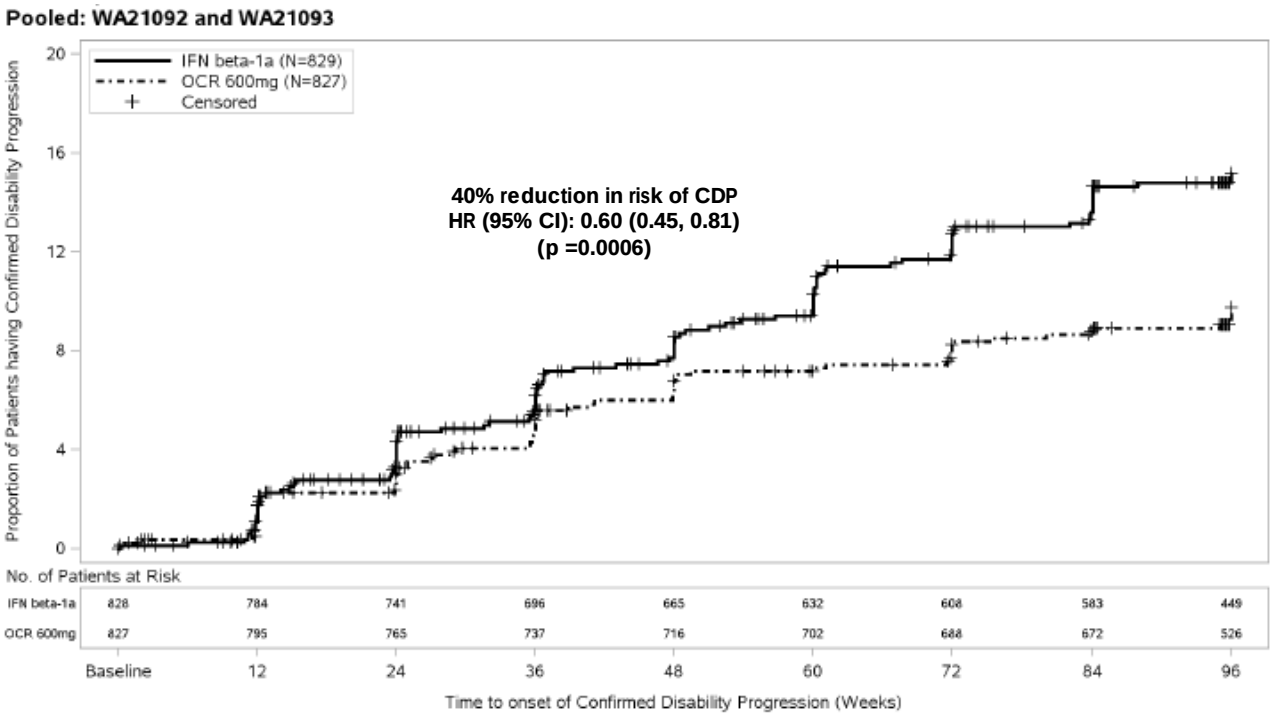
The results of these studies show that ocrelizumab significantly suppressed relapses, sub-clinical disease activity measured by MRI, and disease progression compared with interferon beta-1a 44 mcg subcutaneous.

Table 3 Key clinical and MRI endpoints from Studies WA21092 and WA21093 (RMS)

Endpoints	Study 1: WA21092 (OPERA I)		Study 2: WA21093 (OPERA II)	
	Ocrelizumab 600 mg (n=410)	IFN 44 mcg (n=411)	Ocrelizumab 600 mg (n=417)	IFN 44 mcg (n=418)
Clinical Endpoints				
Annualised Relapse Rate (ARR) (primary endpoint)[8]	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% Ocrelizumab vs 15.2% IFN 40% (p=0.0006)[7]			
Risk Reduction (Pooled Analysis[1])	43 % (p=0.0139)[7]		37 % (p=0.0169)[7]	
Risk Reduction (Individual Studies[2])				
Proportion of patients with 24 week Confirmed Disability Progression (CDP)[3]	7.6% Ocrelizumab vs 12.0% IFN 40% (p=0.0025)[7]			
Risk Reduction (Pooled Analysis[1])	43 % (p=0.0278)[7]		37 % (p=0.0370)[7]	
Risk Reduction (Individual Studies[2])				
Proportion of patients with at least 12 weeks Confirmed Disability Improvement[4]	20.7% Ocrelizumab 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] CDP 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 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
[8] Confirmed relapses (accompanied by a clinically relevant change in EDSS).

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 ocrelizumab compared to interferon beta-1a (p=0.0006) were highly consistent with the results sustained for at least 24 weeks (40% risk reduction for ocrelizumab 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 ocrelizumab on ARR and 12 week CDP was consistent with the overall population.

Primary progressive multiple sclerosis (PPMS)

Efficacy and safety of ocrelizumab 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 4.

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 III PPMS study, patients received 600 mg ocrelizumab 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 ocrelizumab 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 4 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 *(Minimum 120 weeks and 253 confirmed disability progression events)* *(Median follow-up time:* Ocrelizumab *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: Ocrelizumab 600 mg Group B: Placebo, in 2:1 randomisation	
Baseline characteristics	Ocrelizumab 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 5 and Figure 2.

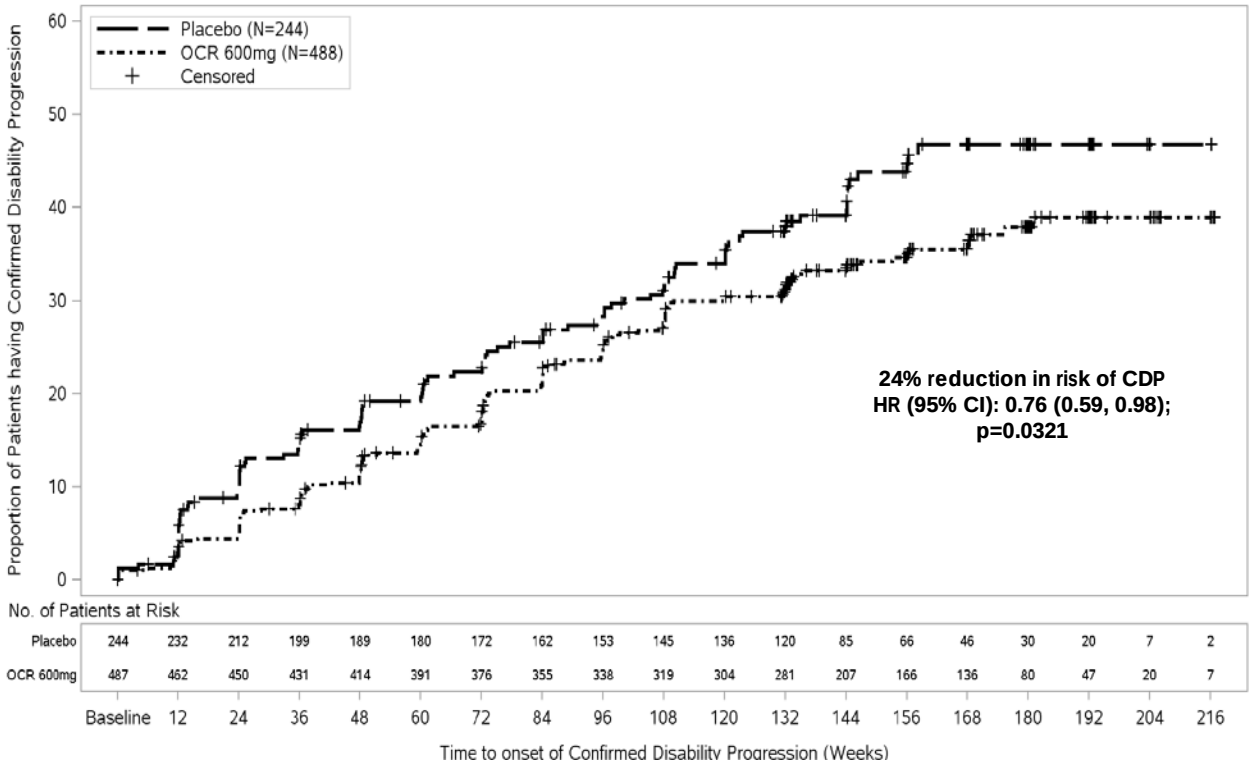
The results of this study show that ocrelizumab significantly delays disease progression and reduces deterioration in walking speed compared with placebo.

Table 5 Key clinical and MRI endpoints from Study WA25046 (PPMS)

	Study 3	
	WA25046 (Oratorio)	
Endpoints	Ocrelizumab 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 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]).

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 ocrelizumab 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. As these results were exploratory in nature and included data after unblinding, the results should be interpreted with caution.

Immunogenicity

Subcutaneous formulation

Across OCARINA I and OCARINA II, no patients had treatment-emergent anti-drug antibodies (ADAs) to ocrelizumab. Patients in OCARINA II were tested at baseline and every 6 months post treatment for the duration of the trial for ADAs. Transient ADAs may therefore not be detected between the assessed time points.

The incidence of treatment-emergent anti-rHuPH20 (hyaluronidase) antibodies in patients treated with subcutaneous ocrelizumab in OCARINA I was 2.3% (3/132). No patients from OCARINA II had treatment-emergent anti-rHuPH20 antibodies.

Intravenous formulation

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 ADAs. Out of 1311 patients treated with ocrelizumab, 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 ocrelizumab.

Immunisations

In a randomised open-label study in RMS patients (N=102), the percentage of patients with a positive response to tetanus vaccine at 8 weeks after vaccination was 23.9% in the intravenous ocrelizumab group compared to 54.5% in the control group (no disease-modifying therapy except interferon-beta). Geometric mean anti-tetanus toxoid specific antibody titres at 8 weeks were 3.74 and 9.81 IU/ml, respectively. Positive response to ≥5 serotypes in 23-PPV at 4 weeks after vaccination was 71.6% in the intravenous ocrelizumab group and 100% in the control group. In patients treated with intravenous ocrelizumab a booster vaccine (13-PCV) given 4 weeks after 23-PPV did not markedly enhance the response to 12 serotypes in common with 23-PPV. The percentage of patients with seroprotective titres against five influenza strains ranged from 20.0–60.0% and 16.7–43.8% pre-vaccination and at 4 weeks post vaccination from 55.6–80.0% in patients treated with intravenous ocrelizumab and 75.0–97.0% in the control group, respectively. See sections 4.4 and 4.5.

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.

After administration of 920 mg subcutaneous ocrelizumab, the predicted mean exposure (AUC over the 24 week dosing interval) was 3730 µg/mL•day. The primary PK endpoint in OCARINA II, AUC_{w1-12}, after 920 mg subcutaneous ocrelizumab was shown to be non-inferior to 600 mg intravenous ocrelizumab. The geometric mean ratio for AUC_{w1-12} was 1.29 (90% CI: 1.23–1.35).

Absorption

The estimated bioavailability after subcutaneous administration of 920 mg ocrelizumab was 81%. The mean C_{max} was 132 µg/mL and t_{max} was reached after approximately 4 days (range 2-13 days).

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 ocrelizumab 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.

Special populations

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of ocrelizumab in children and adolescents less than 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 ocrelizumab 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 two pre- and post-natal development studies in cynomolgus monkeys, administration of intravenous ocrelizumab from gestation day 20 to at least parturition was associated with glomerulopathy, lymphoid follicle formation in bone marrow, lymphoplasmacytic renal inflammation, and decreased testicular weight in offspring. The maternal doses administered in these studies resulted in maximum mean serum concentrations (C_{max}) that were 4.5- to 21-fold above those anticipated in the clinical setting.

There were five cases of neonatal moribundities, one attributed to weakness due to premature birth accompanied by opportunistic bacterial infection, one due to an infective meningoencephalitis involving the cerebellum of the neonate from a maternal dam with an active bacterial infection (mastitis) and three with evidence of jaundice and hepatic damage, with a viral aetiology suspected, possibly a polyomavirus. The course of these five confirmed or suspected 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.

Hyaluronidase

Non-clinical data for recombinant human hyaluronidase reveal no special hazard based on conventional studies of repeated dose toxicity including safety pharmacology endpoints.

Hyaluronidase (rHuPH20) is found in most tissues of the human body. Subcutaneous administration of ocrelizumab with hyaluronidase was well tolerated in rats and minipigs in local tolerance studies.

Reproductive toxicology studies with rHuPH20 revealed embryofetal toxicity in mice, with no effect level >1,100-fold higher than the suggested clinical dose, however, without evidence of teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
Sodium acetate trihydrate (E 262)
Glacial acetic acid
α,α-trehalose dihydrate
Polysorbate 20 (E 432)
L-methionine
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

2 years

Prepared syringe

- Chemical and physical in-use stability has been demonstrated for 30 days at 2 °C to 8 °C and additionally for 8 hours unprotected from light at ≤30 °C.
- From a microbiological point of view, the product should be used immediately once transferred from the vial to the syringe. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and normally not longer than 24 hours at 2 °C to 8 °C, unless the preparation has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Do not freeze. Do not shake.
Keep the vials in the outer carton in order to protect from light.

If necessary, the unopened vial may be stored outside the refrigerator at temperatures ≤25 °C for up to 12 hours.

The vials can be removed and placed back into the refrigerator so that the total combined time out of the refrigerator of the unopened vial may not exceed 12 hours at ≤25 °C.

For storage conditions after preparation of the syringe, see section 6.3.

6.5 Nature and contents of container

23 mL of solution for injection in a vial (colourless Type I glass).
Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

The medicinal product should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

The medicinal product is for single use only and should be prepared by a healthcare professional using aseptic technique.

No incompatibilities between this medicinal product and polypropylene (PP), polycarbonate (PC), polyethylene (PE), polyvinyl chloride (PVC), polyurethane (PUR) and stainless steel have been observed.

Preparation of the syringe

- Prior to use, the vial should be removed from the refrigerator to allow the solution to come to room temperature.
- Withdraw the entire contents of Ocrevus solution for injection from the vial with a syringe and transfer needle (21G recommended).
- Remove the transfer needle and attach a subcutaneous infusion set (e.g., winged/butterfly) containing a 24 – 26G needle for injection. Use a subcutaneous infusion set with residual hold-up volume NOT exceeding 0.8 mL for administration.
- Prime the subcutaneous infusion line with the solution for injection to eliminate the air in the infusion line and stop before the fluid reaches the needle.
- Ensure the syringe contains exactly 23 mL of the solution after priming and expelling any excess volume from the syringe.
- Administer immediately to avoid needle clogging. Do not store the prepared syringe that has been attached to the already-primed subcutaneous infusion set.

If the dose is not administered immediately, refer to “Storage of the syringe” below.

Storage of the syringe

- If the dose is not to be administered immediately, use aseptic technique to withdraw the entire contents of Ocrevus solution for injection from the vial into the syringe to account for the dose volume (23 mL) and priming volume for the subcutaneous infusion set. Replace the transfer needle with a syringe closing cap. Do not attach a subcutaneous infusion set for storage.
- If the syringe was stored in a refrigerator, allow the syringe to reach room temperature prior to adminsitration.

Disposal

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/1/17/1231/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 January 2018
Date of latest renewal: 21 September 2022

10 DATE OF REVISION OF THE TEXT

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

Roche Singapore Technical Operations, Pte. Ltd
10 Tuas Bay Link
637394 Singapore
Singapore

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 (PSURs)**

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

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 injections

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

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ocrevus 920 mg solution for injection
ocrelizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 920 mg ocrelizumab in 23 ml solution.

3. LIST OF EXCIPIENTS

Also contains recombinant human hyaluronidase (rHuPH20), sodium acetate trihydrate, glacial acetic acid, α,α-trehalose dihydrate, polysorbate 20, L-methionine, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
920 mg/23mL
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
For subcutaneous use only
Do not shake the vial

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

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1231/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

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 920 mg solution for injection
ocrelizumab
For subcutaneous use only

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

920 mg/23 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ocrevus 300 mg concentrate for solution for infusion
ocrelizumab

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 Ocrevus.
- **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).
- Your doctor may recommend that you are given a seasonal influenza vaccine.
- 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

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. 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.
- Talk to your doctor before vaccinating your baby.

Contraception for women

Women who could become pregnant must use contraception:

- during treatment with Ocrevus and
- for 4 months after your last infusion of Ocrevus.

Breast-feeding

Ocrevus can be used during breastfeeding. Talk to your doctor about the best way to feed your baby if you are given Ocrevus.

Driving and using machines

It is not known whether Ocrevus can affect your ability 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, that is to say 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 (intravenous 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 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. Depending on the rate of the subsequent infusion, each infusion will either last about 3 hours 30 minutes or 2 hours.

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).

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:

Serious side effects:

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)
    - sore throat and runny nose (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)
- discharge from the eye with itching, redness and swelling (conjunctivitis)
- cough
- a build-up of thick mucus in the nose, throat or chest
- low levels of a type of white blood cell (neutropenia)

Not known (it is not known how often these side effects happen)
- a reduction in white blood cells which can be delayed

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 (2ºC - 8ºC). 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 (see Section 2 'Ocrevus contains sodium'), glacial acetic acid, trehalose dihydrate, polysorbate 20 and water for injections.

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

Roche Pharma AG
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This leaflet was last revised in

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.

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

Posology

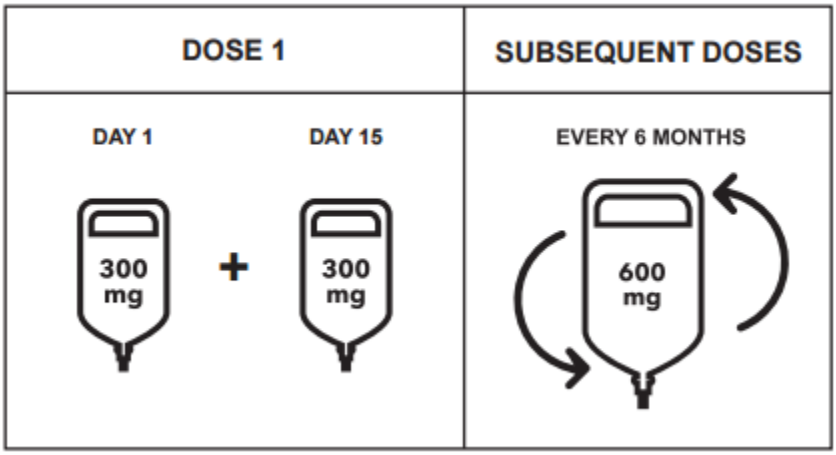
- Initial dose

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 ocrelizumab thereafter are administered as a single 600 mg intravenous infusion every 6 months (see 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 ocrelizumab.

Figure 1: Dose and Schedule of Ocrevus



Management of IRRs before the infusion

- 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 ocrelizumab infusion to reduce the frequency and severity of IRRs:
  - 100 mg intravenous methylprednisolone (or an equivalent) approximately 30 minutes prior to each infusion;
  - antihistamine approximately 30-60 minutes prior to each infusion;

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

- Hypotension, as a symptom of IRR, may occur during 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

- The product should be prepared by a healthcare professional using aseptic technique. Do not shake the vial. A sterile needle and syringe should be used to prepare the diluted infusion solution.
- The product is intended for single use only.
- Concentrate may contain fine translucent and/or reflective particles associated with enhanced opalescence. Do not use the concentrate if discoloured or if the concentrate contains foreign particulate matter.
- Medicinal product must be diluted before administration. Solutions for intravenous administration are prepared by dilution of the concentrate into an infusion bag containing isotonic sodium chloride 9 mg/mL (0.9%) solution for infusion (300mg/250mL or 600mg/500mL), to a final ocrelizumab 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 should be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Method of administration

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

Table 1: Dose and schedule

<table>
<tr><th colspan="2"></th><th>Amount of ocrelizumab to be administered</th><th>Infusion instruction</th></tr>
<tr><td rowspan="2">Initial dose (600 mg)
divided into 2 infusions</td><td>Infusion 1</td><td>300 mg in 250 mL</td><td rowspan="2">• 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.</td></tr>
<tr><td>Infusion 2
(2 weeks later)</td><td>300 mg in 250 mL</td></tr>
<tr><td rowspan="4">Subsequent doses (600 mg)
single infusion once every 6 months</td><td>Option 1

Infusion of approx. 3.5 hours duration</td><td>600 mg in 500 mL</td><td>• 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.</td></tr>
<tr><td colspan="3">OR</td></tr>
<tr><td>Option 2

Infusion of approx. 2 hours duration</td><td>600 mg in 500 mL</td><td>• Initiate the infusion at a rate of 100 mL/hour for the first 15 minutes
• Increase the infusion rate to 200 mL/hour for the next 15 minutes
• Increase the infusion rate to 250 mL/hour for the next 30 minutes
• Increase the infusion rate to 300 mL/hour for the remaining 60 minutes
• Each infusion should be given over approximately 2 hours.</td></tr>
</table>

<u>Management of IRRs during and after the infusion</u>

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

Severe IRRs

If a patient experiences a severe IRR (such as dyspnoea) 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 clinically indistinguishable 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 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

2 years

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.

Package leaflet: Information for the patient

Ocrevus 920 mg solution for injection
ocrelizumab

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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

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
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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.

Injection reactions

- Injection reactions are the most common side effect of Ocrevus treatment given as an injection under your skin (subcutaneous injection).
- **Tell your doctor or nurse straight away if you have any injection reaction** (see section 4 for a list of injection reactions). Injection reactions can happen during the injection or up to 24 hours after the injection.
- To reduce the risk of injection reactions, your doctor will give you other medicines before each injection of Ocrevus (see section 3) and you will be observed during the injection and for at least one hour after the initial injection 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 injections, 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 Ocrevus.
- **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).
- Your doctor may recommend that you are given a seasonal influenza vaccine.
- 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.

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

Pregnancy

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. 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.
- Talk to your doctor before vaccinating your baby.

Contraception for women

Women who could become pregnant must use contraception:

- during treatment with Ocrevus and
- for 4 months after your last dose of Ocrevus.

Breast-feeding

Ocrevus can be used during breastfeeding. Talk to your doctor about the best way to feed your baby if you are given Ocrevus.

Driving and using machines

It is not known whether Ocrevus can affect your ability 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, that is to say essentially ‘sodium-free’.

3. How Ocrevus is given

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 injection reactions (see sections 2 and 4 for information about injection reactions).
You will receive a corticosteroid and an anti-histamine before each injection and you may also receive medicines to reduce fever.

How much and how often you will be given Ocrevus

You will be given a total dose of 920 mg of Ocrevus every 6 months.

How Ocrevus is given

- Ocrevus will be given to you by a doctor or a nurse. It will be given as an injection under your skin (subcutaneous injection).
- Injections will be given in the stomach in approximately 10 minutes.
- Your doctor or nurse will make sure each injection is given in the stomach, where the skin is not red, bruised, tender, hard, or areas where there are moles or scars.
- You will be observed while you are being given Ocrevus and for at least 1 hour after the initial injection has been given. This is in case you have any side effects such as injection reactions. The injection may be temporarily stopped or permanently stopped if you have an injection reaction, depending on how serious it is (see sections 2 and 4 for information about injection reactions).

If you miss an injection of Ocrevus

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

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:

<u>Serious side effects:</u>

Injection reactions

- Injection reactions are the most common side effect of Ocrevus treatment given as a subcutaneous injection (very common: may affect more than 1 in 10 people). In most cases these are mild or moderate reactions but serious reactions have happened with Ocrevus treatment given as an infusion in a vein (intravenous infusion).
- **Tell your doctor or nurse straight away if you experience any signs or symptoms of an injection reaction during the injection or up to 24 hours after the injection.** Symptoms can include, but are not limited to:
  - itchy skin
  - rash
  - hives

- redness of the skin
- pain or swelling at the injection site
- 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 injection reaction, you may be given medicines to treat it and the injection may need to be stopped. If the injection 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)
    - sore throat and runny nose (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)

<u>Other side effects:</u>

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)
- discharge from the eye with itching, redness and swelling (conjunctivitis)
- cough
- a build-up of thick mucus in the nose, throat or chest
- low levels of a type of white blood cell (neutropenia)

Not known (it is not known how often these side effects happen)
- a reduction in white blood cells which can be delayed

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 ($2^{o}C$ - $8^{o}C$). It is not to be frozen. The vials are to be kept in the outer carton to protect them from light. Do not shake.

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 920 mg of ocrelizumab in 23 mL (40 mg/mL).
- The other ingredients are recombinant human hyaluronidase (rHuPH20), sodium acetate trihydrate (see Section 2 'Ocrevus contains sodium'), glacial acetic acid, α,α-trehalose dihydrate, polysorbate 20, L-methionine and water for injections.

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 solution for injection.
- Ocrevus is available in a pack containing 1 glass vial.

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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.

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

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient by the correct route, as prescribed.

The medicinal product should be inspected visually to ensure there is no particulate matter or discolouration prior to administration.

The medicinal product is for single use only and should be prepared by a healthcare professional using aseptic technique.

No incompatibilities between this medicinal product and polypropylene (PP), polycarbonate (PC), polyethylene (PE), polyvinyl chloride (PVC), and polyurethane (PUR) and stainless steel have been observed.

Preparation of the syringe

- Prior to use, the vial should be removed from the refrigerator to allow the solution to come to room temperature.
- Withdraw the entire contents of Ocrevus solution for injection from the vial with a syringe and transfer needle (21G recommended).
- Remove the transfer needle and attach a subcutaneous infusion set (e.g., winged/butterfly) containing a 24-26G needle for injection. Use a subcutaneous infusion set with residual hold-up volume NOT exceeding 0.8 mL for administration.
- Prime the subcutaneous infusion line with the solution for injection to eliminate the air in the infusion line and stop before the fluid reaches the needle.
- Ensure the syringe contains exactly 23 mL of the solution after priming and expelling any excess volume from the syringe.
- Administer immediately to avoid needle clogging. Do not store the prepared syringe that has been attached to the already-primed subcutaneous infusion set.

If the dose is not administered immediately, refer to “Storage of the syringe” below.

Storage of the syringe

- If the dose is not to be administered immediately, use aseptic technique to withdraw the entire contents of Ocrevus solution for injection from the vial into the syringe to account for the dose volume (23 mL) and priming volume for the subcutaneous infusion set. Replace the transfer needle with a syringe closing cap. Do not attach a subcutaneous infusion set for storage.
- Chemical and physical in-use stability has been demonstrated for 30 days at 2 °C to 8 °C and additionally for 8 hours unprotected from light at ≤30 °C.
- From a microbiological point of view, the product should be used immediately once transferred from the vial to the syringe. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and normally not longer than 24 hours at 2 °C to 8 °C, unless the preparation has taken place in controlled and validated aseptic conditions.
- If the syringe was stored in a refrigerator, allow the syringe to reach room temperature prior to administration.

Method of administration

Ocrevus 920 mg solution for injection is not intended for intravenous administration and should always be administered via a subcutaneous injection by a healthcare professional.

Patients may start treatment using intravenous or subcutaneous ocrelizumab and patients currently receiving intravenous ocrelizumab may continue treatment with intravenous ocrelizumab or transition to Ocrevus 920 mg solution for injection.

Prior to administration, the medicinal product should be removed from refrigeration to allow the solution to come to room temperature. For instructions on use and handling of the medicinal product prior to administration, see section 6.6.

The 920 mg dose should be administered as a subcutaneous injection in the abdomen in approximately 10 minutes. Use of a subcutaneous infusion set (e.g., winged/butterfly) is recommended. Any residual hold-up volume remaining in the subcutaneous infusion set should not be administered to the patient.

The injection site should be the abdomen, except for 5 cm around the navel. Injections should never be given into areas where the skin is red, bruised, tender, or hard, or areas where there are moles or scars.

Ocrevus solution for injection should always be administered by a healthcare professional. For the initial dose, post-injection monitoring with access to appropriate medical support to manage severe reactions such as IRs, for at least one hour after injection is recommended. For subsequent doses, the need for post-injection monitoring is at the treating physician’s discretion (see section 4.4).