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Ocrevus®

Ocrelizumab

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Recombinant humanized anti-CD20 monoclonal antibody.

ATC Code: L04AG08

1.2 TYPE OF DOSAGE FORM

- Intravenous (IV) formulation: Concentrate for solution for infusion
- Subcutaneous (SC) formulation: Solution for subcutaneous injection

1.3 ROUTE OF ADMINISTRATION

Intravenous (IV) Infusion

Subcutaneous (SC) Injection

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile Product

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: ocrelizumab

Ocrevus IV

Ocrevus solution for intravenous (IV) infusion is a clear or slightly opalescent, and colorless to pale brown solution supplied as a single-use formulation containing 30 mg/mL ocrelizumab in 20 mM sodium acetate, 106 mM trehalose dihydrate and 0.02% (w/v) polysorbate 20 at pH 5.3. The drug product is supplied at a volume of 10.0 mL containing a total of 300mg ocrelizumab (in a 15 mL glass vial).

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

Ocrevus SC

Ocrevus solution for subcutaneous (SC) injection is a clear to slightly opalescent, and colorless to pale brown, preservative-free solution supplied in sterile ready-to-use, non-pyrogenic single-dose vials containing 40 mg/mL ocrelizumab. The drug product is supplied at a volume of 23 mL containing a total of 920mg ocrelizumab (in a 50 mL vial).

Excipients:
Ocrevus SC contains recombinant human hyaluronidase (rHuPH20) at a concentration of 1,000 U/mL, an enzyme that increases dispersion and absorption of co-administered drugs when administered subcutaneously.

All other excipients: α,α-trehalose dihydrate, glacial acetic acid, L-methionine, polysorbate 20, sodium acetate trihydrate, water for injection.

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

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

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

2.2 DOSAGE AND ADMINISTRATION

General

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

It is important to check the product labels to ensure that the correct formulation (Ocrevus IV or Ocrevus SC) is being administered to the patient by the correct route as prescribed. Patients may start Ocrevus treatment using Ocrevus IV or SC and patients currently receiving Ocrevus IV may continue treatment with Ocrevus IV or Ocrevus SC.

Ocrevus IV

Premedication for infusion-related reactions

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

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

Administration of Ocrevus

Ocrevus IV is not intended for subcutaneous administration.

Ocrevus IV is administered as an IV infusion through a dedicated line under the close supervision of an experienced healthcare professional (HCP) with access to appropriate medical support to manage severe reactions such as serious infusion-related reactions (IRRs). Ocrevus IV infusions should not be administered as an intravenous push or bolus. Use isotonic 0.9% sodium chloride solution as the infusion vehicle. In the event an IV infusion cannot be completed the same day, the remaining liquid in the infusion bag must be discarded (see section *4.1 Storage and 4.2 Special Instructions for Use, Handling and Disposal*).

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

Initial Dose

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

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

Subsequent Doses

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

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

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

Table 1 Dose and Schedule of Ocrevus IV

		Amount of Ocrevus IV to be administered*	Infusion instruction
Initial Dose (600 mg) divided into 2 infusions	Infusion 1	300 mg in 250 mL	• Initiate the infusion at a rate of 30 mL/hr • Thereafter, the rate can be increased in 30 mL/hr increments every 30 minutes to a maximum of 180 mL/hr. • Each infusion should be given over approximately 2.5 hr
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent Doses (600 mg)** single infusion once every 6 months	Option 1 Infusion of approximately 3.5 hours duration	600mg in 500 mL	• Initiate the infusion at a rate of 40 mL/hr • Thereafter, the rate can be increased in 40 mL/hr increments every 30 minutes to a maximum of 200 mL/hr. • Each infusion should be given over approximately 3.5 hr
	OR		
	Option 2 Infusion of approximately 2 hours duration	600mg in 500 mL	• Initiate the infusion at a rate of 100 mL/hr for the first 15 minutes • Increase the infusion rate to 200 mL/hr for the next 15 minutes • Increase the infusion rate to 250 mL/hr for the next 30 minutes • Increase the infusion rate to 300 mL/hr for the remaining 60 minutes • Each infusion should be given over approximately 2 hr

* Solutions of Ocrevus for IV infusion are prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride, to a final drug concentration of approximately 1.2 mg/mL.
** First single infusion should be administered 6 months after Infusion 1 of Initial Dose.

Infusion Adjustments during Treatment:

No dose reductions of Ocrevus IV are recommended.

In case of infusion-related reactions (IRRs) during any infusion, see the following adjustments. Additional information on IRRs can be found in section *2.4.1 Warnings and Precautions, General, Infusion-Related Reactions and Injection Reactions*.

Life-threatening IRRs

Immediately stop Ocrevus IV if there are signs of a life-threatening or disabling infusion-related reaction during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. The patient should receive appropriate supportive treatment.

Permanently discontinue Ocrevus IV in these patients.

Severe IRRs

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

Mild to Moderate IRRs

If a patient experiences a mild to moderate IRR (e.g. headache), the infusion rate should be reduced to half the rate at the onset of the event. This reduced rate should be maintained for at least 30 minutes. If tolerated, the infusion rate may then be increased according to the patient's initial infusion schedule.

See section *2.4.1 Warnings and Precautions, General, Infusion-Related Reactions and Injection Reactions* for full description of symptoms associated with IRRs.

Ocrevus SC

Premedication for injection reactions

Premedicate orally with 20 mg dexamethasone (or equivalent) and an antihistaminic drug (e.g., desloratadine) shortly before each Ocrevus SC administration (see *section 2.4 Warnings and Precautions, General, Infusion-Related Reactions and Injection Reactions*) to reduce the risk of local and systemic injection reactions.

The administration of an antipyretic (e.g., acetaminophen/paracetamol) may also be considered shortly before each Ocrevus SC administration.

Administration of Ocrevus SC

Ocrevus SC is not intended for intravenous administration.

Ocrevus SC must be administered as a subcutaneous injection only, under the supervision of an HCP (see *section 4.2 Special Instructions for Use, Handling and Disposal*). Prior to administration, remove Ocrevus SC from refrigeration and allow the solution to come to room temperature.

For the initial dose, post-injection monitoring with access to appropriate medical support to manage any severe injection reactions, for at least one hour after injection is recommended. For subsequent doses, the suitable administration setting (e.g., clinic or home) and post-injection monitoring is at the treating physician's discretion.

Administer 23 mL (920 mg) of Ocrevus SC solution subcutaneously in the abdomen in approximately 10 minutes. Use of a SC infusion set (e.g., winged/butterfly) is recommended. DO NOT administer any residual hold-up volume remaining in the SC infusion set to the patient.

The injection site should be the abdomen, except for 2 inches (5 cm) around the navel. Ocrevus SC injections should not be administered into areas where the skin is red, bruised, tender or hard, or areas where there are moles or scars.

Dose and schedule

Ocrevus SC is administered as a 920 mg subcutaneous injection 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 Ocrevus.

Delayed or Missed Doses

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

2.2.1 Special Dosage Instructions

Pediatric Use

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

Geriatric Use

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

Renal Impairment

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

Hepatic Impairment

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

2.3 CONTRAINDICATIONS

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

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

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

Infusion-Related Reactions (IRRs) and Injection Reactions (IRs)

IRRs are associated with the administration of Ocrevus IV and IRs are associated with the administration of Ocrevus SC, IRRs and IRs may be related to cytokine release and/or other chemical mediators. Physicians should alert patients that IRRs and IRs can occur during or within 24 hours of administration.

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

For premedication to reduce the frequency and severity of IRRs and risk of IRs see section *2.2 Dosage and Administration.*

Infusion-Related Reactions with Ocrevus IV

Symptoms of IRRs may occur during any infusion, but have been more frequently reported during the first infusion. (see section *2.6 Undesirable Effects*). These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia, and anaphylaxis (see section *2.6 Undesirable Effects*). Patients treated with Ocrevus IV should be observed for at least one hour after the completion of the infusion for any symptom of IRR.

For premedication to reduce the frequency and severity of IRRs see section 2.2 Dosage and Administration.

Managing infusion-related reactions with Ocrevus IV:

For patients experiencing life-threatening, severe or mild to moderate IRR symptoms see section 2.2 Dosage and Administration, Infusion Adjustments during Treatment.

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

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

Injection Reactions (IRs) with Ocrevus SC

Symptoms of IRs may occur during or within 24 hours of an injection. 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 2.6 Undesirable Effects*). Patients treated with the initial dose of Ocrevus SC should be observed for at least one hour after the completion of injection for any symptom of severe IR. For subsequent doses, the suitable administration setting (e.g., clinic or home) and post-injection monitoring is at the treating physician's discretion. If IRs occur, symptomatic treatment is recommended.

Immediately stop Ocrevus SC if there are signs of a life-threatening IR. The patient should receive supportive treatment. Permanently discontinue Ocrevus 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 the symptoms have resolved.

Hypersensitivity Reactions

Hypersensitivity may be clinically indistinguishable from IRRs or IRs in terms of 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. If a hypersensitivity reaction is suspected, the administration and treatment must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to ocrelizumab or any excipients must not be treated (see section *2.3 Contraindications*).

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

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

Since a risk of PML cannot be ruled out, physicians should be vigilant for early signs and symptoms of PML, which can include any new onset, or worsening of neurological signs or symptoms as these can be similar to an MS relapse.

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

If PML is confirmed, discontinue treatment permanently.

Hepatitis B reactivation
Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has been reported in patients treated with anti-CD20 antibodies.

HBV screening should be performed in all patients before initiation of treatment with Ocrevus as per local guidelines. Patients with active Hepatitis B virus (HBV), (i.e. an active infection confirmed by positive results for HBsAg and anti HB testing) should not be treated with Ocrevus. Patients with positive serology (i.e. negative for HBsAg and positive for HB core antibody [HBcAb+]; carriers of HBV [positive for surface antigen, HBsAg+]) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

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

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

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

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

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

Due to the potential of B-cell depletion in neonates and infants of mothers who have been administered Ocrevus during pregnancy, measuring CD19-postivie B-cell levels prior to vaccination with live or live-attenuated vaccines is recommended in such neonates and infants. If B-cell levels are below the lower limit of normal (LLN), it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cell levels have recovered.

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

Liver Injury
Clinically significant liver injury, without findings of viral hepatitis, has been observed rarely in the post-marketing setting in patients treated with Ocrevus. Signs of liver injury, including markedly elevated serum hepatic enzymes with elevated total bilirubin, have occurred from days to months after administration of the first dose.

Liver function tests should be performed before initiation of treatment with Ocrevus, and patients should be monitored for signs and symptoms of any hepatic injury during treatment. Serum aminotransferases, alkaline phosphatase, and bilirubin levels should be measured in patients who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, nausea, vomiting, right upper abdominal discomfort, dark urine, or jaundice.

If liver injury is confirmed, discontinue Ocrevus. If an alternative etiology is identified, treatment with Ocrevus can be resumed only when the event has been fully resolved.

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

Immune-Mediated Colitis
Immune-mediated colitis, which can present as a severe and acute-onset form of colitis, has been reported in patients receiving Ocrevus in the post-marketing setting. Some cases of colitis were serious, requiring hospitalisation, with a few patients requiring surgical intervention. The time from treatment initiation to onset of symptoms in these cases ranged from a few weeks to years. Monitor patients for immune-mediated colitis during Ocrevus treatment and evaluate promptly if signs and symptoms that may indicate immune-mediated colitis, such as persistent diarrhoea or other gastrointestinal signs and symptoms, occur.

2.4.2 Drug Abuse and Dependence
No studies on drug abuse and dependence have been conducted.

2.4.3 Ability to Drive and Use Machines
Ocrevus has no or negligible influence on the ability to drive and use machines.

2.5 USE IN SPECIAL POPULATIONS

2.5.1 Females and Males of Reproductive Potential
Fertility
(see section *3.3.3 Impairment of Fertility*).

Contraception
Women of childbearing potential should use contraception while receiving Ocrevus and for 4 months after the last infusion of Ocrevus (see section *3.2.4 Pharmacokinetic Properties, Elimination*).

2.5.2 Pregnancy
Over 1100 prospectively collected pregnancies with known outcomes have been collected from clinical trials, a prospective pregnancy registry, literature, and post-marketing experience. Of these, there were more than 500 prospectively collected pregnancies with in-utero exposure (defined as Ocrevus administered within the last 3 months prior to the last menstrual period (LMP) and/or during pregnancy). These data include more than 300 pregnancies with Ocrevus administered within the last 3 months prior to the LMP (median [interquartile range (IQR)]: 41.0 [24.5 – 67.0] days before the LMP) and more than 150 pregnancies with Ocrevus administered during the first trimester (median [IQR]: 22.0 [13.0 – 30.0] days after the LMP). These data indicate no malformative or feto-neonatal toxicity.

A prospective, multicentre, open-label clinical study (MINORE, Study MN42988) was conducted in 35 women with singleton pregnancies whose last dose of Ocrevus was administered any time between 6 months before the LMP (3-6 months before LMP: n=18; 0-3 months before LMP: n=14) or during the first trimester (n=3). Ocrelizumab was undetectable in 94.3% (33/35) of umbilical cord blood samples at birth and in serum of 97.0% (32/33) infants at week 6 of life, indicating minimal placental transfer of ocrelizumab to infants *in utero*. Where detected (n=2), ocrelizumab was close to the lower limit of quantification. No B-cell depletion was observed in infants at week 6 of life; all infants' B-cell levels (34/34) were above the age-specific LLN. The observed adverse events in women were expected with ocrelizumab treatment (see section *2.6 Undesirable Effects*) and/or commonly occurring in the studied populations (pregnant/postpartum women and neonates/infants).

Of the 34 infants whose B-cell levels were measured, 2 infants were from mothers who were administered Ocrevus during the first trimester. B-cell levels in neonates and infants following administration of Ocrevus to the mother during the second and third trimester have not been studied in clinical trials. The duration of a potential B-cell depletion in neonates and infants potentially exposed in utero during the second and third trimester is unknown.

Due to the potential of B-cell depletion in neonates and infants of mothers who have been administered Ocrevus during pregnancy, measuring CD19-positive B-cell levels prior to vaccination with live or live-attenuated vaccines is recommended in such neonates and infants. If B-cell levels are below the LLN, it is recommended that vaccination with live or live-attenuated vaccines should be delayed until B-cell levels have recovered (see section *2.4 Warnings and Precautions, 2.4.1 General, Vaccinations*).

Ocrevus is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier. Since placental transfer of human endogenous IgG is known to be significant after the first trimester and data with second or third trimester administration is limited, Ocrevus should be avoided during the second and third trimester of pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. Ocrevus should be used during the first trimester of pregnancy only if clinically needed.

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

2.5.3 Lactation
Human IgGs are known to be excreted in breast milk during the first few days after birth (colostrum period), which decrease to low concentrations soon afterwards.

In a prospective, multicenter, open-label study (SOPRANINO, Study MN42989), 13 lactating women (delivering 13 healthy, full-term infants) were administered Ocrevus 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 %], calculated as the average oral daily infant dosage divided by the maternal dosage over 60 days multiplied by 100), indicating minimal transfer of ocrelizumab to breastmilk. At 30 days after the mother's first post-partum Ocrevus infusion, ocrelizumab was undetectable in all available serum samples of breastfed infants (n=9), and infant B-cell levels were within the normal range in all available blood samples (n=10). No effects of ocrelizumab on health, growth and development were observed in breastfed infants of treated mothers over a follow-up period of 44.6 weeks (range 8.6-62.7 weeks).

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 also observed in 29 lactating women who were administered ocrelizumab at a median of 4.3 months (range 0.1-36 months) postpartum in a separate prospective clinical study.. 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.

The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Ocrevus and any potential adverse effects on the breastfed infant from Ocrevus.

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

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

2.5.6 Renal Impairment
The safety and efficacy of Ocrevus in patients with renal impairment has not been formally studied. Patients with mild renal impairment were included in clinical trials. Ocrevus is a monoclonal antibody and cleared via catabolism (rather than renal excretion), and a change in dose is not expected to be required for patients with renal impairment (see section *3.2.5 Pharmacokinetics in Special Populations, Renal Impairment*).

2.5.7 Hepatic Impairment
The safety and efficacy of Ocrevus in patients with hepatic impairment has not been formally studied. Patients with mild hepatic impairment were included in clinical trials. Ocrevus is a monoclonal antibody and cleared via catabolism (rather than hepatic metabolism), and a change in dose is not expected to be required for patients with hepatic impairment (see section *3.2.5 Pharmacokinetics in Special Populations, Hepatic Impairment*).

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials
The safety profile of ocrelizumab is based on data in patients with RMS and PPMS who were administered ocrelizumab intravenously or subcutaneously.

The safety of Ocrevus has been evaluated in 1311 patients from pivotal MS clinical studies with Ocrevus IV, which includes 825 patients in active-controlled (RMS) clinical trials and 486 patients in a placebo-controlled (PPMS) study. Table 2 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Ocrevus IV in the controlled period of the pivotal clinical trials. The most frequently reported ADRs were IRRs and respiratory tract infections.

A total of 2,376 patients were included in the controlled period of the pivotal clinical trials; of these patients, 1,852 entered the Open-Label Extension (OLE) phase. All patients switched to Ocrevus IV 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.

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

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

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

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

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

[1] Interferon beta-1a 44 mcg s.c. or Placebo
[2] PPMS patients were randomized 2:1 (Ocrevus:placebo).
[3] Symptoms reported as IRRs within 24 hours of infusion are described below in "Infusion-related reactions"

Ocrevus SC
The safety of Ocrevus SC has been evaluated in 312 patients from MS clinical studies with Ocrevus SC, which includes patients from the pivotal study OCARINA II and patients from OCARINA I. Of those 312 patients, 181 patients from OCARINA II and 118 patients from OCARINA I were given at least one dose of Ocrevus SC 920 mg.

The safety observed for Ocrevus SC was consistent with the known safety profile of Ocrevus IV presented in Table 2, except for the very common ADR of IRs, which are observed with the SC route of administration.

Description of selected adverse drug reactions from clinical trials
Infusion-related reactions (IRRs with Ocrevus IV)
Across the RMS and PPMS trials, symptoms associated with IRRs included, but are not limited to: pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal edema, nausea, tachycardia. In the controlled clinical trials there were no fatal IRRs.

In active-controlled (RMS) clinical trials, IRRs were the most common adverse event in patients treated with Ocrevus 600 mg with an overall incidence of 34.3% compared with an incidence of 9.9% in the interferon beta-1a treatment group (placebo infusion). The incidence of IRRs was highest during Dose 1, infusion 1 (27.5%) and decreased over time to <10% at Dose 4. The majority of IRRs in both treatment groups were mild to moderate.

In the placebo-controlled (PPMS) clinical trial, the incidence of IRRs was highest during Dose 1, infusion 1 (27.4%) and decreased with subsequent Doses to <10% at Dose 4. A greater proportion of patients in each group experienced IRRs with the first infusion of each dose compared with the second infusion of that dose. The majority of IRRs were mild to moderate.
Over the controlled period and OLE phase of RMS and PPMS clinical trials, patients were given approximately 20 doses of Ocrevus IV 600 mg. 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, the incidence of IRR remained low. The majority of IRRs were mild during the OLE phase (see section 2.4 Warnings and Precautions, 2.4.1 General, Infusion-Related Reactions and Injection Reactions).

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

Injection Reactions (IRs) with Ocrevus SC
Based on the observed symptoms, IRs are categorized into systemic IRs and local IRs.

In OCARINA II (ocrelizumab naïve patients), the most common symptoms reported with systemic IRs and local IRs included: headache, nausea, injection site erythema, injection site pain, injection site swelling, and injection site pruritus. 118 patients received the first injection. IRs occurred in 48.3% of these patients after the first injection. Of the 118 patients, 11.0% and 45.8% 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 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 injections of Ocrevus SC 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, of which 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.

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

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

Over the OLE phase in RMS and PPMS patients, the rate of SIs did not increase from that observed during the controlled period. Throughout the controlled period and OLE phase, 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 autoimmune conditions other than MS, 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 Ocrevus IV pivotal MS clinical studies. Risk factors for SIs in RMS patients include having at least 1 comorbidity, recent clinical relapse, and 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 <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 the Ocrevus treated patients compared to interferon and placebo. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections (including nasopharyngitis) and bronchitis (see Table 2).

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

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

SIs from Clinical Trials in Autoimmune Conditions Other than MS
Ocrevus in combination with concomitant immunosuppressive medications (e.g. chronic steroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) has been studied in other autoimmune conditions.

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

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

Laboratory Abnormalities
Immunoglobulins
Treatment with Ocrevus resulted in a decrease in total immunoglobulins over the controlled period of the Ocrevus IV studies, mainly driven by reduction in IgM.

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

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

The pooled data of the Ocrevus IV pivotal clinical studies (RMS and PPMS) and their open-label extensions (approximately 10 years of exposure) have shown an apparent association between decreased levels of immunoglobulins and increased rate of SIs, and was most apparent for IgG (2.1% of RMS patients had a SI during a period with IgG < LLN and 2.3% of PPMS patients had a SI during a period with IgG < LLN). The difference in the 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 Ocrevus IV 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.

Neutrophils
In the active-controlled (RMS) treatment period, decreased neutrophils were observed in 14.7% of Ocrevus IV patients as compared to 40.9% of patients treated with interferon beta-1a. In the placebo-controlled (PPMS) clinical trial, the proportion of Ocrevus patients presenting decreased neutrophils was slightly higher (12.9%) than placebo patients (10.0%).
The majority of the decreased neutrophils were transient (only observed once for a given patient treated with Ocrevus IV) and were Grade 1 and 2 in severity. Overall, approximately 1% of the patients in the Ocrevus group had Grade 3 or 4 neutropenia and was not temporally associated with an infection.

2.6.2 Post-marketing Experience
The following adverse events have been identified from post-marketing with Ocrevus (Table 3). Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: 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); unknown (cannot be estimated from the available data).

Table 3 Adverse Drug Reactions from Post-marketing Experience

ADR (preferred term, MedDRA)	Frequency category
Hepatobiliary disorders	
Liver injury[1]	Rare
Gastrointestinal disorders	
Immune-mediated colitis[2]	Unknown

[1]See section 2.4.1 Warnings and Precautions, General. This adverse reaction was identified through post-marketing surveillance. The frequency category was derived from a statistical calculation based on post-marketing and clinical trial data. Based on the approach taken, only the frequency category is provided.
[2] Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency and/or establish a causal relationship to Ocrevus exposure.

2.7 OVERDOSE
There is limited clinical trial experience with doses higher than the approved dose of Ocrevus. The highest dose tested to date in MS patients is 2000 mg, administered as two 1000 mg IV infusions separated by 2 weeks (Phase II dose finding study in RRMS) and 1200 mg, administered as a SC injection (Phase Ib dose finding study). The adverse drug reactions were consistent with the safety profile for Ocrevus in the pivotal clinical studies.

There is no specific antidote in the event of an overdose; interrupt the infusion or injection immediately and observe the patient for infusion-related reactions or injection reactions (see section *2.4 Warnings and Precautions, 2.4.1 General, Infusion-Related Reactions and Injection Reactions*).

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No formal drug interaction studies have been performed, as no drug interactions are expected via the CYP and other metabolizing enzymes or transporters.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 PHARMACODYNAMIC PROPERTIES
3.1.1 Mechanism of Action
Ocrelizumab is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-cells.

CD20 is a cell surface antigen found on pre-B-cells, mature and memory B-cells but not expressed on lymphoid stem cells and plasma cells.

The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in MS are not fully elucidated but is presumed to involve immunomodulation through the reduction in the number and function of CD20-expressing B-cells. Following cell surface binding, ocrelizumab selectively depletes CD20-expressing B-cells through antibody-dependent cellular phagocytosis (ADCP), antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. The capacity of B-cell reconstitution and pre-existing humoral immunity are preserved. In addition, innate immunity and total T-cell numbers are not affected.

Pharmacodynamic effects
Treatment with Ocrevus leads to rapid depletion of CD19+ B-cells in blood by 14 days post treatment (first time-point of assessment) as an expected pharmacologic effect. This was sustained throughout the treatment period with Ocrevus IV. For the B-cell counts, CD19 is used as the presence of Ocrevus interferes with the recognition of CD20 by the assay (see section *3.1.1 Mechanism of Action*).

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

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

3.1.2 Clinical / Efficacy Studies
Ocrevus IV

Relapsing forms of MS
Efficacy and safety of Ocrevus were evaluated in two randomized, double-blind, double-dummy, active comparator-controlled clinical trials with identical design, in patients with relapsing forms of MS (in accordance with McDonald criteria 2010). Study design and baseline characteristics of the study population are summarized in Table 4.

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

Key clinical and MRI efficacy results are presented in Table 5 and Figure 1.

Table 4 Study Design and Demographic Characteristics

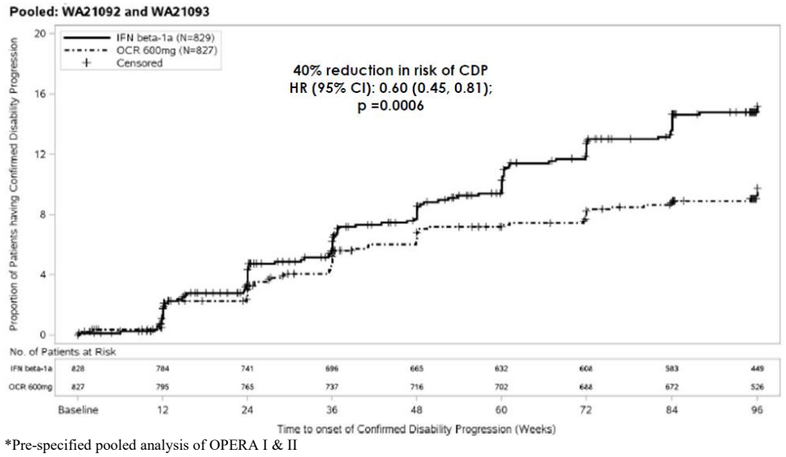
	Study 1	Study 2
Study name	**WA21092 (OPERA I) (n=821)**	**WA21093 (OPERA II) (n=835)**
Study design		
Study population	Patients with relapsing forms of MS	
Disease history at screening	At least two relapses within the prior two years or one relapse within the prior year; EDSS between 0 and 5.5, inclusive	
Study duration	2 years (96 weeks)	
Treatment groups	Group A: Ocrevus 600 mg Group B: interferon beta-1A (Rebif®), 44 mcg s.c. (IFN)	
Baseline characteristics	Ocrevus 600mg (n=410) / IFN 44 mcg (n=411)	Ocrevus 600mg (n=417) / IFN 44 mcg (n=418)
Mean age (years)	37.1 / 36.9	37.2 / 37.4
Gender distribution (% male/% female)	34.1/65.9 / 33.8/66.2	35.0/65.0 / 33.0/67.0
Mean/Median duration since onset of MS symptoms (years)	6.74/4.88 / 6.25/4.62	6.72/5.16 / 6.68/5.07
Mean/Median disease duration since diagnosis (years)	3.82/1.53 / 3.71/1.57	4.15/2.10 / 4.13/1.84
Mean number of relapses in the last year	1.31 / 1.33	1.32 / 1.34
Mean Gd-enhancing T1 lesion count	1.69 / 1.87	1.82 / 1.95
Mean T2 lesion count	51.04 / 51.06	49.26 / 51.01
Mean EDSS	2.82 / 2.71	2.73 / 2.79

Table 5 Key Clinical and MRI Endpoints from Studies WA21092 and WA21093

Endpoints	Study 1: WA21092 (OPERA I)		Study 2: WA21093 (OPERA II)	
	Ocrevus 600mg (n=410)	IFN 44 mcg (n=411)	Ocrevus 600mg (n=417)	IFN 44 mcg (n=418)
Clinical Endpoints				
Annualized Relapse Rate (primary endpoint)	0.156	0.292	0.155	0.290
Relative Reduction	46% (p<0.0001)		47% (p<0.0001)	
Proportion of patients with 12-week Confirmed Disability Progression[3]	9.8% Ocrevus vs 15.2% IFN			
Risk Reduction (Pooled Analysis[1])	40% (p=0.0006)			
Risk Reduction (Individual Studies[2])	43% (p=0.0139)		37% (p=0.0169)	
Proportion of patients with 24-week Confirmed Disability Progression[3]	7.6% Ocrevus vs 12.0% IFN			
Risk Reduction (Pooled Analysis[1])	40% (p=0.0025)			
Risk Reduction (Individual Studies[2])	43% (p=0.0278)		37% (p=0.0370)	
Proportion of patients with at least 12-weeks Confirmed Disability Improvement[4] (Pooled)	20.7% Ocrevus vs 15.6% IFN			
Relative Increase (Pooled Analysis[1])	33% (p=0.0194)			
Relative Increase (Individual Studies[2])	61% (p=0.0106)		14% (p=0.4019)	
Mean change from baseline in Multiple Sclerosis Functional Composite (MSFC)	0.213	0.174	0.276	0.169
Difference	0.039 (p= 0.3261)		0.107 (p=0.0040)	
Proportion of patients with No Evidence of Disease Activity (NEDA)[5]	48%	29%	48%	25%
Relative Increase[2]	64% (p<0.0001)		89% (p<0.0001)	
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI scan	0.016	0.286	0.021	0.416
Relative reduction	94% (p<0.0001)		95% (p<0.0001)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI scan	0.323	1.413	0.325	1.904
Relative reduction	77% (p<0.0001)		83% (p<0.0001)	
Mean number of new T1-hypo-intense lesions (chronic black holes) per MRI scan	0.420	0.982	0.449	1.255
Relative reduction	57% (p<0.0001)		64% (p<0.0001)	
Percentage change in brain volume from Week 24 to week 96	-0.572	-0.741	-0.638	-0.750
Relative reduction in brain volume loss	22.8% (p=0.0042)[6]		14.9% (p=0.0900)	
Quality of Life				
Mean change from baseline in SF-36 Physical Component Summary	0.036	-0.657	0.326	-0.833
Difference	0.693 (p=0.2193)		1.159 (p=0.0404)[6]	

[1] Data prospectively pooled from Study 1 & 2
[2] Non-confirmatory p-value; analysis not part of the pre-specified testing hierarchy
[3] Defined as an increase of ≥ 1.0 point from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or ≥ 0.5 when the baseline score is > 5.5, Kaplan-Meier estimates at Week 96
[4] Defined as decrease of ≥ 1.0 point from the baseline EDSS score for patients with baseline EDSS score ≥ 2 and ≤ 5.5, or ≥ 0.5 when the baseline score is > 5.5. Patients with baseline score < 2 were not included in analysis.
[5] NEDA defined as absence of protocol defined relapses, Confirmed Disability Progression (CDP), and any MRI activity (either Gd-enhancing T1 lesions, or new or enlarging T2 lesions) during the whole 96-week treatment. Exploratory result based on complete ITT population.
[6] Non-confirmatory p-value; hierarchical testing procedure terminated before reaching endpoint

Figure 1 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring during the Double-blind Treatment Period (Pooled ITT Population)*



*Pre-specified pooled analysis of OPERA I & II

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

Shorter Infusion Substudy

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

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

Primary Progressive MS

Efficacy and safety of Ocrevus were also evaluated in a randomized, double-blind, placebo-controlled clinical trial in patients with primary progressive MS (Study WA25046). Study design and baseline characteristics of the study population are presented in Table 6.

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

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

Table 6 Study design and baseline characteristics for Study WA25046

Study Name	Study WA25046 ORATORIO (n=732)	
Study design		
Study population	Patients with primary progressive form of MS	
Study duration	Event-driven *(Minimum 120 weeks and 253 confirmed disability progression events)* *Median follow-up time: Ocrevus 3.0 years, Placebo 2.8 years*	
Disease history at screening	Age 18-55 years, EDSS of 3.0 to 6.5	
Treatment groups	Group A: Ocrevus 600 mg Group B: Placebo, in 2:1 randomization	
Baseline characteristics	Ocrevus 600 mg (n=488)	Placebo (n=244)
Mean Age (years)	44.7	44.4
Gender distribution (% male/% female)	51.4/48.6	49.2/50.8
Mean/Median duration since onset of MS symptoms (years)	6.7/6.0	6.1/5.5
Mean/Median disease duration since PPMS diagnosis (years)	2.9/1.6	2.8/1.3
Mean EDSS	4.7	4.7
Number of Gd-enhancing T1 lesions (%) 0 1 ≥2	 72.5 12.8 14.7	 75.3 11.9 12.8

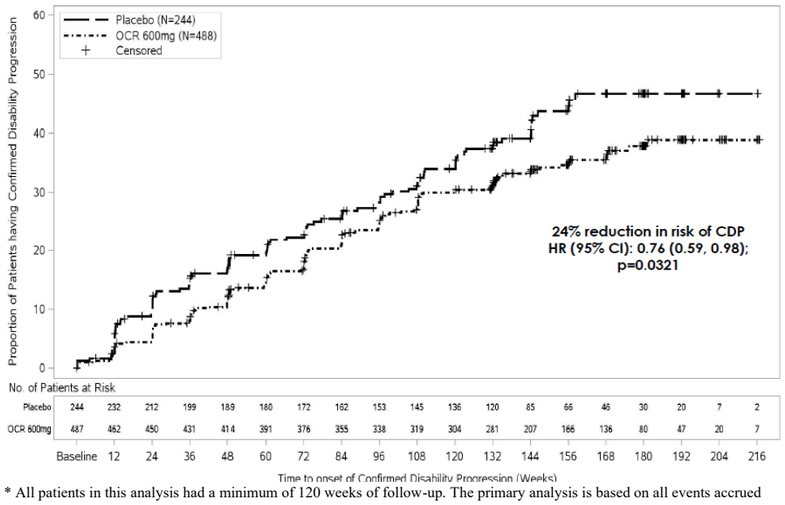
Key clinical and MRI efficacy results are presented in Table 7 and Figure 2.

Table 7 Key Clinical and MRI Endpoints from Study WA25046 (PPMS)

Endpoints	Study 3 WA25046 (Oratorio) Ocrevus 600mg (n=488)	 Placebo (n-244)
Clinical Endpoints		
Primary efficacy endpoint Proportion of patients with 12 weeks - Confirmed Disability Progression[1] (primary endpoint)	30.2%	34.0%
Risk reduction	24% (p=0.0321)	
Proportion of patients with 24 weeks – Confirmed Disability Progression[1]	28.3%	32.7%
Risk reduction	25% (p=0.0365)	
Percentage change in Timed 25-Foot Walk from baseline to Week 120	38.9	55.1
Relative reduction in progression rate of walking time	29.4% (p=0.0404)	
MRI Endpoints		
Percentage change in T2 hyperintense lesion volume, from baseline to Week 120	-3.4	7.4
	(p< 0.0001)	
Percentage change in brain volume from Week 24 to- Week 120	-0.902	-1.093
Relative reduction in rate of brain volume loss	17.5% (p=0.0206)	
Quality of Life		
Mean change from baseline in SF-36 Physical Component Summary	-0.731	-1.108
Difference	0.377 (p= 0.6034)	

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

Figure 2 Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring during the Double-blind Treatment Period (ITT Population)*



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

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

Peripartum disease activity

Peripartum disease activity was evaluated in 99 women receiving Ocrevus across 13 interventional clinical trials, who experienced at least one pregnancy resulting in live birth. The median time of the last Ocrevus administration was 4.3 [IQR: 2.3-5.5] months prior to the LMP. A total of 15 women received Ocrevus during pregnancy at 3.9 [3.0-4.1] gestational weeks and 28 women resumed Ocrevus postpartum at 3.8 [1.9-7.0] months. The annualized relapse rate remained low in the pre-pregnancy year (0.07 [95% confidence interval (CI): 0.02, 0.14]), during pregnancy (0.03 [95% CI: 0.00-0.10]) and up to 1 year postpartum (0.04 [95% CI: 0.01, 0.16]).

These results are consistent with an analysis of 73 term/preterm pregnancies in 69 women receiving Ocrevus from an international MS registry. The median time of last Ocrevus administration was 1.9 [IQR: 0-4.8] months prior to conception. The annualized relapse rate remained low in the pre-pregnancy year (0.15 [95% CI: 0.07, 0.29]), during pregnancy (0 [95% CI: 0, 0.07]) and up to 6 months postpartum (0.09 [95% CI: 0.02, 0.27]).

Ocrevus SC

OCARINA II

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

A total of 236 patients with RMS or PPMS (213 patients with RMS, 23 patients with PPMS), were randomized in a 1:1 ratio to the SC arm or IV arm. During the controlled period (Day 0 to Week 24), patients received either a single 920 mg SC injection at Study Day 1 or two 300 mg IV infusions at Study Day 1 and 14. After the controlled period, all patients had the opportunity to receive further injections of 920 mg SC at Weeks 24 and 48 (Dose 2 and 3). 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 SC arm and 40.0 years in the IV arm. 34.7% of patients were male in the SC arm and 40.7% patients were male in the IV arm. The mean/median duration since MS diagnosis was 5.70/3.10 years in the SC arm and 4.78/2.35 years in the IV arm.

Non-inferiority of the ocrelizumab exposure after administration of 920 mg Ocrevus SC compared to 600 mg Ocrevus IV was demonstrated based on the PK primary endpoint, AUC up to week 12 (AUC_{W1-12}) post-injection (see *3.2 Pharmacokinetic Properties*). The observed PK non-inferiority is expected to result in a comparable benefit-risk profile.

OCARINA I

Study CN41144 (OCARINA I) was a multi-center, randomized, open-label, parallel arm trial conducted to evaluate the pharmacokinetics, safety, tolerability, and immunogenicity of Ocrevus SC compared with Ocrevus IV in patients with RMS or PPMS. A key aim of the study was to determine the bioavailability of Ocrevus SC to select the SC dose for the subsequent Phase 3 Study, CN42097 (OCARINA II). This was done by comparing the pharmacokinetic profile between Ocrevus SC and Ocrevus IV based on the area under the concentration time curve (AUC). The study provides supportive safety, tolerability, and immunogenicity data with repeated SC dosing (see *section 2.6 Undesirable Effects* and *section 3.1.3 Immunogenicity*).

3.1.3 Immunogenicity

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

Ocrevus IV

Patients in MS trials (WA21092, WA21093 and WA25046) were tested at multiple time points (baseline and every 6 months post treatment for the duration of the trial) for antidrug antibodies (ADAs). Out of 1311 patients treated with ocrelizumab, 12 (~1%) tested positive for treatment-emergent ADAs, of which 2 patients tested positive for neutralizing antibodies. The impact of treatment-emergent ADAs on safety and efficacy cannot be assessed given the low incidence of ADA associated with Ocrevus.

Ocrevus SC

Across OCARINA II and OCARINA I, no patients had treatment emergent ADAs to ocrelizumab.

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

3.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics of Ocrevus in the MS studies were described by a two compartment model with time-dependent clearance, and with PK parameters typical for an IgG1 monoclonal antibody. Clearance and central volume were estimated at 0.17 L/day and 2.78 L, peripheral volume and inter-compartment clearance at 2.68 L and 0.294 L/day, and initial time-dependent clearance at 0.0489 L/day which declined with a half-life of 33 weeks.

Ocrevus IV

The overall exposure (AUC over the 24 week dosing intervals) was identical in the 2 x 300 mg in PPMS and 1 x 600 mg in RMS studies, as expected given an identical dose was administered. Area under curve (AUC_τ) after the 4th dose of 600 mg Ocrevus was 3510 µg/mL•day, and mean maximum concentration (C_{max}) was 212 µg/mL in RMS (600 mg infusion) and 141 µg/mL in PPMS (300 mg infusions). Terminal half-life was 26 days.

Ocrevus SC

After administration of 920 mg Ocrevus SC, the estimated 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 Ocrevus SC was shown to be non-inferior to Ocrevus IV. The geometric mean ratio (GMR) for AUC_{w1-12} was 1.29 (90% CI: 1.23–1.35).

3.2.1 Absorption

Ocrevus IV is administered as an IV infusion..

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

3.2.2 Distribution

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

3.2.3 Metabolism

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

3.2.4 Elimination

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

3.2.5 Pharmacokinetics in Special Populations

Pediatric Population

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

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

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

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

3.3 NONCLINICAL SAFETY

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

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

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

No effects on reproductive organs were observed in male monkeys administered ocrelizumab by intravenous injection (three loading doses of 15 or 75 mg/kg, followed by weekly doses of 20 or 100 mg/kg) for 8 weeks. There were also no effects on estrus cycle in female monkeys administered ocrelizumab over three menstrual cycles using the same dosing regimen. The doses tested in monkeys are 2 and 10 times the recommended human dose of 600 mg intravenous ocrelizumab, on a mg/kg basis.

Hyaluronidases are found in most tissues of the body. When subcutaneous recombinant human hyaluronidase was administered to cynomolgus monkeys for 39 weeks at dose levels up to 220,000 U/kg, which is > 668 times higher than the human dose, no evidence of toxicity to the male or female reproductive system was found through periodic monitoring of in-life parameters, e.g., semen analyses, hormone levels, menstrual cycles, and also from gross pathology, histopathology and organ weight data.

3.3.4 Reproductive Toxicity
It is not known whether Ocrevus affects reproductive capacity (see section 2.5.2). In an embryo-fetal developmental study in cynomolgus monkeys, there was no evidence of maternal toxicity, teratogenicity, or embryotoxicity following Ocrevus administration at 75/100 mg/kg (loading dose/study dose).

In a pre- and post-natal development study in cynomolgus monkeys, administration of Ocrevus (15/20 and 75/100 mg/kg loading/study doses, which correspond to human equivalent doses of approximately 3000 mg (approximately 5 x clinical dose) and 15000 mg (approximately 25 x clinical dose), respectively) was associated with glomerulopathy (7/24 animals), lymphoid follicle formation in bone marrow (9/24 animals), and lymphoplasmacytic inflammation in the kidney (2/24 animals). Testicular weights of the neonates were significantly reduced in the 75/100 mg/kg group compared with controls. There were two cases of moribundity on study (2/24), one attributed to weakness due to premature birth accompanied by opportunistic infection and the other to an infective meningoencephalitis involving the cerebellum of the offspring from a maternal dam with an active infection (mastitis). The course of both neonatal infections could have potentially been impacted by B-cell depletion. Newborn offspring of maternal animals exposed to Ocrevus were noted to have depleted B-cell populations during the post-natal phase. Measurable levels of Ocrevus were detected in milk (approximated 0.2% of steady state trough serum levels) during the lactation period (see section *2.5.3 Lactation*).

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

SC administration of ocrelizumab with hyaluronidase was well tolerated in rats and minipigs in local tolerance studies.

No carcinogenicity or genotoxicity studies were conducted for recombinant human hyaluronidase. Reproductive toxicology studies with rHuPH20 revealed embryofetal losses in mice, with no effect level > 1,100-fold higher than the suggested clinical dose and there was no evidence of teratogenicity.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Ocrevus IV

Vials
Store vials at 2-8°C.

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

Do not freeze. Do not shake.

Shelf life
As registered locally.

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

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

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

Ocrevus SC

Vials
Store vials at 2-8°C.

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

Do not freeze. Do not shake.

If necessary, the unopened vial can be left at temperatures ≤ 25°C (77°F) 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 (77°F).

Shelf life
As registered locally.

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

Storage of the syringe
- From a microbiological point of view, the product should be used immediately once transferred from the vial to the syringe since the medicine does not contain any antimicrobial-preservative. 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°C to 8°C.
- If preparation has taken place under controlled and validated aseptic conditions, the closed syringe can be stored for up to 72 hours in the refrigerator at 2°C to 8°C (36°F to 46°F) followed by 8 hours in diffuse daylight at temperatures ≤ 25°C (77°F).

4.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Ocrevus IV

Ocrevus IV should be prepared by a healthcare professional using aseptic technique. A sterile needle and syringe should be used to prepare the diluted infusion solution.

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

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

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

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

Prior to the start of the IV infusion, the content of the infusion bag should be at room temperature.

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

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

Ocrevus SC

Ocrevus SC should be prepared by a healthcare professional using aseptic technique.

Ocrevus SC is a single-dose, ready-to-use solution for subcutaneous injection only and should not be diluted or mixed with other drugs.

Ocrevus SC solution should be visually inspected to ensure that no particulate matter or discoloration is present. Do not use the solution if discolored or if the solution contains discrete foreign particulate matter.

Preparation of the Syringe
Prior to use, remove the vial from the refrigerated storage and allow the solution to come to room temperature.

Withdraw the entire contents of Ocrevus SC solution from the vial with a syringe and transfer needle (21G recommended).

Remove the transfer needle and attach a SC infusion set (e.g., winged / butterfly) containing a 24-26G needle for injection. Use a SC infusion set with residual hold-up volume NOT exceeding 0.8 mL for administration.

Prime the SC infusion line with the drug product solution to eliminate the air in the infusion line and stop before the fluid reaches the needle.

Ensure the syringe contains exactly 23 mL of drug product solution after priming and expelling any excess volume from the syringe.

Administer immediately to avoid needle clogging.

Immediate use is recommended as Ocrevus SC does not contain any antimicrobial preservative. If the dose is not administered immediately, refer to “Storage of the syringe” below. DO NOT store the prepared syringe that has been attached to the already-primed SC infusion set.

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

Incompatibilities

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

Ocrevus IV and SC

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

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

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

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

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

Medicine: keep out of reach of children

Current at February 2026

Roche F. Hoffmann-La Roche Ltd, Basel, Switzerland