AUSTRALIAN PRODUCT INFORMATION
Ocrevus® (ocrelizumab)

1. NAME OF THE MEDICINE

Ocrevus (ocrelizumab)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ocrevus (ocrelizumab) is a recombinant humanised anti-CD20 monoclonal antibody (IgG1 subtype).

Ocrevus intravenous (IV) formulation: concentrate for solution for infusion
Ocrevus concentrate solution for intravenous (IV) infusion is a clear or slightly opalescent, and colourless to pale brown solution at pH 5.3, supplied as a single-use vial containing 30 mg/mL ocrelizumab. Each vial contains 300 mg of ocrelizumab in a 10 mL vial.

Ocrevus subcutaneous (SC) formulation: solution for subcutaneous injection
Ocrevus solution for subcutaneous (SC) injection is a clear to slightly opalescent, and colourless to pale brown, preservative-free solution supplied as a single-use vial containing 40 mg/mL ocrelizumab. Each vial contains 920 mg ocrelizumab in 23 mL in a 50 mL vial.
Excipients with known effect: Ocrevus SC contains the excipient vorhyaluronidase alfa, an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously.

For the full list of excipients, see section 6.1 (List of Excipients).

3. PHARMACEUTICAL FORM

Ocrevus IV
Ocrevus is supplied in a single-dose vial containing 10 mL of preservative-free concentrate solution for infusion.

Ocrevus SC
Ocrevus is supplied in a single-dose vial containing 23 mL of preservative-free solution for injection.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ocrevus is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS) to delay the progression of physical disability and to reduce the frequency of relapse.

Ocrevus is indicated for the treatment of patients with primary progressive multiple sclerosis (PPMS) to delay the progression of physical disability.

4.2 DOSE AND METHOD OF ADMINISTRATION

Patients may start Ocrevus treatment using Ocrevus IV or SC. Patients currently receiving Ocrevus IV may switch to Ocrevus SC.

Ocrevus IV

Ocrevus IV is not intended for subcutaneous administration.

Dosage

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 6.3 Shelf-Life).

Observe the patient for at least one hour after the completion of the infusion (see section 4.4 Special Warnings and Precautions for Use). After the initial dose IRRs are not increased in severity or frequency when Ocrevus IV is given as a single 600 mg dose compared with 2 x 300 mg doses separated by 2 weeks (see section 4.8 Adverse Effects (Undesirable Effects)).

Premedication for Infusion Related Reactions (IRR)

Premedicate with 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes prior to each Ocrevus infusion (see section 4.4 Special Warnings and Precautions for Use) and with an antihistaminic drug approximately 30-60 minutes before each infusion of Ocrevus IV to further reduce the frequency and severity of IRRs.

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

Dosing

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

Initial Dose

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

Subsequent Doses

Subsequent doses of Ocrevus IV thereafter are administered as a single 600 mg IV infusion every 6 months (see Table 1). A minimum interval of 5 months should be maintained between each dose of Ocrevus IV.

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 section 4.8 Adverse effects (undesirable effects), Clinical Trials and Section 5.1 Pharmacodynamic properties, Clinical Trials).

Table 1 Dose and Schedule of Ocrevus IV

		Quantity of Ocrevus IV to be administered*	Infusion Instructions
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 hrs
	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	600 mg 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 hrs
		OR	
	Option 2 Infusion of approximately 2 hours duration	600mg in 500mL	• 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 250mL/hr for the next 30 minutes • Increase the infusion rate to 300mL/hr for the remaining 60 minutes • Each infusion should be given over approximately 2 hours

* 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

** The first single infusion should be administered 6 months after Infusion 1 of the Initial dose

Infusion Adjustments during Treatment

No dose reductions of Ocrevus IV are recommended.

In case of IRRs during any infusion, see the following adjustments below. Additional information on IRRs can be found under section 4.4 Special Warnings and Precautions for Use.

Life-threatening IRRs
Immediately stop Ocrevus IV if there are signs of a life-threatening or disabling IRR during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. The patient should receive appropriate supportive treatment. Permanently discontinue Ocrevus in these patients.

Severe IRRs
If a patient experiences a severe 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 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 4.4 Special Warnings and Precautions for Use for a full description of the symptoms associated with IRRs.

Ocrevus SC
Ocrevus SC is not intended for intravenous administration.

Dosage
Ocrevus SC must be administered as a subcutaneous injection only, under the supervision of an HCP. 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 over 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 the area 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.

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 4.4 Special Warnings and Precautions for Use) to reduce the risk of local and systemic injection reactions.

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

Dosing
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 SC.

Ocrevus IV and Ocrevus SC

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.

Special populations

Children: The safety and efficacy of Ocrevus in children and adolescents below 18 years of age have not been established.

Elderly: The safety and efficacy of Ocrevus in patients > 65 years of age have not been established.

Renal Impairment: The safety and efficacy of Ocrevus in patients with renal impairment have not been formally studied. A change in dose is not expected to be required for patients with renal impairment (see section 5.2 Pharmacokinetic Properties).

Hepatic Impairment: The safety and efficacy of Ocrevus in patients with hepatic impairment have not been formally studied. A change in dose is not expected to be required for patients with hepatic impairment (see section 5.2 Pharmacokinetic Properties).

Method of Administration

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.

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

Instructions for dilution
Ocrevus IV must be diluted before administration. Solutions of Ocrevus for IV administration are prepared by dilution 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 must be at room temperature to avoid an infusion reaction to the administration of the solution at low temperatures.

Ocrevus SC
Ocrevus SC should be prepared by a HCP 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 discolouration is present. Do not use the solution if discoloured 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.

Aseptically 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, aseptically 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 storage is necessary, the syringe must be closed with a syringe cap. The closed syringe can be held at 2°C - 8°C for up to 72 hours followed by 8 hours at ambient temperatures ≤ 25°C in diffuse daylight (see Section 6.4 Special Precautions for Storage).

- If the syringe was stored in a refrigerator, allow the syringe to reach room temperature prior to administration.

4.3 CONTRAINDICATIONS

Ocrevus is contraindicated in patients with

- A known hypersensitivity to ocrelizumab or any of the excipients listed in section 6.1 List of Excipients.
- Current active infection (see section 4.4 Special Warnings and Precautions for Use).
- Patients in a severely immunocompromised state (see section 4.4 Special Warnings and Precautions for Use).
- Known active malignancies (see section 4.4 Special Warnings and Precautions for Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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 4.2 Dosage and Administration.

Infusion Related Reactions (IRRs) with Ocrevus IV
Symptoms of IRRs may occur during any infusion, but have been more frequently reported during the first infusion (see Section 4.8 Adverse Effects (Undesirable Effects)). 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. Patients treated with Ocrevus 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 4.2 Dose and Method of Administration.

Managing IRRs with Ocrevus IV
For patients experiencing life-threatening, severe or mild to moderate IRR symptoms see section 4.2 Dose and Method of Administration.

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 in the controlled clinical trials.

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 4.8 Adverse Events (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
Symptoms of a hypersensitivity reaction may be clinically indistinguishable from IRRs or IRs. 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 Ocrevus or any excipients must not be treated (see section 4.3 Contraindications).

Infections
Serious, including life-threatening or fatal, bacterial, fungal, and new or reactivated viral infections have been observed during and following completion of treatment with anti-CD20 B-cell depleting therapies.

Delay Ocrevus administration in patients with an active infection until the infection is resolved (see section 4.3 Contraindications).

Progressive Multifocal Leukoencephalopathy (PML)
JC virus infection resulting in PML has been observed very rarely in patients treated with anti-CD20 antibodies, including Ocrevus, and is mostly associated with risk factors (patient population e.g.lymphopenia, advanced age polytherapy with immunosuppressants).

Since a risk of PML cannot be ruled out, physicians should be vigilant for any new or worsening neurological symptoms or signs suggestive of PML as these can be similar to an MS relapse. Physicians treating patients should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Physicians should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). If such symptoms occur, further administration of Ocrevus should be immediately suspended until a diagnosis of PML has been excluded. To establish or exclude a diagnosis of PML evaluation including MRI scan, CSF testing for JC viral DNA and repeat neurological assessments, should be considered. Once PML has been excluded, the administration of Ocrevus may resume.

If a diagnosis of PML is confirmed, Ocrevus must be permanently discontinued. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

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 institutional guidelines. Patients with active HBV (i.e. an active infection confirmed by positive results for Hepatitis B surface antigen (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+)) and carriers of HBV (positive for surface antigen (HBsAg+)) should consult liver disease experts before start of treatment and should be monitored and managed according to current clinical practice.

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

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.

Treatment with immunosuppressants before, during or after Ocrevus
Patients in a severely immunocompromised state must not be treated until the condition resolves (see section 4.3 Contraindications).

In other auto-immune conditions, use of Ocrevus concomitantly with immunosuppressive medications (e.g. chronic corticosteroids, non-biologic and biologic disease-modifying antirheumatic drugs [DMARDS], mycophenolate mofetil, cyclophosphamide, azathioprine) resulted in an increase of serious infections, including opportunistic infections. Infections included and were not limited to atypical pneumonia and pneumocystis jirovecii pneumonia, varicella pneumonia, tuberculosis, histoplasmosis. In rare cases, some of these infections were fatal. Risk factors for serious infections included higher doses of Ocrevus than recommended in MS, other comorbidities, chronic use of immunosuppressants/ corticosteroids, and patients from Asia.

Ocrevus should not be co-administered with other disease-modifying MS therapies. It is not recommended to use other immunosuppressives concomitantly with Ocrevus except corticosteroids for symptomatic treatment of relapses.

When initiating Ocrevus after an immunosuppressive therapy or initiating an immunosuppressive therapy after Ocrevus, the potential for overlapping pharmacodynamic effects should be taken into consideration (see section 5.1 Pharmacodynamic Properties). Exercise caution when prescribing Ocrevus taking into consideration the pharmacodynamics of other disease-modifying MS therapies.

Vaccinations
The safety of immunisation with live or live-attenuated vaccines following Ocrevus therapy has not been studied and vaccination with live or live-attenuated vaccines is not recommended during treatment and until B-cell repletion (see section 5.1 Pharmacodynamic Properties).

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

In a randomised 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.

Physicians should review the immunisation status of patients before starting treatment with Ocrevus. Patients should complete vaccinations at least 6 weeks prior to initiation of Ocrevus, although for seasonal influenza vaccines, it is still recommended to vaccinate patients on Ocrevus.

Exposure in utero to ocrelizumab and vaccination of neonates and infants with live or live-attenuated vaccines
Due to the potential depletion of B-cells in neonates and infants of mothers who have been exposed to Ocrevus during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines be delayed until B-cell levels have recovered. It is therefore recommended to measure the CD19-positive B-cell level in neonates and infants prior to vaccination and to discuss the safety and timing of vaccination with the infant's physician.

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

Malignancy
Immunomodulatory drugs may increase the risk of malignancy. In controlled trials, malignancies, including breast cancer, occurred more frequently in Ocrevus-treated patients although 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 Ocrevus (see section 4.3 Contraindications). 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 cancer screening guidelines.

Liver injury
Clinically significant liver injury, without findings of viral hepatitis, has been observed with unknown frequency in the post-marketing setting in patients treated with anti-CD20 B-cell depleting therapies approved for the treatment of MS, including Ocrevus (see section 4.8 Adverse Effects (Undesirable Effects)).

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 aetiology is identified, treatment with Ocrevus can be resumed only when the event has been fully resolved.

Use in renal impairment
The safety and efficacy of Ocrevus in patients with renal impairment have 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 5.2 Pharmacokinetic Properties).

Use in hepatic impairment
The safety and efficacy of Ocrevus in patients with hepatic impairment have 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 5.2 Pharmacokinetic Properties and section 4.4 Warnings and Precautions for Use, Liver Injury).

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

Use in the elderly
The safety and efficacy of Ocrevus in patients > 55 years of age have not been established.

Effects on Laboratory tests
See section 4.8 Adverse Effects (Undesirable Effects).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Preclinical data reveal no special hazards for humans based on studies of male and female fertility in cynomolgus monkeys. No impact on male or female fertility as assessed by fertility indices was detected in male and female cynomolgus monkeys in which Ocrevus was administered intravenously at weekly doses of up to 100 mg/kg. Exposure (based on serum area under curve (AUC)) in these studies was up to at least 150 times that expected in patients at the recommended clinical dose.

Use in pregnancy – Category C
Ocrevus should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. Ocrevus is a humanised monoclonal antibody and immunoglobulins are known to cross the placental barrier. Women of child bearing potential should use effective contraception while receiving Ocrevus and for 4 months after the last dose of Ocrevus (see section 5.2 Pharmacokinetic Properties).

There are no adequate and well-controlled data from studies in pregnant women, however transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy.

Postponing vaccination with live or live-attenuated vaccines is recommended for neonates and infants who have been exposed to Ocrevus in utero until B-cell levels have recovered. B-cell levels in neonates and infants following maternal exposure to Ocrevus have not been studied in clinical trials and the potential duration of B-cell depletion in neonates and infants is unknown (see section 4.4 Special Warnings and Precautions for use, Vaccinations).

It is not known whether Ocrevus affects human reproductive capacity. In an embryo-fetal developmental study in cynomolgus monkeys, there was no evidence of maternal toxicity, teratogenicity or embryotoxicity following weekly intravenous ocrelizumab administration at doses up to 100 mg/kg (at least 200 times the anticipated exposure, based on serum AUC, than in patients at the recommended clinical dose). IgG molecules are known to cross the placental barrier and ocrelizumab causes depletion of B-cells in the fetuses of treated cynomolgus monkeys.

In a pre- and post-natal development study in cynomolgus monkeys, weekly intravenous administration of ocrelizumab at 20 and 100 mg/kg (associated with respective exposures at least 40 and 175 times the clinical exposure, based on serum AUC) was associated with glomerulopathy (7/24 neonates), and lymphoplasmacytic inflammation in the kidney (2/24 neonates). Testicular weights of the neonates were significantly reduced in the 100 mg/kg group compared with controls, although relationship to treatment is uncertain. There were two cases of moribundity (2/24) at 100 mg/kg, 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 ocrelizumab were noted to have depleted B-cell populations during the post-natal phase.

Labour and Delivery
The safe use of Ocrevus during labour and delivery has not been established.

Use in 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 clinical study, low ocrelizumab concentrations in breastmilk (median relative infant dose of 0.1% [range 0.07-0.7%]) over 90 days after the mother's first postpartum infusion were observed in 29 lactating women who received ocrelizumab at a median of 4.3 months postpartum (range 0.1-36 months). Follow-up of 21 infants breastfed for at least 2 weeks showed normal growth and development up to 1 year. However, the potential for Ocrevus absorption leading to B-cell depletion is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ocrevus. If clinically needed, Ocrevus could be used during breastfeeding starting a few days after birth.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of Ocrevus on the ability to drive and to use machines have been performed. The pharmacological activity and adverse events reported to date do not indicate such an effect is likely.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

The safety of Ocrevus has been established 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 trial. Table 2 summarises 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 2376 patients received treatment in the controlled period of the pivotal clinical trials; of these patients, 1852 entered the Open-Label Extension (OLE) phase. All patients switched to Ocrevus 600 mg during the OLE phase. 1155 patients completed the OLE phase, resulting in approximately 10 years of continuous Ocrevus 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.

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

PPMS
The ADRs described in this section were identified based on data from a placebo-controlled study (WA25046) evaluating the efficacy and safety of Ocrevus in adults with 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 two weeks during the entire study).

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10,000 to < 1/1000) and very rare (< 1/10,000). Adverse reactions are presented in order of decreasing frequency.

Table 2 Summary of ADRs associated with Ocrevus IV (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 reactions[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 randomised 2:1 (Ocrevus:placebo)
[3] Symptoms reported as IRRs within 24 hours of infusion are described below under *Infusion Related Reactions*

In an additional placebo-controlled phase IIIb study in 1012 PPMS patients (Study WA40404) who received at least one dose of either Ocrevus (n=506) or placebo (n=506), COVID-19 and COVID-19 pneumonia were observed more frequently in patients treated with Ocrevus compared to the placebo group (see COVID-19 and COVID-19 Pneumonia below).

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

In the active-controlled RMS clinical trials, IRRs were the most common adverse event in patients treated with Ocrevus IV 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 pivotal 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.

Due to overall more infusions with the two x 300 mg regimen in the PPMS pivotal clinical trial, the total number of IRRs were higher. Therefore, after Dose 1 it is recommended to administer Ocrevus in a single 600 mg infusion in patients with RMS or PPMS (see Table 6) to reduce the total number of infusions (and concurrent exposure to prophylactic methylprednisolone) and IRRs (see section 4.4 Special Warnings and Precautions for Use).

Over the controlled period and OLE phase, patients were given a median of 18 and 16 doses of Ocrevus 600 mg in the RMS and PPMS clinical trials, respectively. The 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 4.4 Special Warnings and Precautions for Use).

Alternative Shorter Infusion of Subsequent Doses
In a study (MA30143 Shorter Infusion Substudy) designed to characterise 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 5.1 Pharmacodynamic properties, Clinical Trials).

Ocrevus SC
The safety of Ocrevus SC has been evaluated in 312 patients from MS clinical studies 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.

Injection Reactions (IRs) with Ocrevus SC
Based on the observed symptoms, IRs are categorised 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 at least one injection of Ocrevus SC 920 mg. 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 of 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 which is a higher dose tested than the recommended dose. 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 (SIs) associated with Ocrevus treatment. In RMS patients the rate of serious infections was lower than for interferon beta-1a, and in PPMS patients the rate was similar to placebo.

In the active-controlled RMS and pivotal placebo-controlled PPMS clinical trials with Ocrevus 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 in pivotal studies, the overall risk of SIs (non-COVID-19 terms) 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 pivotal MS clinical studies. 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/m^2, 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 the Ocrevus treated patients compared to interferon and placebo in pivotal studies. The infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections (including nasopharyngitis) and bronchitis (see Table 2).

COVID-19 and COVID-19 Pneumonia
In a placebo-controlled phase IIIb study in 1012 patients with PPMS (Study WA40404), COVID-19 was observed more frequently, with the frequency ‘very common’, in patients treated with Ocrevus compared to the placebo group (16.0% vs 11.3%). In patients treated with Ocrevus, COVID-19 was predominantly mild to moderate in severity (14.2%). COVID-19 pneumonia was observed more frequently, with the frequency ‘common’ in patients treated with Ocrevus compared to the placebo group (3.2% vs 1.8%), and was predominantly observed as a serious infection (2.6% vs 1.6%). Fatalities due to COVID-19 pneumonia were uncommon, occurring in 0.8% of Ocrevus treated patients and 0.2% of the placebo group, and were associated with known risk factors in both arms.

Herpes
In the 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 pivotal 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.

Serious Infections (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 and 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 SI 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 clinical trials, the proportion of patients at baseline reporting IgG, IgA and IgM < lower limit of normal (LLN) in the Ocrevus IV treatment arm was 0.5%, 1.5% and 0.1%, respectively. Following treatment, the proportion of Ocrevus-treated patients reporting IgG, IgA and IgM < LLN at 96 weeks was 1.5%, 2.4% and 16.5%, respectively.

In the placebo-controlled PPMS clinical trial, 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 IV-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 during the controlled period and OLE phase. Throughout the 10 years of continuous Ocrevus treatment, mean IgG levels of RMS and PPMS patients remained above LLN.

Neutrophils
In the active-controlled treatment period of the RMS clinical trials, 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%).

In the majority of cases 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. These were not temporally associated with an infection.

In clinical trials, the highest frequency of neutropenia was observed during the first year of treatment. Prolonged treatment with Ocrevus has not been associated with an increase in the incidence or severity of neutropenia. Clinical trial cases resolved with the standard of care without interrupting Ocrevus treatment.

Neutropenia has been reported in the post-marketing setting in patients treated with Ocrevus. 72.3% of cases were late onset, occurring more than 4 weeks after the latest dose of Ocrevus. The severity ranged from Grade 1 to 4, including cases of febrile neutropenia and rare cases of agranulocytosis; events resolved spontaneously, with the standard of care or with treatment interruption (see section 4.4 Special Warnings and Precautions for Use, Late neutropenia).

Post-marketing experience
The following adverse drug reactions have been identified from post-marketing experience with Ocrevus (Table 3) (see section 4.4 Special Warnings and Precautions for Use). 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.

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]	Unknown
Gastrointestinal disorders	
Immune-mediated colitis[2]	Unknown
Respiratory, thoracic, and mediastinal disorders	
Interstitial Lung Disease (ILD)	Unknown

[1] See section 4.4 Warnings and Precautions for Use, Liver Injury.

[2] See section 4.4 Warnings and Precautions for Use, Immune-mediated colitis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 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 two weeks (Phase II dose finding study in RRMS) and 1200 mg, administered as a SC injection (Phase Ib dose finding study). The ADRs were consistent with the safety profile for Ocrevus in the pivotal clinical studies. There was an overall greater incidence of AEs on 1200mg SC.

There is no specific antidote in the event of an overdose. Interrupt the infusion or injection immediately and observe the patient for IRRs or IRs (see section 4.4 Special Warnings and Precautions for Use).

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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.

Pharmacodynamic effect

The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in multiple sclerosis (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, it is hypothesised that ocrelizumab selectively depletes CD20-expressing B-cells through antibody-dependent cellular phagocytosis, antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis. It is presumed that the capacity of B-cell reconstitution and pre-existing humoural immunity are preserved since the cell surface antigen CD20 is expressed on pre-B cells and mature and memory B cells, but not on lymphoid stem cells and plasma cells. In addition, total numbers of cells of the innate immune system and total T-cell numbers are not affected.

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 detection of CD20 by the assay.

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 primary progressive MS (PPMS) and relapsing forms of MS (RMS) trials.

The longest follow up time after the last Ocrevus infusion (Phase II WA21493, n=51) indicates that the median time to B-cell repletion (return 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.

Clinical trials

OCREVUS IV

Relapsing Forms of MS (RMS)
The efficacy and safety of Ocrevus were evaluated in two randomised, double-blind, double-dummy, active comparator-controlled clinical trials with identical design in patients with RMS. Study design and baseline characteristics of the study population are summarised 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 - two x 300 mg IV infusions, administered two 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 subcutaneous (s.c.) injection three times per week.

Key clinical and magnetic resonance imaging (MRI) efficacy results are presented in Table 5 and Figure 1.

Table 4 Study design and demographic characteristics for studies WA21092 and WA21093 (RMS)

	Study 1		**Study 2**	
Study name	**WA21092 (OPERA I) (n=821)**		**WA21093 (OPERA II) (n=835)**	
Study Design				
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	• Two years (96 weeks)			
Treatment groups	• Group A: Ocrevus 600 mg • Group B: interferon beta-1a (Rebif®), 44 mcg s.c. (IFN)			
Baseline Characteristics	Ocrevus 600 mg (n=410)	IFN 44 mcg (n=411)	Ocrevus 600 mg (n=417)	IFN 44 mcg (n=418)
Mean age (years)	37.1	36.9	37.2	37.4
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 EDSS	2.82	2.71	2.73	2.79
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

Table 5 Key clinical and MRI endpoints from studies WA21092 and WA21093

	Study 1: WA21092 (OPERA I)		**Study 2: WA21093 (OPERA II)**	
	Ocrevus 600 mg (n=410)	**IFN 44 mcg (n=411)**	**Ocrevus 600 mg (n=417)**	**IFN 44 mcg (n=418)**
Clinical Endpoints				
Primary efficacy endpoint Annualised Relapse Rate	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-week 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

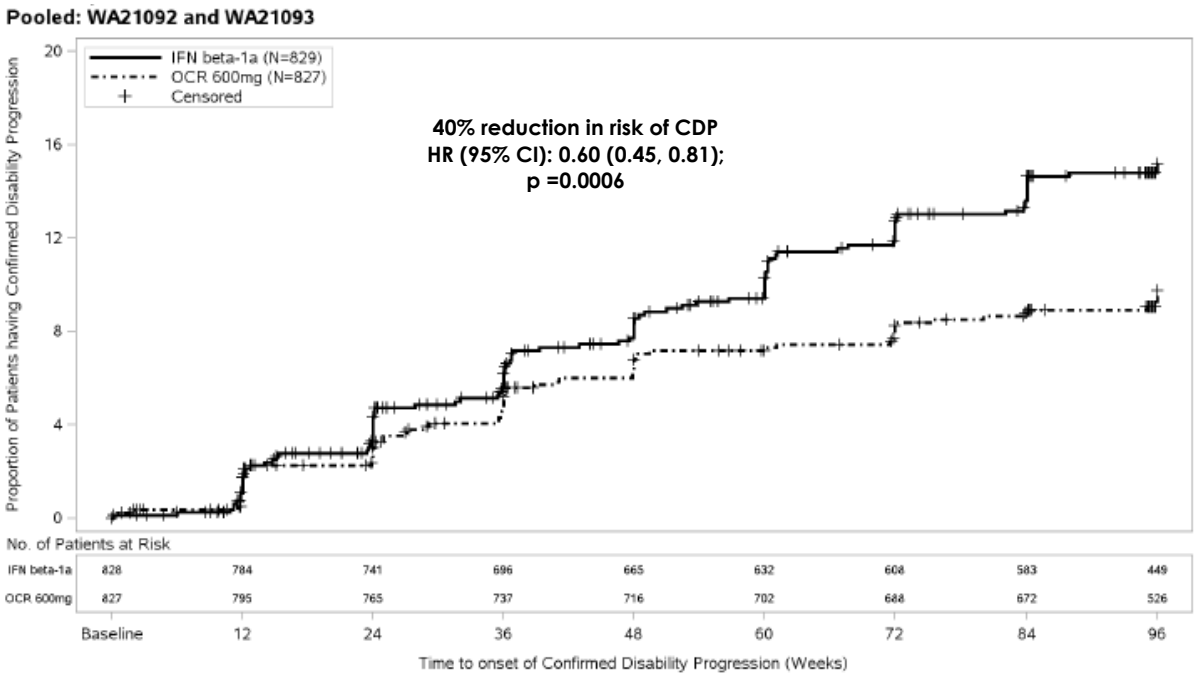
[3] Defined as an increase of ≥ 1.0 point from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline EDSS score of 5.5 or less, or ≥ 0.5 when the baseline score is > 5.5; Kaplan-Meier estimates at Week 96

[4] Defined as decrease of ≥ 1.0 point from the baseline EDSS score for patients with baseline EDSS score of ≥ 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 and any MRI activity (either Gd-enhancing T1 lesions, or new or enlarging T2 lesions) during the whole 96 week treatment period. 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, multicentre, 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 of Ocrevus IV was administered as two 300 mg infusions (600 mg total) separated by 14 days. Patients were randomised 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 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 randomized infusion of Ocrevus IV. 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 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 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.

Primary Progressive MS (PPMS)
The efficacy and safety of Ocrevus were evaluated in a randomised, double-blind, placebo-controlled clinical trial in patients with PPMS (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.

Throughout the treatment period patients receiving Ocrevus (Group A) were given 600 mg every 6 months (as two x 300 mg IV infusions, administered two weeks apart) (see section 4.2 Dose and Method of Administration). Patients in Group B were administered placebo. The two x 300 mg infusions in PPMS demonstrated consistent PK/PD profiles to the 600 mg infusions in RMS.

Table 6 Study design and baseline characteristics for study WA25046

Study name	**WA25046 (ORATORIO) (n=732)**	
Study Design		
Population	• Patients with primary progressive MS	
Disease history at screening	• Age 18 – 55 years • EDSS between 3.0 and 6.5	
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	
Treatment groups	• Group A: Ocrevus 600 mg • Group B: placebo, 2:1 randomisation	
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 diagnosis (years)	2.9 / 1.6	2.8 / 1.3

Mean EDSS	4.7	4.7
Number of Gd-enhancing T1 lesions (%)		
0	72.5	75.3
1	12.8	11.9
≥ 2	14.7	12.8

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

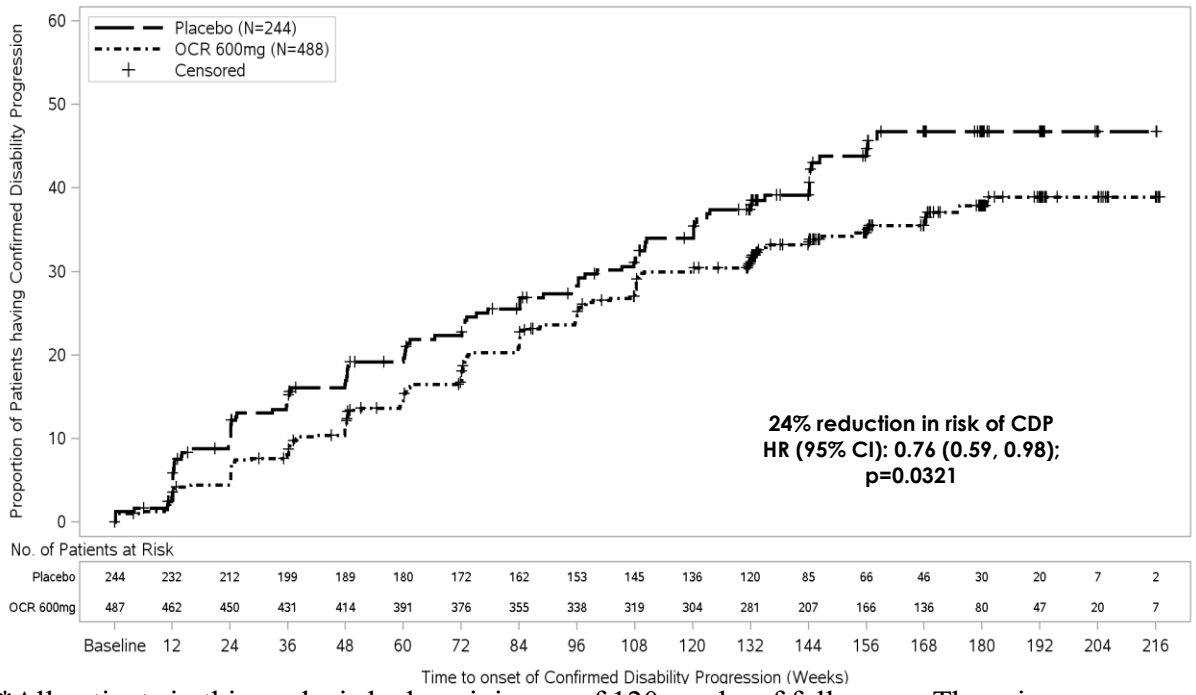
Table 7 Key clinical and MRI endpoints from study WA25046 (PPMS)

	Study 3: WA25046 (ORATORIO)	
	Ocrevus 600 mg (n=488)	**Placebo (n=244)**
Clinical Endpoints		
Primary efficacy endpoint Proportion of patients with 12 weeks Confirmed Disability Progression[1]	30.2%	34.0%
Risk Reduction	24% (p=0.0321)	
Time for 30% of patients to reach 12 weeks Confirmed Disability Progression (weeks)[2]	120.0	100.1
Proportion of patients with 24 weeks Confirmed Disability Progression[1]	28.3%	32.7%
Risk Reduction	25% (p=0.0365)	
Time for 30% of patients to reach 24 weeks Confirmed Disability Progression (weeks)[2]	134.4	108.1
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 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 ≥ 0.5 when the baseline score is > 5.5; Kaplan-Meier estimates at week 120

[2] As the proportion of patients experiencing a CDP event remained below 50% until the end of the controlled treatment period in study WA25046, median times are not estimable

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 accurred

A post-hoc analysis suggested that patients who are 50 years of age or below, or patients who have inflammation determined by MRI (Gd enchancing or T2 lesion) may receive a greater treatment benefit than patients who are over 50 years of age or patients who do not have inflammation by MRI.

OCREVUS SC

OCARINA II

Study CN42097 (OCARINA II) was a multicentre, randomised, 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 post-injection/infusion (AUC_{w1-12}).

A total of 236 patients with RMS or PPMS (213 patients with RMS, 23 patients with PPMS), were randomised in a 1:1 ratio to the 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).

OCARINA I
Study CN41144 (OCARINA I) was a multi-center, randomised, 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. The study was used 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 modelling, comparing the pharmacokinetic profile between Ocrevus SC and Ocrevus IV based on the area under the concentration time curve (AUC) (see section 4.8 Adverse Events (Undesirable Effects) and section 5.1 Pharmacodynamics Properties, Immunogenicity).

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics of ocrelizumab in the MS studies were described by a two compartment model with time-dependent clearance, and with pharmacokinetic (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 PPMS study and the 1 x 600 mg RMS studies, as expected given an identical dose of 600 mg IV was administered. AUCτ after the fourth dose of 600 mg Ocrevus IV 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 600 mg Ocrevus IV. The geometric mean ratio (GMR) for AUC_{w1-12} was 1.29 (90% CI: 1.23–1.35).

Absorption
Ocrelizumab IV is administered intravenously.

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).

Distribution
The population PK 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.

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

Excretion
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.

Pharmacokinetics in Special Populations
Elderly Patients: No studies have been conducted to investigate the PK of ocrelizumab in patients ≥ 65 years.

Paediatric Patients: No studies have been conducted to investigate the PK of ocrelizumab in children and adolescents (< 18 years of age).

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

Hepatic impairment: No formal PK study has been conducted. Patients with mild hepatic impairment were included in clinical trials and no change in the PK of ocrelizumab was observed in those patients.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Genotoxicity studies have not been conducted with ocrelizumab. As ocrelizumab is a monoclonal antibody it would not be expected to have genotoxic potential.

Carcinogenicity
Carcinogenicity studies with ocrelizumab have not been conducted.

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

No carcinogenicity, genotoxicity, or fertility studies were conducted for vorhyaluronidase alfa. Reproductive toxicology studies with vorhyaluronidase alfa revealed embryofetal losses in mice, with no effect level 4675 times higher than the clinical dose. There was no evidence of teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Ocrevus IV
Sodium acetate trihydrate, trehalose dihydrate, acetic acid, polysorbate 20, water for injections

Ocrevus SC
Vorhyaluronidase alfa (an enzyme used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously), sodium acetate trihydrate, trehalose dihydrate, acetic acid, polysorbate 20, methionine, water for injections

6.2 INCOMPATIBILITIES

Ocrevus IV
No incompatibilities between Ocrevus IV and polyvinyl chloride or polyolefine bags, and IV administration sets have been observed. Do not use diluents other than 0.9% sodium chloride to dilute Ocrevus IV since use has not been tested.

Ocrevus SC

No incompatibilities between Ocrevus SC and polypropylene, polycarbonate, polyethylene, polyvinyl chloride, polyurethane and stainless steel have been observed.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Ocrevus IV
Store vial in a refrigerator at 2℃ to 8℃. Keep vial in the outer carton in order to protect from light. Do not freeze. Do not shake. Do not use after the expiry date (EXP) shown on the pack.

Storage of the reconstituted solution
Ocrevus does not contain any anti-microbial preservative; therefore, care must be taken to ensure the sterility of the prepared solution. Product is for single dose in one patient only. Discard any residue.

To reduce microbiological hazard, the prepared infusion solution should be used immediately. If storage is necessary, the prepared infusion can be held at 2°C - 8°C for up to 24 hours and subsequently 8 hours at room temperature.

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

Ocrevus SC
Ocrevus does not contain any anti-microbial preservative; therefore, care must be taken to ensure the sterility of the solution. Product is for single dose in one patient only. Discard any residue.

Store vial in a refrigerator at 2℃ to 8℃. Keep vial in the outer carton in order to protect from light. Do not freeze. Do not shake. Do not use after the expiry date (EXP) shown on the pack.

If necessary, the unopened vial can be left at temperatures ≤ 25°C for up to 12 hours.

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

Storage of the syringe
To reduce microbiological hazard, the prepared syringe should be used immediately. If storage is necessary, the syringe must be closed with a syringe cap. The closed syringe can be held at 2°C - 8°C for up to 72 hours followed by 8 hours at ambient temperatures ≤ 25°C in diffuse daylight.

6.5 NATURE AND CONTENTS OF CONTAINER

Ocrevus IV is a concentrate for solution for infusion supplied at a volume of 10 mL in a 15 mL glass vial.

Ocrevus SC is a solution for injection supplied at a volume of 23 mL in a 50 mL glass vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

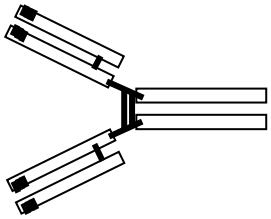
Disposal of unused/expired medicines – Ocrevus IV and SC
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

The following 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)

6.7 PHYSIOCHEMICAL PROPERTIES



CAS: 637334-45-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4. Prescription Only Medicine.

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA
Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

13 July 2017

10. DATE OF REVISION OF THE TEXT

5 November 2026

Summary of Changes Table

Section Changed	Summary of new information
Section 4.8	Addition of further characterisation of neutropenia
Section 4.8	Addition of Interstitial Lung Disease as an ADR from post-marketing experience.