PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 PROPRIETARY NAME AND DOSAGE FORM

Ocrevus® 300 mg Concentrate solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ocrevus contains ocrelizumab as the active substance.

Each 10 mL contains 300 mg ocrelizumab.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A clear to slightly opalescent, and colourless to pale brown solution. Do not use the solution if the solution contains foreign particulate matter.

CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ocrevus is indicated for the treatment of patients with relapsing forms of multiple sclerosis (RMS) to suppress relapses and disease progression (clinical and subclinical disease activity).

Ocrevus is indicated for the treatment of patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed.

4.2 Posology and method of administration

General

Substitution by any other biological medicine approved for the indication requires the consent of the prescribing medical practitioner.

Premedication for infusion-related reactions

Premedicate with 100 mg IV methylprednisolone (or an equivalent) approximately 30 minutes prior to each Ocrevus infusion (see section 4.4) and with an antihistamine (e.g. diphenhydramine) approximately 30 - 60 minutes before each infusion of Ocrevus to reduce the frequency and severity of infusion-related reactions.

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

Administration of Ocrevus

Ocrevus is administered as an IV infusion through a dedicated line under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious IRRs. Ocrevus 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 6.6, Special Instructions for Use, Handling and Disposal).

Observe the patient for at least one hour after the completion of the infusion (see section 4.4, Infusion-Related Reactions).

Initial Dose

Ocrevus 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 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.

If patients did not experience a serious infusion-related reaction (IRR) with any previous Ocrevus infusion, a shorter (2-hour) infusion can be administered for subsequent doses (see Table 1, Option 2) (*see section 4.8 Undesirable Effects*).

Table 1: Dose and Schedule of Ocrevus.

		Amount of Ocrevus to be administered*	**Infusion instruction**
Initial Dose (600 mg) divided into 2 infusions	Infusion 1	300 mg in 250 mL	• 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	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 hr
	or		
	Option 2 Infusion of approximately 2 hours duration	600 mg 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 final product into an infusion bag containing 0,9 % sodium chloride, to a final concentration of approximately 1,2 mg/mL.

** First single infusion should be administered 6 months after Infusion 1 of Initial dose.

Delayed or Missed Doses

If a planned infusion of Ocrevus is missed, it should be administered as soon as possible; do not wait until the next planned dose. The treatment interval for Ocrevus should be maintained between doses.

Infusion Adjustments during Treatment:

No dose reductions of Ocrevus 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 4.4, Infusion-Related Reactions.

Life-threatening IRRs

Immediately stop Ocrevus 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 in these patients.

Severe IRRs

If a patient experiences a severe infusion-related reaction 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 infusion-related reaction (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, Infusion-Related Reactions for full description of symptoms associated with IRRs.

Special Dosage Instructions

Paediatrics

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

Elderly/Geriatrics

The safety and efficacy of Ocrevus in patients ≥ 65 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. 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*, Pharmacokinetics in Special Populations, Renal Impairment*).

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 5.2, *Pharmacokinetics in Special Populations, Hepatic Impairment*).

Special Instructions for use, Handling and Disposal: see section 6.6

Incompatibilities: see section 6.2

4.3 Contraindications

- Patients with known hypersensitivity to ocrelizumab or to any of the excipients in Ocrevus.
- The occurrence of a life threatening infusion reaction to Ocrevus.
- Active hepatitis B virus infection or Active hepatitis C virus infection.
- Active infection (irrespective of pathogen), including active tuberculosis, at the time of a planned infusion.
- Patients receiving Ocrevus must not receive live attenuated vaccines.
- Women of childbearing potential should use contraception while receiving Ocrevus and for 6 months after the last infusion of Ocrevus (see section 4.6).

4.4 Special warnings and precautions for use

Safety and efficacy in patients with HIV has not been established.

General

In order to improve traceability of biological medicines, 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)

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

Symptoms of IRRs may occur during any infusion, but have been more frequently reported during the first infusion. IRRs can occur within 24 hours of the infusion. These reactions may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal

oedema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis (see section 4.8).

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

A hypersensitivity reaction could also occur (acute allergic reaction to Ocrevus). IRRs 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 see section 4.2.

Managing infusion-related reactions:

For patients experiencing life-threatening, severe or mild to moderate IRR symptoms see section 4.2, *Infusion adjustments during treatment*.

Patients who experience severe pulmonary symptoms, such as bronchospasm or asthma exacerbation, must have their infusion interrupted immediately and permanently (see section 4.3). 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.

Immunogenicity

Out of 1 311 patients treated with Ocrevus, 12 (~1 %) tested positive for treatment-emergent anti-drug antibodies (ADAs), of which 2 patients tested positive for neutralising antibodies. The impact of

treatment-emergent ADAs on safety and efficacy cannot be assessed given the low incidence of ADA associated with Ocrevus.

Hypersensitivity Reactions

Hypersensitivity may be difficult to distinguish from IRRs in terms of symptoms. A hypersensitivity reaction may present during any infusion, although typically would not present during the first infusion. For subsequent infusions, more severe symptoms than previously experienced, or new severe symptoms, should prompt consideration of a potential hypersensitivity reaction. If a hypersensitivity reaction is suspected during infusion, the infusion must be stopped immediately and permanently. Patients with known IgE-mediated hypersensitivity to Ocrevus must not be treated (see section 4.3).

Infections

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

Progressive multifocal leukoencephalopathy (PML)

John Cunningham (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, Medical practitioners 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 magnetic resonance scan (MRI) preferably with contrast (compared with pre-treatment MRI), confirmatory cerebrospinal fluid (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 Hepatitis B surface antigen (HBsAg) and anti-HB testing) should not be treated with Ocrevus (see section 4.3). Patients with positive serology (i.e. negative for HBsAg and positive for HB core antibody [HBcAb+]; carriers of HBV [positive for surface antigen, HBsAg+]) should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

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 pharmacodynamic effects should be taken into consideration (see section 5.1). 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 immunisation with live or live-attenuated viral vaccines, following Ocrevus therapy has not been studied and vaccination with live-attenuated or live vaccines is contraindicated during treatment and until B-cell repletion (see section 4.3 and section 5.1).

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

In a randomised open-label study, RMS patients treated with Ocrevus were able to mount humoral responses, albeit decreased, to tetanus toxoid, 23-valent pneumococcal polysaccharide, keyhole limpet

haemocyanin neoantigen, and seasonal influenza vaccines. It is still recommended to vaccinate patients treated with Ocrevus with seasonal influenza vaccines that are inactivated.

Medical practitioners should review the immunisation status of patients before starting treatment with Ocrevus. Patients who require vaccination should complete their immunisations at least 6 weeks prior to initiation of Ocrevus.

Exposure in utero to Ocrevus 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 should be delayed until B-cell levels have recovered; therefore, measuring CD19-positive B-cell level, in neonates and infants, prior to vaccination is recommended.

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

4.5 Interaction with other medicines and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Ocrevus is contraindicated in pregnancy and lactation

Pregnancy

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

Ocrevus should not be used during pregnancy (see section 4.3).

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

Postponing vaccination with live or live-attenuated vaccines should be considered for neonates and infants born to mothers who have been exposed to Ocrevus in utero. 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 2.4 Warnings and Precautions).

Contraception

Women of childbearing potential should use contraception while receiving Ocrevus and for 6 months after the last infusion of Ocrevus (see section 5.2, Pharmacokinetic properties, *Elimination*).

Breastfeeding/Lactation

Human IgG is excreted in human milk, therefore women should not breastfeed their infants during Ocrevus therapy

4.7 Interference with daily activities

Infusion related reactions may occur up to 24 hours post infusion and may impair a patients' ability to drive or to use machines.

4.8 Undesirable effects

a. Summary of the safety profile:

Clinical Trials

The safety of Ocrevus has been evaluated in 1 311 patients across MS clinical studies, which includes 825 patients in active-controlled RMS clinical trials and 486 patients in a placebo-controlled PPMS study. Table 2 summarises the adverse drug reactions (ADRs) that have been reported in association with the use of Ocrevus in clinical trials. The most frequently reported ADRs were IRRs and respiratory tract infections.

Relapsing forms of MS

The ADRs were identified based on data from two active-controlled studies to evaluate the efficacy and safety of Ocrevus in 825 adults with relapsing forms of MS (RMS). The controlled period of the study was 96 weeks (4 doses of Ocrevus).

Primary Progressive MS

The ADRs were identified based on data from a single study with 486 adult patients, to evaluate the efficacy and safety of Ocrevus in primary progressive MS (PPMS).

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.

b. Tabulated list of adverse reactions

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

ADR (MedDRA)	***Frequency category***	***RMS Pooled WA21092 & WA21093 n=825***	***PPMS WA25046*** [2] ***n=486***

Injury, Poisoning and Procedural Complications			
Infusion-related reaction [3]	Very common	283 (34,3 %)	195 (40,1 %)
Infections and infestations			
Upper respiratory tract infection	Very common	125 (15,2 %)	59 (12,1 %)
Nasopharyngitis	Very common	123 (14,9 %)	117 (24,1 %)
Sinusitis	Common	46 (5,6 %)	19 (3,9 %)
Bronchitis	Common	42 (5,1 %)	31 (6,4 %)
Influenza	Very common	38 (4,6 %)	57 (11,7 %)
Gastroenteritis	Common	25 (3,0 %)	22 (4,5 %)
Oral herpes	Common	25 (3,0 %)	13 (2,7 %)
Respiratory tract infection	Common	19 (2,3 %)	13 (2,7 %)
Viral infection	Common	18 (2,2 %)	15 (3,1 %)
Herpes zoster	Common	17 (2,1 %)	8 (1,6 %)
Conjunctivitis	Common	9 (1,1 %)	10 (2,1 %)
Cellulitis	Common	7 (0,8 %)	11 (2,3 %)
Respiratory, thoracic and mediastinal disorders			
Cough	Common	25 (3,0 %)	34 (7,0 %)
Catarrh	Common	0	10 (2,1 %)

[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 in “Infusion-related reactions”

c. Description of selected adverse events

Infusion-related reactions

Across the RMS and PPMS trials, symptoms associated with IRRs included, but were not limited to: pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, nausea, tachycardia. None of the IRRs were fatal.

In RMS clinical trials, IRRs were the most common adverse event in patients treated with Ocrevus 600 mg with an overall incidence of 34,3 % 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 (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 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.

Alternative Shorter Infusion of Subsequent Doses

In the Shorter Infusion Substudy, designed to characterise the safety profile of shorter (2-hour) Ocrevus infusions in patients with RRMS, the incidence, intensity, and types of symptoms of IRRs were consistent with those of infusions administered over 3,5 hours.

Infection

In the RMS and PPMS clinical trials, respiratory tract infections and herpes infections were reported with Ocrevus.

Respiratory Tract Infections

The infections were predominately of upper respiratory tract infections (including nasopharyngitis) and bronchitis (see Table 2).

Herpes

In clinical trials, herpes infections were reported which included herpes zoster (2,1 %), herpes simplex, (0,7 %) and oral herpes (3,0 %), genital herpes (0,1 %), herpes virus infection (0,1 %).

Serious Infections 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 anti-rheumatic 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 serious infections was observed, including, but not limited to, atypical pneumonia and *pneumocystis jiroveci* pneumonia, varicella pneumonia, tuberculosis, histoplasmosis in the Ocrevus-immunosuppressant group. Some of these infections were fatal.

Risk factors for serious infections 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 studies, mainly driven by reduction in IgM, with no apparent association with serious infections.

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-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 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.

Neutrophils

In the active-controlled (RMS) treatment period, decreased neutrophils were observed in 14,7 % of Ocrevus patients. In the placebo-controlled (PPMS) clinical trial, the proportion of Ocrevus patients presenting decreased neutrophils was (12,9 %).

The majority of the decreased neutrophils were transient (only observed once for a given patient treated with Ocrevus) and were Grade 1 and 2 in severity.

Overall, approximately 1 % of the patients in the Ocrevus group had Grade 3 or 4 neutropenia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Report Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

There is no specific antidote in the event of an overdose; interrupt the infusion immediately and observe the patient for infusion-related reactions (see section 4.4*, Infusion-Related Reactions*).

Treatment is palliative and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: selective immunosuppressants group, ATC code: L04AA36

Ocrelizumab is a recombinant humanised monoclonal antibody that selectively targets CD20-expressing B-cells. CD20 is a cell surface antigen found on pre-B-cells, mature and memory B-cells but not expressed on lymphoid stem cells and plasma cells.

The precise mechanisms through which ocrelizumab exerts its therapeutic clinical effects in 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, 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.

Following the last ocrelizumab infusion, 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.

5.2 Pharmacokinetic properties

Pharmacokinetics (PK) of ocrelizumab in the multiple sclerosis (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. 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 relapsing multiple sclerosis (RMS) studies, as expected given an identical dose was administered. Area under curve (AUC_τ) after the 4th dose of 600 mg ocrelizumab was 3 510 µg/mL•day, and mean maximum concentration (Cmax) was 212 µg/mL in RMS (600 mg infusion) and 141 µg/mL in primary progressive multiple sclerosis (PPMS) (300 mg infusions). Terminal half-life was 26 days.

Absorption

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

Distribution

The population pharmacokinetics estimate of the central volume of distribution was 2,78 L. Peripheral volume and inter-compartment clearance were estimated at 2,68 L and 0,294 L/day.

Metabolism

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

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.

Pharmacokinetics in Special Populations

Paediatrics

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

Elderly

No studies have been conducted to investigate the pharmacokinetics of ocrelizumab in patients ≥ 65 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 ocrelizumab 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.

Post-hoc analyses were performed in the Extended Controlled Period (ECP), which includes double-blinded treatment and approximately 9 additional months of controlled follow-up before continuing into the Open-Label Extension (OLE) or until withdrawal from study treatment. The proportion of patients

with 24 week Confirmed Disability Progression of EDSS≥7.0 (24W-CDP of EDSS≥7.0, time to wheelchair) was 9.1% in the placebo group compared to 4.8% in the 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. As these results were exploratory in nature and included data after unblinding, the results should be interpreted with caution.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients:

polysorbate 20

sodium acetate trihydrate

α,α-trehalose dihydrate

water for injection

6.2 Incompatibilities

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

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

This medicine must not be mixed with other medicines except those mentioned in section 6.6

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store vial in a refrigerator at 2 - 8°C.

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

Do not freeze. Do not shake.

Store out of reach of children.

Do not use after the expiry date (EXP) shown on the pack.

Prepared 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 - 8 ^{0}C and 8 hours at room temperature.

From a microbiological point of view, the prepared infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 - 8 °C and subsequently for 8 hours at room temperature, unless dilution is undertaken in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Ocrevus is a 10 mL concentrate for solution for infusion supplied in either one or two 15 mL single-use, colourless type 1 glass vials with grey rubber stoppers, laminated with fluororesin film and crimped with an aluminium seal, fitted with a green plastic flip-off cap. The vials are packed into white cardboard boxes with black printing and a green marking over dosage form.

Not all packs may be marketed

6.6 Special precautions for disposal and other handling

Ocrevus 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 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.

Ocrevus must be diluted before administration. Solutions of Ocrevus for IV administration are prepared by dilution of the product into an infusion bag containing 0,9 % sodium chloride (300 mg/250 mL or 600 mg/500 mL), to a final 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 due to the administration at low temperatures.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road,

Hertford Office Park,

Building E, Vorna Valley,

Midrand, Johannesburg,1685

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER(S)

52/30.1/0581

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 14 July 2020

10. DATE OF REVISION OF THE TEXT

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