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 dyspnea) or a complex of flushing, fever, and throat pain symptoms, the infusion should be interrupted immediately, and the patient should receive symptomatic treatment. The infusion should be restarted only after all symptoms have resolved. The initial infusion rate at restart should be half of the infusion rate at the time of onset of the reaction. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

Mild to moderate IRRs

If a patient experiences a mild to moderate IRR (e.g., headache), the infusion rate should be reduced to half the rate at the onset of the event. This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion rate. No infusion adjustment is necessary for subsequent new infusions, unless the patient experiences an IRR.

Dose modifications during treatment

The above examples of dose interruption and slowing (for mild/moderate and severe IRRs) will result in a change in the infusion rate and increase the total duration of the infusion, but not the total dose. No dose reductions 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</td><td>600 mg in 500</td><td>• Initiate the infusion at a rate of 100 mL/hour</td></tr>
</table>

		Amount of ocrelizumab to be administered	Infusion instructions
	Infusion of approximately 2 hours duration	mL	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

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 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). 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.

<u>Malignancies</u>

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 hemocyanin 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 titers 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 hemocyanin 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 titers 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 child bearing potential

Women of childbearing potential should use contraception while receiving ocrelizumab and for 12 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

It is unknown whether ocrelizumab/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of

ocrelizumab in milk (see section 5.3). A risk to neonates and infants cannot be excluded. Women should be advised to discontinue breast-feeding during therapy.

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) ≥ 6.0. Risk factors for SIs in PPMS patients include body mass index greater than 25 kg/m2, having at least 2 comorbidities, EDSS ≥ 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 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 < LNN 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 1,500 cells/mm^3) and 2 (between 1,000 and 1,500 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 1,000 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 2,000 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

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 2,000 mg, administered as two 1,000 mg intravenous infusions separated by 2 weeks (Phase II dose finding study in RRMS) and 1,200 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

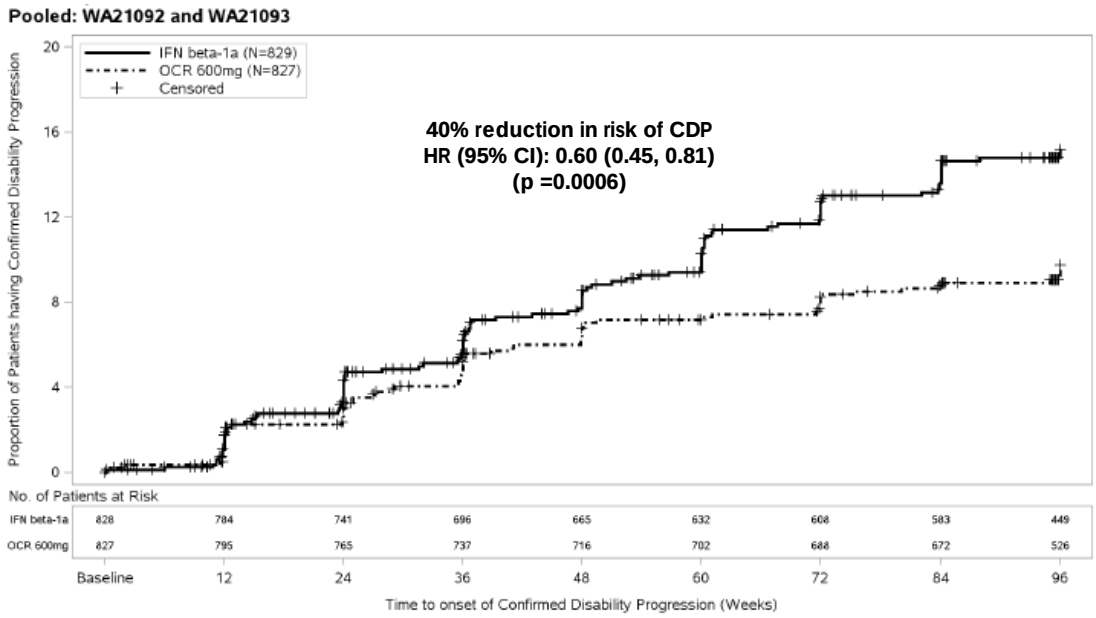
[4] Defined as decrease of ≥ 1.0 point from the baseline EDSS score for patients with baseline EDSS score ≥ 2 and ≤ 5.5, or ≥0.5 when the baseline score is > 5.5. Patients with baseline score < 2 were not included in analysis.

[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.

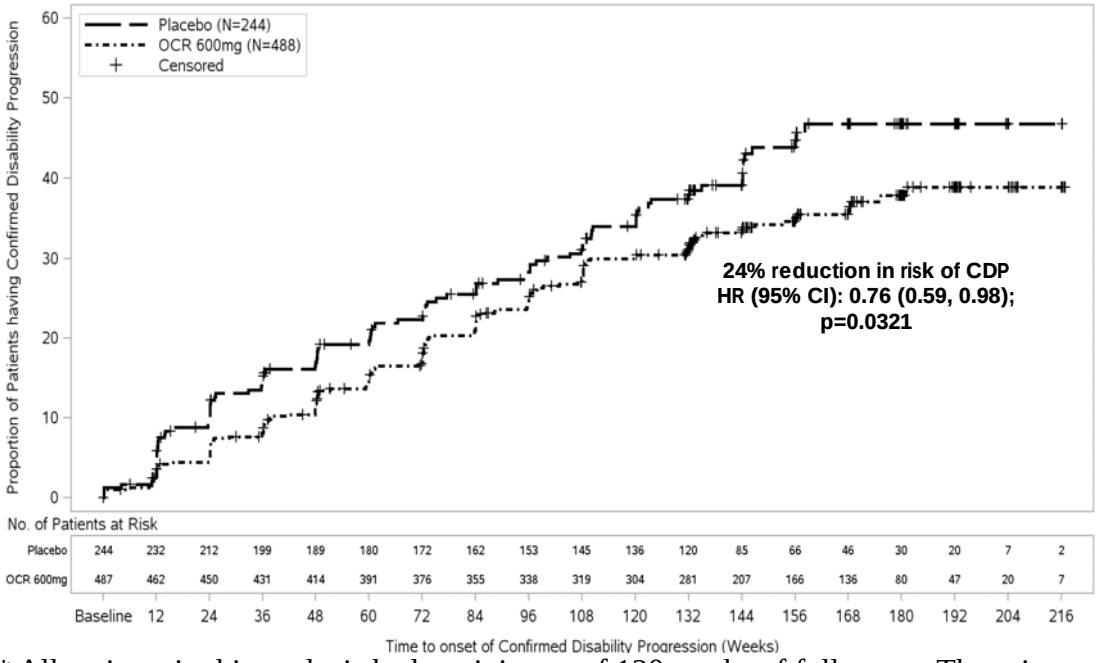
Table 6 Key clinical and MRI endpoints from Study WA25046 (PPMS)

	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 1,311 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 titers 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 titers 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 3,510 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 (Cmax) 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. Measurable levels of ocrelizumab were detected in milk (approximated 0.2% of steady state trough serum levels) during the lactation period.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate (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 glass 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

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 Products Limited
6 Falcon Way, Shire Park
Welwyn Garden City,
AL7 1TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00031/0889

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021 / 11/10/2022

10 DATE OF REVISION OF THE TEXT

29/11/2024