

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **OCREVUS**®

ocrelizumab for injection

Concentrate for intravenous infusion

300 mg/10 mL (30 mg/mL)

Selective Immunomodulator

OCREVUS®, indicated for:

- the management of adult patients with early primary progressive multiple sclerosis (PPMS) as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for OCREVUS®, please refer to Health Canada's Notice of Compliance with conditions - drug products web site: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html>

OCREVUS®, indicated for:

- the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features has been issued market authorization without conditions.

Treatment with OCREVUS (ocrelizumab) should be initiated and supervised by neurologists experienced in the treatment of patients with MS and who have fully familiarized themselves with the efficacy and safety profile of OCREVUS.

Hoffmann-La Roche Limited
7070 Mississauga Road
Mississauga, Ontario
L5N 5M8
www.rochecanada.com

Date of Initial Authorization:
AUG 14, 2017

Date of Revision:
JAN 09, 2023

Submission Control Number: 266929

OCREVUS® Registered trade-mark of F. Hoffmann-La Roche AG, used under license
© Copyright 2022, Hoffmann-La Roche Limited

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.1 Dosing Considerations	12/2022
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	04/2021
4 Dosage and Administration, 4.3 Reconstitution	02/2021
7 Warnings and Precautions	12/2022

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	5
1 INDICATIONS	5
1.1 Pediatrics	5
1.2 Geriatrics	5
2 CONTRAINDICATIONS	5
4 DOSAGE AND ADMINISTRATION	6
4.1 Dosing Considerations	6
4.2 Recommended Dose and Dosage Adjustment	7
4.3 Reconstitution	9
4.4 Administration	9
4.5 Missed Dose	9
5 OVERDOSAGE	9

6	DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	10
7	WARNINGS AND PRECAUTIONS.....	10
7.1	Special Populations	16
7.1.1	Pregnant Women	16
7.1.2	Breast-feeding.....	16
7.1.3	Pediatrics	16
7.1.4	Geriatrics	17
8	ADVERSE REACTIONS	17
8.1	Adverse Reaction Overview	17
8.2	Clinical Trial Adverse Reactions	17
8.3	Less Common Clinical Trial Adverse Reactions	20
8.4	Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data	20
8.5	Post-Market Adverse Reactions	21
9	DRUG INTERACTIONS.....	21
9.2	Drug Interactions Overview	21
9.3	Drug-Behavioural Interactions	21
9.4	Drug-Drug Interactions	21
9.5	Drug-Food Interactions	22
9.6	Drug-Herb Interactions	22
9.7	Drug-Laboratory Test Interactions	22
10	CLINICAL PHARMACOLOGY	22
10.1	Mechanism of Action	22
10.2	Pharmacodynamics	22
10.3	Pharmacokinetics	23
11	STORAGE, STABILITY AND DISPOSAL	23
12	SPECIAL HANDLING INSTRUCTIONS	24
PART II: SCIENTIFIC INFORMATION		24
13	PHARMACEUTICAL INFORMATION	24
14	CLINICAL TRIALS	25
14.1	Clinical Trials by Indication	25

15	MICROBIOLOGY	33
16	NON-CLINICAL TOXICOLOGY	33
	PATIENT MEDICATION INFORMATION	35

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Relapsing Remitting Multiple Sclerosis (RRMS)

OCREVUS (ocrelizumab for injection) is indicated for:

- the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features (see 14 CLINICAL TRIALS).

Primary Progressive Multiple Sclerosis (PPMS)

NOC/c OCREVUS (ocrelizumab for injection) is indicated for:

- the management of adult patients with early primary progressive multiple sclerosis (PPMS) as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity (see 14 CLINICAL TRIALS).

OCREVUS treatment should be initiated and supervised by neurologists experienced in the treatment of patients with MS and who are familiar with the efficacy and safety profile of OCREVUS (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION).

Specific pre-medication should be administered before injecting OCREVUS (see 4 DOSAGE AND ADMINISTRATION).

Resources for the treatment of hypersensitivity and anaphylactic reactions should be immediately available.

Patients treated with OCREVUS must be informed about the risks of OCREVUS.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 55 years of age): The safety and efficacy of OCREVUS in patients > 55 years of age has not been established.

NOC/c 2 CONTRAINDICATIONS

Ocrevus is contraindicated in patients:

- Who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- With a history of life-threatening infusion reaction to Ocrevus (see 7 WARNINGS AND PRECAUTIONS).
- With active HBV infection (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

- With severe, active infections (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).
- Who have or have had confirmed progressive multifocal leukoencephalopathy (PML) (see 7 WARNINGS AND PRECAUTIONS).
- Who are in a severely immunocompromised state (see 7 WARNINGS AND PRECAUTIONS).
- With known active malignancies (see 7 WARNINGS AND PRECAUTIONS).

NOC/c 4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Ocrevus treatment should be initiated and supervised by a neurologist experienced in the treatment of patients with MS. Ocrevus should be administered under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage the most frequent adverse reactions (especially autoimmune conditions including infusion reactions and infections). Resources for the treatment of hypersensitivity and anaphylactic reactions should be immediately available.

Patients treated with Ocrevus must be informed about the risks of Ocrevus (also see package leaflet).

Specific pre-medication should be provided prior to Ocrevus administration (see Recommended Premedication).

Ocrevus infusions should not be administered as an intravenous push or bolus (see 4.2 Recommended Dose and Dosage Adjustment, Table 1).

Assessment Prior to First Dose of Ocrevus

Hepatitis B Virus Screening

Prior to initiating Ocrevus, perform Hepatitis B virus (HBV) screening. Ocrevus is contraindicated in patients with active HBV confirmed by positive results for HBsAg and anti-HBV tests. For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment (see 7 WARNINGS AND PRECAUTIONS).

Serum Immunoglobulins

Prior to initiating Ocrevus, perform testing for quantitative serum immunoglobulins. For patients with low serum immunoglobulins, consult immunology experts before initiating treatment with Ocrevus (see 7 WARNINGS AND PRECAUTIONS).

Vaccinations

Because vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion, administer all necessary immunizations according to immunization guidelines at least 6 weeks prior to initiation of Ocrevus (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

Preparation before Every Infusion

Infection Assessment

Prior to every infusion of Ocrevus, determine whether there is an active infection. In case of active infection, delay infusion of Ocrevus until the infection resolves (see 7 WARNINGS AND PRECAUTIONS).

Risk of Hypotension

Prior to every infusion of Ocrevus, verify whether the patient is receiving antihypertensive treatments. Hypotension may occur during Ocrevus infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Ocrevus infusion (see 7 WARNING AND PRECAUTIONS).

Recommended Premedication

Pre-medicate with 100 mg of methylprednisolone (or an equivalent corticosteroid) administered intravenously approximately 30 minutes prior to each Ocrevus infusion to reduce the frequency and severity of infusion reactions (see 7 WARNINGS AND PRECAUTIONS). Pre-medicate with an antihistamine drug (e.g. diphenhydramine) approximately 30-60 minutes prior to each infusion of Ocrevus to further reduce the frequency and severity of infusion reactions.

The addition of an antipyretic (e.g. acetaminophen) may also be considered.

4.2 Recommended Dose and Dosage Adjustment

- Initial dose: 300 mg intravenous infusion, followed 2 weeks later by a second 300 mg intravenous infusion.
- Subsequent doses: single 600 mg intravenous infusion every 6 months (see Table 1).
- Observe the patient for at least one hour after the completion of the infusion (see 7 WARNINGS AND PRECAUTIONS).
- 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 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS).

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

Table 1 - Recommended Dose, Infusion Rate, and Infusion Duration for RRMS and PPMS

		Amount and Volume ¹	Infusion Rate and Duration ³
Initial Dose (two infusions)	Infusion 1	300 mg in 250 mL	<ul style="list-style-type: none">• Start at 30 mL per hour• Increase by 30 mL per hour every 30 minutes• Maximum: 180 mL per hour• Duration: 2.5 hours or longer
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent Doses (one infusion every 6 months) ²	Option 1	600 mg in 500 mL	<ul style="list-style-type: none">• Start at 40 mL per hour• Increase by 40 mL per hour every 30 minutes• Maximum: 200 mL per hour• Duration: 3.5 hours or longer
	Infusion of approximately 3.5 hours duration		
	OR		
	Option 2 (If no serious infusion reaction with any previous Ocrevus infusion)	600 mg in 500 mL	<ul style="list-style-type: none">• Start at 100 mL per hour for the first 15 minutes• Increase to 200 mL per hour for the next 15 minutes• Increase to 250 mL per hour for the next 30 minutes• Increase to 300 mL per hour for the remaining 60 minutes• Duration: 2 hours or longer
	Infusion of approximately 2 hours duration		

¹ 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.

² Administer the first subsequent Dose 6 months after Infusion 1 of Initial Dose.

³ Infusion time may take longer if the infusion is interrupted or slowed (see 4 DOSAGE AND ADMINISTRATION).

Dose Modifications Because of Infusion Reactions

Dose modifications in response to infusion reactions depend on the infusion reactions severity.

Life-threatening Infusion Reactions

Immediately stop Ocrevus if there are signs of a life-threatening or disabling infusion reaction during an infusion, such as acute hypersensitivity or acute respiratory distress syndrome. Provide appropriate supportive treatment. Permanently discontinue Ocrevus in these patients.

Severe Infusion Reactions

If a patient experiences a severe infusion reaction or a complex of flushing, fever, and throat pain symptoms, immediately interrupt the infusion and provide appropriate supportive treatment. Restart the infusion only after all symptoms have resolved. When restarting, begin at half of the infusion rate at the time of onset of the infusion reaction (see 4 DOSAGE AND ADMINISTRATION). If this rate is tolerated, increase the rate as described in Table 1. This change in rate will increase the total duration of the infusion but not the total dose.

Mild to Moderate Infusion Reactions

If a patient experiences a mild to moderate infusion reaction (e.g. headache), reduce the infusion rate

to half the rate at the onset of the infusion reaction. This reduced rate should be maintained for at least 30 minutes. If this rate is tolerated, increase the rate as described in Table 1. This change in rate will increase the total duration of the infusion but not the total dose.

See 7 WARNINGS AND PRECAUTIONS, General, Infusion Reactions for full description of symptoms associated with IRRs.

4.3 Reconstitution

Parenteral Products:

Preparation of the Dilute Solution for Infusion and Administration

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

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

Visually inspect for particulate matter and discolouration prior to administration. Do not use the solution if discoloured or if the solution contains discrete foreign particulate matter. Do not shake. Withdraw intended dose and further dilute into an infusion bag containing 0.9% Sodium Chloride Injection, to a final drug concentration of approximately 1.2 mg/mL.

- Withdraw 10 mL (300 mg) of Ocrevus and inject into 250 mL
- Withdraw 20 mL (600 mg) of Ocrevus and inject into 500 mL

Do not use other diluents to dilute Ocrevus since their use has not been tested. The product contains no preservative and is intended for single use only.

Incompatibilities

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

4.4 Administration

Administer Ocrevus under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion reactions.

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

4.5 Missed Dose

If a planned infusion of Ocrevus is missed, administer Ocrevus as soon as possible; do not wait until the next scheduled dose. Reset the dose schedule to administer the next sequential dose 6 months after the missed dose is administered.

5 OVERDOSAGE

There is no specific antidote in the event of an overdose; interrupt the infusion immediately and observe the patient for infusion reactions (see 7 WARNINGS AND PRECAUTIONS, General, Infusion Reactions).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	300 mg per vial (30 mg/mL concentrate for solution for infusion)	Glacial acetic acid, polysorbate 20, sodium acetate trihydrate, α,α trehalose dihydrate, and water for injection.

Ocrevus is supplied as a preservative-free, sterile solution in a single-use glass vial. Each 15 mL vial contains 10 mL of Ocrevus for IV infusion. There is one vial per pack.

NOC/c 7 WARNINGS AND PRECAUTIONS

General

Infusion Reactions

Fatal infusion reactions have been observed in patients treated with other anti-CD20 antibodies. Ocrevus can cause infusion reactions, which can include pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia, and anaphylaxis. In multiple sclerosis (MS) clinical trials (WA21092, WA21093 and WA25046), the incidence of infusion reactions in Ocrevus-treated patients [who received methylprednisolone (or an equivalent steroid) and possibly other pre-medication to reduce the risk of infusion reactions prior to each infusion] was 34 to 40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of Ocrevus-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization.

Observe all patients treated with Ocrevus for infusion reactions during the infusion and for at least one hour after completion of the infusion. Inform patients that infusion reactions can occur up to 24 hours after the infusion (see 7 WARNINGS AND PRECAUTIONS).

Reducing the Risk of Infusion Reactions and Managing Infusion Reactions

Administer pre-medication (e.g., methylprednisolone or an equivalent corticosteroid, and an antihistamine) to reduce the frequency and severity of infusion reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered (see 4 DOSAGE AND ADMINISTRATION).

Management recommendations for infusion reactions depend on the type and severity of the reaction (see 4 DOSAGE AND ADMINISTRATION). For life-threatening infusion reactions, immediately and permanently stop Ocrevus and administer appropriate supportive treatment. For less severe infusion

reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

Patients should be administered Ocrevus under the close supervision of an experienced healthcare professional in a setting where medications and supportive care measures for the treatment of hypersensitivity reactions (e.g., epinephrine, antihistamines, glucocorticoids) are immediately available in the event of an allergic reaction during administration.

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.

Dependence/Tolerance

No studies on drug abuse and dependence have been conducted.

Driving and Operating Machinery

No studies on the effects on the ability to drive and to use machines have been performed.

Hepatic/Biliary/Pancreatic

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. No significant change in the pharmacokinetics of Ocrevus was observed (see 10 PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Immune

Immunogenicity

Patients in the RRMS studies (Study WA21092, Study WA21093) 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 807 patients treated with ocrelizumab and who had evaluable samples, 3 (~ 0.4%) tested positive for treatment-emergent ADAs, of which 1 patient tested positive for neutralizing antibodies. The impact of treatment-emergent ADAs on safety and efficacy cannot be assessed given the low incidence of ADA associated with Ocrevus.

Patients in the PPMS (Study 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 481 patients treated with ocrelizumab and who had evaluable samples, 9 (~ 1.9%) tested positive for treatment-emergent ADAs, of which 1 patient tested positive for neutralizing antibodies. The impact of treatment-emergent ADAs on safety and efficacy cannot be assessed given the low incidence of ADA associated with Ocrevus.

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.

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 hospitalization, with a few patients requiring surgical intervention. Systemic corticosteroids were required in many of these patients. 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 new or persistent diarrhea or other gastrointestinal signs and symptoms, occur.

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 ocrelizumab must not be treated (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, General, Infusion Reactions).

Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants

When initiating Ocrevus after an immunosuppressive therapy or initiating an immunosuppressive therapy after Ocrevus, the potential for increased immunosuppressive effects should be taken into consideration (see 10 CLINICAL PHARMACOLOGY, 10.1 Mechanism of Action). Ocrevus has not been studied in combination with other disease modifying MS therapies. The concomitant use of OCREVUS and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of immunosuppression. When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating OCREVUS. Exercise caution when prescribing Ocrevus, taking into consideration the pharmacodynamics of other disease modifying MS therapies. (See 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions).

Patients in a severely immunocompromised state must not be treated until the condition resolves (see 2 CONTRAINDICATIONS).

Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with Ocrevus treatment (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data). Monitor the level of immunoglobulins at the beginning of treatment. Monitor during and after discontinuation of treatment with Ocrevus, until B-cell repletion, especially when recurrent serious infections are suspected. Consider discontinuing Ocrevus in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins (see 4 DOSAGE AND ADMINISTRATION).

Vaccination

The safety of immunization with live or live-attenuated vaccines, following Ocrevus therapy has not been studied and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion (see 10 CLINICAL PHARMACOLOGY, 10.1 Mechanism of Action).

Ocrevus may interfere with the effectiveness of non-live vaccines (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Vaccination).

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

initiation of Ocrevus (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Vaccination and 10 CLINICAL PHARMACOLOGY).

Vaccination of neonates and infants born to mothers treated with Ocrevus during pregnancy

There are no adequate and well-controlled studies on the effects of Ocrevus in neonates and infants of mothers who have been exposed to Ocrevus during pregnancy. Due to the potential depletion of B-cells in infants of mothers who have been exposed to Ocrevus during pregnancy, it is recommended that vaccination with live or live-attenuated vaccines are delayed until the recovery of B-cells has been confirmed as measured by CD19⁺ B-cells. Depletion of B-cells in these infants may increase the risks from live or live attenuated vaccines (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology, Reproductive Toxicity and 10 CLINICAL PHARMACOLOGY, 10.1 Mechanism of Action).

It is recommended that all vaccinations other than live or live-attenuated may follow the local immunization schedule, but physicians should assess whether a protective immune response was mounted. Physicians may consult vaccination experts as the efficacy of the vaccination of a neonate or infant may be decreased following Ocrevus exposure (see 9 DRUG INTERACTIONS, 9.4 Drug-Drug Interactions, Vaccination).

Infections

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

A higher proportion of Ocrevus-treated patients experienced infections compared to patients taking IFN or placebo. Ocrevus increased the risk for upper respiratory tract infections, lower respiratory tract infections, and herpes-related infections (see 8 ADVERSE REACTIONS).

In RRMS clinical trials (Study WA21092 and Study WA21093), 58% of Ocrevus-treated patients experienced one or more infections compared to 52% of IFN-treated patients. There were 2 (0.2%) Grade 4 infections in the Ocrevus group, whereas no Grade 4 infection in the IFN group. The proportion of patients reporting serious infections was 2.9% for IFN versus 1.3% for Ocrevus.

In the PPMS clinical trial (Study WA25046), 71.0% of Ocrevus-treated patients experienced one or more infections compared to 67.8% of placebo-treated patients. There were 8 (1.6%) Grade 4 (life-threatening) and 2 (0.4%) Grade 5 (fatal) infections in the Ocrevus group, versus 1 (0.4%) Grade 4 infection and 0 Grade 5 in the placebo group. The proportion of patients reporting serious infections was 6.7% for placebo versus 6.2% for Ocrevus.

In PPMS (Study WA25046), patients with swallowing difficulties are at a higher risk of aspiration pneumonia. Ocrevus treatment may further increase the risk of severe pneumonia in these patients. Physicians should take prompt action for patients presenting with pneumonia.

Fatal infections have also been observed in clinical trials in patients treated with other anti-CD20 antibodies.

Respiratory Tract Infections

A higher proportion of Ocrevus-treated patients experienced respiratory tract infections compared to patients taking IFN. In RRMS clinical trials (Study WA21092 and Study WA21093), 40% of Ocrevus-treated patients experienced upper respiratory tract infections compared to 33% of IFN-treated patients, and 8% of Ocrevus-treated patients experienced lower respiratory tract infections compared to 5% of IFN-treated patients.

A higher proportion of Ocrevus-treated patients experienced respiratory tract infections compared to patients taking placebo. In PPMS clinical trial (Study WA25046), 49% of Ocrevus-treated patients experienced upper respiratory tract infections compared to 43% of placebo-treated patients, and 10% of Ocrevus-treated patients experienced lower respiratory tract infections compared to 9% of placebo-treated patients.

The respiratory tract infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections and bronchitis.

Herpes

In RRMS clinical trials (Study WA21092 and Study WA21093), herpes infections were reported more frequently in Ocrevus-treated patients than in IFN-treated patients, including herpes zoster (2.1% vs. 1.0%), herpes simplex (0.7% vs. 0.1%), oral herpes (3.0% vs. 2.2%), genital herpes (0.1% vs. 0%), and herpes virus infection (0.1% vs. 0%). Infections were predominantly mild (Grade 1) to moderate (Grade 2) in severity.

In the PPMS clinical trial, oral herpes infections were reported more frequently in Ocrevus-treated patients than in placebo-treated patients for oral infections (2.7% vs 0.8%).

Serious cases of infections caused by herpes simplex virus and varicella zoster virus, including central nervous system infections (encephalitis and meningitis), intraocular infections, and disseminated skin and soft tissue infections, have been reported in the post-marketing setting in multiple sclerosis patients receiving Ocrevus. Serious herpes virus infections may occur at any time during treatment with Ocrevus. Some cases were life-threatening.

If serious herpes infections occur, Ocrevus should be discontinued or withheld until the infection has resolved, and appropriate treatment should be administered. Advise patients to promptly contact their healthcare provider if they experience any signs or symptoms of herpes infections.

Progressive Multifocal Leukoencephalopathy (PML)

PML is an opportunistic viral infection of the brain caused by the John Cunningham (JC) virus that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability.

JC virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies, including Ocrevus. PML has occurred in Ocrevus-treated patients who had not been treated previously with natalizumab (which has a known association with PML), were not taking any immunosuppressive or immunomodulatory medications associated with the risk of PML prior to or concomitantly with Ocrevus, and did not have any known ongoing systemic medical conditions resulting in compromised immune system function.

At the first sign or symptom suggestive of PML, withhold Ocrevus and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is confirmed, discontinue treatment of Ocrevus permanently.

Hepatitis B Reactivation

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

HBV screening should be performed in all patients before initiation of treatment with Ocrevus as per local guidelines. Patients with active Hepatitis B virus (HBV), (i.e. an active infection confirmed by positive results for HBsAg and anti HB testing) should not be treated with Ocrevus. Patients with positive serology (i.e. negative for HBsAg and positive for HB core antibody [HBcAb+] or are 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. In the event of HBV reactivation, Ocrevus and concomitant medications should be discontinued until the active infection is resolved.

Malignancies

An increased risk of malignancy with Ocrevus may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in Ocrevus-treated patients. Breast cancer occurred in 6 of 781 females treated with Ocrevus, including 4/240 (1.7%) female patients with PPMS and 2/541 (0.4%) female patients with RRMS. None of 668 females treated with REBIF or placebo reported breast cancer. Patients with a known active malignancy should not be treated with Ocrevus (see 2 CONTRAINDICATIONS). Patients should follow standard breast cancer screening guidelines.

Psychiatric

Depression and Suicide

In RRMS clinical trials, depression including suicide occurred in 8.5% and 7.9% of patients receiving Ocrevus and IFN, respectively.

In PPMS clinical trial, depression including suicide occurred in 9.7% and 13.8% of patients receiving Ocrevus and placebo, respectively. Four events (0.8%) related to suicide (including suicide attempts, depression suicidal and suicidal ideation) occurred in the Ocrevus group and one event (depression suicidal; 0.4%) occurred in the placebo group.

Ocrevus should be used with caution in patients with previous or current depression, a condition that is common in people with multiple sclerosis. Patients treated with Ocrevus should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients developing depression during Ocrevus therapy should be monitored closely and cessation of therapy should be considered.

Renal

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. No significant change in the pharmacokinetics of Ocrevus was observed (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

Reproductive Health: Female and Male Potential

Women of childbearing potential should use contraception while receiving Ocrevus and for 6 months after the last infusion of Ocrevus (see 10 CLINICAL PHARMACOLOGY, 10.1 Mechanism of Action, and 10.3 Pharmacokinetics, Elimination).

Serious Adverse Events Reported in Other Anti-CD20 Antibodies

Serious cardiovascular events and severe mucocutaneous reactions have occurred rarely in patients treated with other anti-CD20 antibodies. Patients experiencing a severe mucocutaneous reaction should discontinue treatment with Ocrevus and seek prompt medical evaluation.

7.1 Special Populations

7.1.1 Pregnant Women

Ocrevus is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier. Ocrevus should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus.

There are no adequate data on the developmental risk associated with use of Ocrevus 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. Following administration of ocrelizumab to pregnant monkeys at doses similar to or greater than those used clinically, increased perinatal mortality, depletion of B-cell populations, in addition to renal, bone marrow, and testicular toxicity were observed in the offspring in the absence of maternal toxicity (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

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 7 WARNINGS AND PRECAUTIONS, Immune, Vaccination).

In Ocrevus clinical trials (WA21092, WA21093 and WA25046), the rate of induced abortion reported was 16.7% (8/48). In the general population worldwide, the overall rate of pregnancies ending in induced abortion is 20% and in MS patients it is 26.5% as reported in literature. The overall rate of birth defects (defined as any abnormality affecting body structure or function) was 12.5% (6/48) and the rate of structural malformations was 6.3% (3/48). The background risk of major birth defects and miscarriage for the indicated population is unknown.

7.1.2 Breast-feeding

Ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Ocrevus and any potential adverse effects on the breast-fed infant from Ocrevus or from the underlying maternal condition.

There are no data on the presence of ocrelizumab in human milk, the effects on the breast-fed infant, or the effects of the drug on milk production. Animal studies have shown excretion of ocrelizumab in breast milk (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). Human IgG is excreted in human milk, and the potential for ocrelizumab absorption leading to B-cell depletion is unknown. Women should be advised to discontinue breast-feeding during Ocrevus therapy.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 55 years of age): The safety and efficacy of Ocrevus in patients > 55 years of age has not been established.

NOC/c 8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of Ocrevus has been evaluated in 1311 patients across MS clinical studies, which includes 825 patients in active-controlled (RRMS) clinical trials and 486 patients in a placebo-controlled (PPMS) study WA25046. Table 3 summarizes the adverse drug reactions (ADRs) that have been reported in association with the use of Ocrevus in clinical trials.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Relapsing Remitting Multiple Sclerosis (RRMS)

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

The most common (incidence $\geq 10\%$) adverse reactions for Ocrevus in the RRMS trials were (Ocrevus vs. IFN): infusion reactions (34% vs. 10%), upper respiratory tract infections (15% vs. 11%), nasopharyngitis (15% vs. 10%). Serious adverse events (SAEs) were reported in 7.0% of patients receiving Ocrevus and in 8.8% of patients receiving IFN.

Primary Progressive Multiple Sclerosis (PPMS)

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

The most common (incidence $\geq 10\%$) adverse reactions for Ocrevus in the PPMS trials were (Ocrevus vs. placebo): infusion reactions (40% vs. 26%), upper respiratory tract infections (12% vs. 6%), influenza (12% vs. 8%). Serious adverse events (SAEs) were reported in 21% of patients receiving Ocrevus and in 23% of patients receiving placebo. In the WA25046 PPMS trial, 20 of 618 patients (3.2%) treated with Ocrevus discontinued treatment due to an adverse event; 2 patients (0.3%) discontinued treatment due to breast cancer and 2 patients (0.3%) discontinued due to an IRR.

Table 3 Summary of ADRs associated with Ocrevus in RRMS or PPMS with an incidence of $\geq 1\%$ and higher than the comparator¹

ADR (MedDRA) System organ class (SOC) Preferred Term	RRMS Pooled WA21092 & WA21093		PPMS WA25046 ³	
	Ocrevus 600 mg IV, every 24 weeks ¹ n=825	Interferon beta-1a 44mcg S. C., 3 times per week n=826	Ocrevus n=486	Placebo n=239
Injury, Poisoning and Procedural Complications				
Infusion related reaction ²	283 (34.3%)	82 (9.9%)	195 (40.1%)	61 (25.5%)
Infections and Infestations				
Upper respiratory tract infection	125 (15.2%)	88 (10.7%)	59 (12.1%)	14 (5.9%)
Nasopharyngitis	123 (14.9%)	84 (10.2%)	117 (24.1%)	67 (28.0%)
Sinusitis	46 (5.6%)	45 (5.4%)	19 (3.9%)	7 (2.9%)
Bronchitis	42 (5.1%)	29 (3.5%)	31 (6.4%)	15 (6.3%)
Influenza	38 (4.6%)	39 (4.7%)	57 (11.7%)	20 (8.4%)
Gastroenteritis	25 (3.0%)	19 (2.3%)	22 (4.5%)	12 (5.0%)
Oral herpes	25 (3.0%)	18 (2.2%)	13 (2.7%)	2 (0.8%)
Respiratory tract infection	19 (2.3%)	17 (2.1%)	13 (2.7%)	2 (0.8%)
Viral infection	18 (2.2%)	23 (2.8%)	15 (3.1%)	4 (1.7%)
Herpes zoster	17 (2.1%)	8 (1.0%)	8 (1.6%)	4 (1.7%)
Rhinitis	12 (1.5%)	3 (0.4%)	17 (3.5%)	9 (3.8%)
Lower Respiratory Infections	10 (1.2%)	4 (0.5%)	6 (1.2%)	1 (0.4%)
Conjunctivitis	9 (1.1%)	5 (0.6%)	10 (2.1%)	1 (0.4%)
Cellulitis	7 (0.8%)	5 (0.6%)	11 (2.3%)	1 (0.4%)
Psychiatric disorders				
Insomnia	46 (5.6%)	38 (4.6%)	28 (5.8%)	15 (6.3%)
Respiratory, thoracic and mediastinal disorders				
Cough	25 (3.0%)	12 (1.5%)	34 (7.0%)	8 (3.3%)
Catarrh	0	0	10 (2.1%)	2 (0.8%)

¹ The first dose was given as two separate 300 mg infusions at Weeks 0 and 2.

² Symptoms reported as an infusion related reaction (IRR) within 24 hours of infusion are described below in "Infusion reactions"

³ PPMS patients were randomized 2:1 (Ocrevus:placebo).

PPMS: Each dose of Ocrevus 600 mg was administered as two IV infusions of 300 mg Ocrevus.

PPMS: at least 120 weeks controlled treatment period.

RRMS: 96 weeks controlled treatment period.

Further information on selected adverse drug reactions from clinical trials:

Infusion reactions

Across the RRMS and PPMS trials, symptoms associated with infusion reactions (IRs) included, but are not limited to: pruritus, rash, urticaria, erythema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal edema, nausea, tachycardia. In the controlled clinical trials there were no fatal IRRs.

In active-controlled (RRMS) clinical trials, IRs were the most common adverse event in patients treated with Ocrevus 600 mg with an overall incidence of 34.3% compared with an incidence of 9.9% in the interferon beta-1a treatment group (placebo infusion). The incidence of IRs 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 (see 7 WARNINGS AND PRECAUTIONS, General, Infusion Reactions).

In the placebo-controlled (PPMS) clinical trial, IRs were the most common adverse event in patients treated with Ocrevus, with an overall incidence of 40% compared with an incidence of 26% in the placebo group. Five (1.0%) patients in the Ocrevus group had experienced serious IRs. No serious IRs reported in the placebo group. The incidence of IRs 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 IRs with the first infusion of each dose compared with the second infusion of that dose. The majority of IRs were mild to moderate (see 7 WARNINGS AND PRECAUTIONS, General, Infusion Reactions).

Infusion Reactions with Alternative Shorter Infusion of Subsequent Doses

In a study (MA30143 Shorter Infusion Substudy) designed to characterize the safety profile of shorter (2-hour) Ocrevus infusions in patients with Relapsing-Remitting Multiple Sclerosis who did not experience a serious reaction with any previous Ocrevus infusion, the incidence, intensity, and types of symptoms of IRRs were consistent with those of infusions administered over 3.5 hours (see 14 CLINICAL TRIALS).

Infection

There was no increase in serious infections associated with Ocrevus treatment (in RRMS 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 (RRMS) and the placebo-controlled (PPMS) clinical trials, respiratory tract infections and herpes infections (both predominantly mild to moderate) were more frequently reported in the Ocrevus treatment arm (see 7 WARNINGS AND PRECAUTIONS, Infections).

Respiratory Tract Infections

The proportion of respiratory tract infections was higher in the Ocrevus treated patients compared to interferon and placebo. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections (including nasopharyngitis) and bronchitis (see Table 3, see 7 WARNINGS AND PRECAUTIONS, Infections, Respiratory Tract Infections).

Herpes (see 7 WARNINGS AND PRECAUTIONS, Infections, Herpes)

In active-controlled (RRMS) clinical trials, herpes infections were reported more frequently in Ocrevus-

treated patients than interferon beta-1a treated patients.

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

Hepatic/Biliary/Pancreatic

SAEs related to cholecystitis/cholelithiasis/pancreatitis were observed in RRMS clinical trials (Ocrevus vs. IFN): Pancreatitis: 2 (0.2%) vs. 0 (0%), cholecystitis/cholelithiasis: 6 (0.7%) vs. 2 (0.2%).

SAEs related to cholecystitis/cholelithiasis/pancreatitis were observed in the PPMS clinical trial (Ocrevus vs. Placebo): Pancreatitis acute: 2 (0.4%) vs. 0 (0%), cholecystitis acute and cholelithiasis: 1 (0.2%) vs. 1 (0.4%) each, cholecystitis chronic: 0 (0%) vs 1 (0.2%).

Other

In a Phase II trial, one patient, who received 2000 mg of Ocrevus, died of systemic inflammatory response syndrome (SIRS) of unknown etiology, following a magnetic resonance imaging (MRI) examination 12 weeks after the last infusion; an anaphylactoid reaction to the MRI gadolinium-contrast agent could have contributed to the SIRS.

8.3 Less Common Clinical Trial Adverse Reactions

In RRMS and PPMS clinical trials, there are no adverse reactions that occurred at an incidence rate of < 1%.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Immunoglobulins

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

In the active-controlled (RRMS) 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 WA25046, 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.

Clinical trial data have shown an association between decreased levels of IgG (and less so for IgM or IgA) and increased rates of serious infections (SIs). 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.

Neutrophils

In the active-controlled (RRMS) treatment period, decreased neutrophils were observed in 14.7% of Ocrevus patients as compared to 40.9% of patients treated with interferon beta-1a. In the placebo-controlled (PPMS) clinical trial, decreased neutrophils were observed in 12.9% of Ocrevus patients as compared to 10.0% of patients treated with placebo.

The majority of the decreased neutrophils were transient (only observed once for a given patient treated with Ocrevus) and were Grade 1 ($< \text{LLN} - 1.5 \times 10^9/\text{L}$) and 2 ($< 1.5 - 1.0 \times 10^9/\text{L}$) in severity. Overall, approximately 1% of the patients in the Ocrevus group had Grade 3 ($< 1.0 - 0.5 \times 10^9/\text{L}$) or 4 ($< 0.5 \times 10^9/\text{L}$) neutropenia and was not temporally associated with an infection.

Lymphocytes

In RRMS, a decrease in lymphocytes $< \text{LLN}$ was observed in 20.7% of Ocrevus treated patients vs 32.6% of patients treated with interferon beta-1-a.

In PPMS, a decrease in lymphocytes $< \text{LLN}$ was observed in 26.3% of Ocrevus treated patients vs 11.7% of placebo-treated patients.

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

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

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of Ocrevus. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Immune-mediated colitis (see 7 WARNINGS AND PRECAUTIONS).

Infections and Infestations: Serious herpes infections and progressive multifocal leukoencephalopathy (see 7 WARNINGS AND PRECAUTIONS).

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been performed.

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

Immunosuppressive or Immune-Modulating Therapies

The concomitant use of Ocrevus and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of immunosuppression. Consider the risk of additive effects on the immune system when coadministering immunosuppressive therapies with Ocrevus. When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating Ocrevus. (See 7 WARNINGS AND PRECAUTIONS).

Vaccination

A randomized open-label study BN29739 (VELOCE), in 102 RRMS patients (68 patients taking ocrelizumab and 34 patients receiving no disease-modifying therapy except interferon-beta) evaluated the effects of ocrelizumab on humoral immune responses to tetanus toxoid-containing vaccine, pneumococcal polysaccharide, pneumococcal conjugate vaccines, keyhole limpet hemocyanin neoantigen, and seasonal inactivated influenza vaccines.

The observed humoral responses to all vaccines used in the study were decreased in RRMS patients treated with ocrelizumab compared to those not treated with ocrelizumab. For the primary endpoint (response to TT-containing booster vaccine), the proportion of patients with a positive response was decreased in ocrelizumab-treated patients (Group A: 23.9%) compared with patients not treated with ocrelizumab (Group B: 54.5%).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

NOC/c 10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

10.2 Pharmacodynamics

For the B-cell counts, CD19 is used as the presence of Ocrevus interferes with the recognition of CD20 by the assay. Treatment with ocrelizumab leads to depletion of CD19+ B-cells in blood by 14 days post treatment (first time-point of assessment).

In the Phase III studies, between each dose of ocrelizumab, up to 5% of patients showed B-cell repletion (> lower limit of normal (LLN) or baseline) at least at one time point.

In the Phase II RRMS study, the median time to B-cell repletion (returned to baseline/LLN whichever occurred first) was 72 weeks (range 27 - 175 weeks). Ninety percent of all patients had their B-cells repleted to LLN or baseline by approximately two and a half years after the last infusion.

10.3 Pharmacokinetics

Pharmacokinetics of ocrelizumab in the MS studies were described by a two compartment model with time-dependent clearance. 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. Area under curve (AUC_t) after the 4th dose of 600 mg Ocrevus was 3510 µg/mL•day, and mean maximum concentration (C_{max}) was 212 µg/mL in RRMS (600 mg infusion) and 141 µg/mL in PPMS (300 mg infusions).

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.

Special Populations and Conditions

- **Pediatrics:** No studies have been conducted to investigate the pharmacokinetics of Ocrevus in children and adolescents (< 18 years of age).
- **Geriatrics:** No studies have been conducted to investigate the pharmacokinetics of Ocrevus in patients > 55 years.
- **Hepatic Insufficiency:** No formal pharmacokinetic study has been conducted. Patients with mild hepatic impairment were included in clinical trials, and no significant change in the pharmacokinetics was observed in those patients.
- **Renal Insufficiency:** No formal pharmacokinetic study has been conducted. Patients with mild renal impairment were included in clinical trials and no significant change in the pharmacokinetics of ocrelizumab was observed in those patients.

11 STORAGE, STABILITY AND DISPOSAL

Vials

Store vials at 2-8°C.

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

Do not freeze. Do not shake.

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.

This medicine should not be used 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 in the refrigerator up to 24 hours at 2-8°C and 8 hours at room temperature up to 25°C, which includes infusion time.

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

Disposal of Unused/Expired Medicines

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

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

12 SPECIAL HANDLING INSTRUCTIONS

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

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	ocrelizumab
Chemical name:	Immunoglobulin G1, anti-(human CD20[antigen]) (human-mouse monoclonal 2H7 γ1-chain), disulfide with human-mouse monoclonal 2H7 κ-chain, dimer
Molecular formula and molecular mass:	C ₆₄₈₂ H ₉₉₅₂ N ₁₇₁₂ O ₂₀₁₄ S ₄₆ , approximately 145,564 Da (peptide chains only, without heavy chain C-terminal lysine residues)
Structural formula:	Ocrelizumab is a humanized monoclonal antibody based on the human immunoglobulin G1 (IgG1) framework that contains heavy chain VHIII and light chain VκI subgroup sequences. The recombinant antibody consists of two identical 213 residue light chains and two identical 451 or 452 residue heavy chains.

Physicochemical properties:	Concentrate for solution for infusion: clear or slightly opalescent, and colourless to pale brown solution, sterile liquid for intravenous infusion.
Pharmaceutical standard:	Professed

Product Characteristics:

Ocrevus is a recombinant humanized monoclonal antibody that selectively targets CD20-expressing B-cells.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Relapsing Remitting Multiple Sclerosis (RRMS)

Study WA21092 and Study WA21093

Study Demographics and Trial Design

The efficacy and safety of Ocrevus were evaluated in two (Study WA21092 and Study WA21093) 96 week randomized, double-blind, double-dummy, active comparator-controlled clinical trials with identical designs, in patients with relapsing remitting MS (in accordance with McDonald criteria 2010). The dose of Ocrevus was 600 mg every 24 weeks (initial treatment was given as two 300 mg IV infusions administered 2 weeks apart, and subsequent doses were administered as a single 600 mg IV infusion) and placebo subcutaneous injections were given 3 times per week. The dose of REBIF, the active comparator, was 44 mcg given as subcutaneous injections 3 times per week and placebo IV infusions were given every 24 weeks. Randomization was stratified by region (United States versus rest of the world [ROW]) and baseline EDSS (< 4.0 versus ≥ 4.0). Both studies included patients who had experienced at least one relapse within the prior year, or two relapses within the prior two years, and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.5. Patients with primary progressive forms of multiple sclerosis (MS) were excluded. Neurological evaluations were performed every 12 weeks and at the time of a suspected relapse. Brain MRIs were performed at baseline and at Weeks 24, 48, and 96.

The primary outcome of both Study WA21092 and Study WA21093 was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients with confirmed disability progression, the mean number of MRI T1 gadolinium (Gd)-enhancing lesions at Weeks 24, 48, and 96, and new or enlarging MRI T2 hyperintense lesions. Progression of disability was defined as an increase of 1 point or more from the baseline EDSS score attributable to MS when the baseline EDSS score was 5.5 or less, or 0.5 points or more when the baseline EDSS score was above 5.5. Disability progression was considered confirmed when the increase in the EDSS was confirmed at a regularly scheduled visit 12 weeks after the initial documentation of neurological worsening. The primary population for analysis of confirmed disability progression was the pooled population from Studies WA21092 and WA21093.

The study design and baseline characteristics of the study population are summarized in Table 4.

Table 4 - Study Design and Demographic Characteristics

	RRMS Study WA21092 n=821		RRMS Study WA21093 n=835	
Study design				
Study population	Patients with relapsing remitting MS			
Disease history at screening	At least two relapses within the prior two years or one relapse within the prior year; EDSS between 0 and 5.5, inclusive			
Study duration	2 years (96 weeks)			
Treatment groups	Group A: Ocrevus 600 mg Group B: interferon beta-1A (Rebif®), 44 mcg s.c. (IFN)			
Completed the 96 week double blind treatment period	Group A: Ocrevus n= 366 (89.3%) Group B: interferon beta-1A (Rebif®) n=340 (82.7%)		Group A: Ocrevus n= 360 (86.3%) Group B: interferon beta-1A (Rebif®) n=320 (76.6%)	
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 number of relapses in the last year	1.31	1.33	1.32	1.34
Mean Gd-enhancing T1 Lesion count	1.69	1.87	1.82	1.95
Mean T2 lesion count	51.04	51.06	49.26	51.01
Mean EDSS	2.82	2.71	2.73	2.79

Study Results

In Study WA21092 and Study WA21093, Ocrevus significantly lowered the annualized relapse rate and the proportion of patients with disability progression confirmed at 12 weeks after onset compared to REBIF. Results for Study WA21092 and Study WA21093 are presented in Table 5 and Figure 1.

Table 5 - Key Clinical and MRI Endpoints from RRMS Study WA21092 and RRMS Study WA21093

Endpoints	RRMS Study WA21092		RRMS Study WA21093	
	Ocrevus 600 mg (n=410)	IFN 44 mcg (n=411)	Ocrevus600 mg (n=417)	IFN 44 mcg (n=418)
Clinical Endpoints				
Annualized Relapse Rate (primary endpoint)	0.156	0.292	0.155	0.290
Rate ratio (95% CI) ²	0.536 (0.400, 0.719)		0.532 (0.397, 0.714)	
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			
Hazard ratio (95% CI) ⁴	0.60 (0.45, 0.81)			
Risk Reduction (Pooled Analysis ¹)	40% (p=0.0006)			
Proportion of patients with 24-week Confirmed Disability Progression ³	7.6% Ocrevus vs 12.0% IFN			
Hazard ratio (95% CI) ⁴	0.60 (0.43, 0.84)			
Risk Reduction (Pooled Analysis ¹)	40% (p=0.0025)			
MRI Endpoints				
Mean number of T1 Gd-enhancing lesions per MRI scan	0.016	0.286	0.021	0.416
Rate ratio (95% CI) ⁵	0.058 (0.032, 0.104)		0.051 (0.029, 0.089)	
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
Rate ratio (95% CI) ⁶	0.229 (0.174, 0.300)		0.171 (0.130, 0.225)	
Relative Reduction	77% (p<0.0001)		83% (p<0.0001)	

¹ Data prospectively pooled from Study WA21092 & WA21093.

² Rate ratio and p-value were estimated using negative binomial model adjusted by baseline EDSS (< 4.0 vs. ≥ 4.0) and geographical region (US vs. ROW).

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

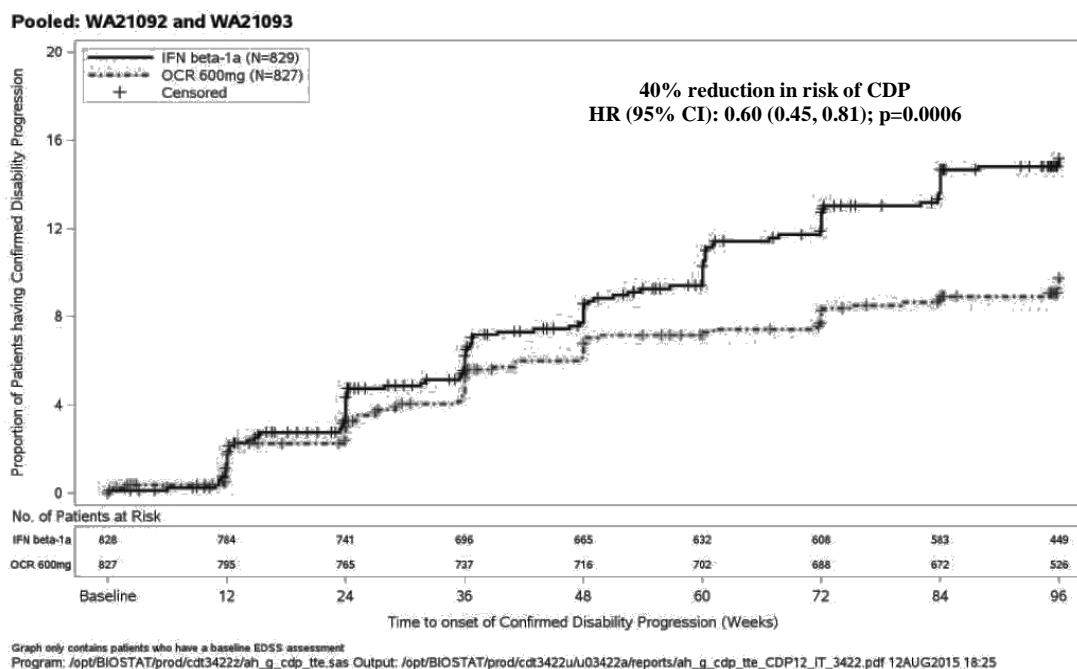
⁴ Hazard ratio was estimated using Cox model stratified by Study, baseline EDSS (< 4.0 vs. ≥ 4.0) and geographical region (US vs. ROW); p-value was estimated using log-rank test stratified by Study, baseline EDSS (< 4.0 vs. ≥ 4.0) and geographical region (US vs. ROW).

⁵ Rate ratio and p-value were estimated using negative binomial model adjusted by baseline T1 Gd-enhancing lesions (present vs. not present), baseline EDSS (< 4.0 vs. ≥ 4.0) and geographical region (US vs. ROW).

⁶ Rate ratio and p-value were estimated using negative binomial model adjusted by baseline T2 hyperintense lesion count, baseline EDSS (< 4.0 vs. ≥ 4.0) and geographical region (US vs. ROW).

Type I error was strictly controlled using hierarchical test procedure.

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 Study WA21092 and Study WA21093*

Safety Study of Shorter (2-hour) Infusion

Study MA30143 Substudy

The safety of the shorter (2-hour) Ocrevus infusion was evaluated in a prospective, multicenter, randomized, double-blind, controlled, parallel arm Study MA30143 substudy in patients with Relapsing-Remitting Multiple Sclerosis who were naïve to other disease modifying treatments and did not experience a serious infusion reaction with any previous Ocrevus infusion. The first dose of Ocrevus was administered as two 300 mg infusions (600 mg total) separated by 14 days. After enrollment in the substudy, starting from their second dose or onwards (Dose 2 to 6), patients were randomized in a 1:1 ratio to receive an Ocrevus infusion over approximately 3.5 hours or 2 hours every 24 weeks, with appropriate premedication prior to each infusion (see 4 DOSAGE AND ADMINISTRATION). The randomization was stratified by region and the dose at which patients were first randomized.

The primary endpoint of this substudy was the proportion of patients with infusion-related reactions (IRRs) occurring during or within 24 hours following the first randomized infusion of Ocrevus. The primary analysis was performed when 580 patients were randomized, most of them (469/579, 81%) received a single randomized infusion of Ocrevus over 3.5 or 2.0 hours. The proportions of patients with IRRs occurring during or within 24 hours following the first randomized infusion were similar (24.4% in the 2-hour infusion group compared to 23.3% in the 3.5-hour infusion group). The stratified group difference was similar. Overall, in all randomized doses, the majority of the IRRs were mild or moderate. Two IRRs were severe in intensity with one severe IRR in each group. There were no life-threatening, fatal, or serious IRRs in this substudy.

NOC/c Primary Progressive Multiple Sclerosis (PPMS)

Study WA25046

Study Demographics and Trial Design

The efficacy and safety of Ocrevus were also evaluated in a randomized, double-blind, placebo-controlled clinical trial in patients with primary progressive MS.

Patients were randomised 2:1 to receive either Ocrevus 600 mg or placebo as 2 x 300 mg IV infusions, administered 2 weeks apart every 24 weeks for at least 120 weeks. Randomization was stratified by region (United States [US] versus rest of the world [RoW]) and age (≤ 45 versus > 45). Selection criteria required a screening EDSS of 3 to 6.5 and a score of 2 or greater for the EDSS pyramidal functional system due to lower extremity findings. In addition, subjects were required to be between 18 to 55 years of age, with disease duration from the onset of MS symptoms less than 10 years in patients with an EDSS at screening ≤ 5.0 or less than 15 years in patients with an EDSS at screening > 5.0 . Neurological assessments were conducted every 12 weeks. An MRI scan was obtained at baseline and at Weeks 24, 48, and 120.

The primary outcome for the study was the time to onset of disability progression attributable to MS confirmed to be present at the next neurological assessment at least 12 weeks later. Disability progression occurred when the EDSS score increased by 1 point or more from the baseline EDSS if the baseline EDSS was 5.5 points or less, or by 0.5 points or more if the baseline EDSS was more than 5.5 points. In the study, confirmed disability progression also was deemed to have occurred if patients who had onset of disability progression discontinued participation in the study before the next assessment. Additional outcome measures included timed 25-foot walk, and percentage change in T2 hyperintense lesion volume.

The study randomized 488 patients to Ocrevus and 244 to placebo; 21% of Ocrevus-treated patients and 34% of placebo-treated patients did not complete the trial. Overall, demographic and baseline characteristics were well balanced across the two treatment groups.

Study design and baseline characteristics of the study population are presented in Table 6.

Table 6 - Study design and baseline characteristics for PPMS Study WA25046

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

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

Table 7 - Key Clinical and MRI Endpoints from PPMS Study WA25046

	PPMS Study WA25046	
Endpoints	Ocrevus 600 mg (n=488)	Placebo (n=244)
Clinical Endpoints		
Primary efficacy endpoint Proportion of patients with 12 weeks - Confirmed Disability Progression ¹ (primary endpoint) Hazard ratio (95% CI) ² Risk reduction	32.9%	39.3%
	0.76 (0.59, 0.98) 24% (p=0.0321)	
Proportion of patients with 24 weeks - Confirmed Disability Progression ¹ Hazard ratio (95% CI) ² Risk reduction	29.6%	35.7%
	0.75 (0.58, 0.98) 25% (p=0.0365)	
MRI Endpoints		
Percentage change in T2 hyperintense lesion volume, from baseline to Week 120 ³	-3.4	7.4
Adjusted Geometric Mean ⁴ (ratio relative to baseline, at week 120)	0.966	1.074
Ratio of Adjusted Geometric Means (95% CI)	0.900 (0.88, 0.92) (p< 0.0001) ⁵	

¹ Defined as an increase of ≥ 1.0 point from the baseline EDSS score for patients with baseline score of 5.5 or less, or ≥ 0.5 when the baseline score is > 5.5

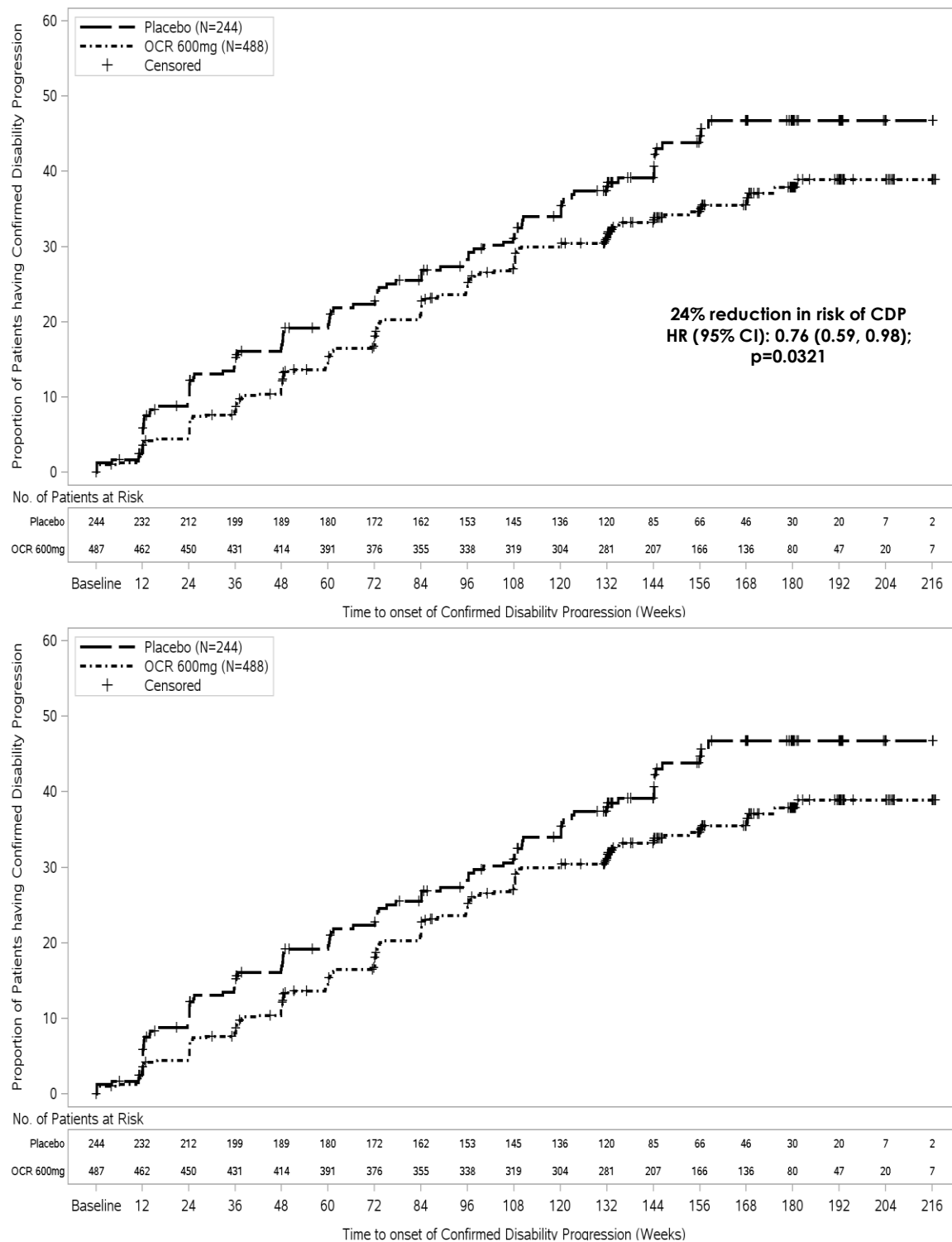
² Hazard ratio was estimated using Cox model stratified by geographical region (US vs. ROW) and age (≤ 45 , > 45 years); p-value was estimated using log-rank test stratified by geographical region (US vs. ROW) and age (≤ 45 , > 45 years).

³ Percentage change calculated as (adj. geometric mean ratio -1) *100

⁴ Estimates (back-transformed) are based on mixed-effect model for repeated measures (MMRM)

⁵ Ranked ANCOVA model adjusting for baseline T2 lesion volume, age and geographical region
Type I error was strictly controlled using hierarchical test procedure.

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 disability progression events accrued including 21 with initial disability progression but without a confirmatory EDSS score at 12 Weeks.

In the overall population in study WA25046, the proportion of patients with 20 percent worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in Ocrevus-treated patients compared to 59% in placebo-treated patients (25% risk reduction).

A sensitivity analysis of the primary endpoint, where patients with initial disease progression who discontinued the study before having a confirmatory visit were treated as having no progression, resulted in a HR of 0.82 [95% CI: 0.63, 1.07], $p=0.1477$.

In exploratory subgroup analyses of study WA25046, the proportion of female patients with disability progression confirmed at 12 weeks after onset was similar in Ocrevus-treated patients and placebo-treated patients (approximately 36% in each group). In male patients, the proportion of patients with disability progression confirmed at 12 weeks after onset was approximately 30% in Ocrevus-treated patients and 43% in placebo treated patients. Other clinical and MRI endpoints generally favoured Ocrevus numerically across these subgroups. These results are exploratory in nature and should be interpreted with caution.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity: No carcinogenicity studies have been performed to assess the carcinogenic potential of ocrelizumab.

Genotoxicity: No studies have been performed to assess the mutagenic potential of ocrelizumab. As an antibody, ocrelizumab is not expected to interact directly with DNA.

Reproductive and Developmental Toxicology:

Impairment of Fertility

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

Reproductive Toxicity

Following intravenous administration of Ocrevus to monkeys during organogenesis (loading doses of 15 or 75 mg/kg on gestation days 20, 21, and 22, followed by weekly doses of 20 or 100 mg/kg), depletion of B-lymphocytes in lymphoid tissue (spleen and lymph nodes) was observed in fetuses at both doses.

Intravenous administration of Ocrevus (three daily loading doses of 15 or 75 mg/kg, followed by weekly doses of 20 or 100 mg/kg) to pregnant monkeys throughout the period of organogenesis and continuing through the neonatal period resulted in perinatal deaths (some associated with bacterial infections), renal toxicity (glomerulopathy and inflammation), lymphoid follicle formation in the bone marrow, and severe decreases in circulating B-lymphocytes in neonates. The cause of the neonatal deaths is uncertain; however, both affected neonates were found to have bacterial infections. Reduced testicular weight was observed in neonates at the high dose.

A no-effect dose for adverse developmental effects was not identified; the doses tested in monkey are 2 and 10 times the recommended human dose of 600 mg, on a mg/kg basis.

Ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys.

Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ocrevus and any potential adverse effects on the breastfed infant from Ocrevus or from the underlying maternal condition (see 7 WARNINGS AND PRECAUTIONS, 7.1 Special Populations, 7.1.2 Breast-feeding).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOCREVUS® (pronounced oak-rev-us)

ocrelizumab for injection

Concentrate for intravenous infusion

Read this carefully before you start taking **Ocrevus** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Ocrevus**.

What is Ocrevus used for?

- Ocrevus is a prescription medicine used to treat adults with active Relapsing Remitting Multiple Sclerosis (RRMS) and Primary Progressive Multiple Sclerosis (PPMS).
- In Multiple Sclerosis (MS), your immune system mistakenly attacks the protective insulation (called 'myelin') around your nerves in the central nervous system (brain and spinal cord), causing inflammation.
- When the inflammation causes you to have symptoms, this is often called a "relapse" or "attack". In Relapsing Remitting MS (RRMS), people will have repeated attacks (relapses) of physical symptoms followed by periods of recovery. Symptoms vary from patient to patient but usually involve physical problems such as difficulty walking, vision and balance problems.
- Symptoms may disappear completely after the relapse is over, but over time, some problems may remain between relapses that can interfere with your daily activities.
- Patients with Primary Progressive MS (PPMS) have symptoms that continuously get worse from the start of the disease. Occasionally relapses occur in PPMS.

For the following indication, Ocrevus® has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- Ocrevus® is indicated for the management of adult patients with early primary progressive multiple sclerosis (PPMS) as defined by disease duration and level of disability, in conjunction with imaging features characteristic of inflammatory activity.

For the following indication, Ocrevus® has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.

- Ocrevus® is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is

reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does Ocrevus work?

Ocrevus is a humanized monoclonal antibody. Monoclonal antibodies are proteins which bind to a unique site (called an antigen) on cells. Ocrevus binds to an antigen, called CD20, which is present at high levels on certain cells of your immune system. Ocrevus works on your immune system so that it may not attack your nervous system as much.

What are the ingredients in Ocrevus?

Medicinal ingredient: ocrelizumab

Non-medicinal ingredients: glacial acetic acid, polysorbate 20, sodium acetate trihydrate, trehalose dihydrate, and water for injection

Ocrevus comes in the following dosage forms:

Single use vial. Each vial contains 300 mg of ocrelizumab in 10 mL at a concentration of 30 mg/mL. One vial is packaged in each carton.

Do not use Ocrevus if:

- You are allergic to ocrelizumab or any of the other ingredients of this medicine (listed above) or component of the container.
- You have a history of life-threatening infusion reactions to Ocrevus (see **Other warnings you should know about**).
- You have severe, active infections (see **Other warnings you should know about**).
- You have active Hepatitis B virus (HBV) infection (see **Other warnings you should know about**).
- You have or have had confirmed progressive multifocal leukoencephalopathy (PML) (see **Other warnings you should know about**).
- You have been told that you have severe problems with your immune system.
- You have cancer.

If you are not sure, talk to your doctor before you are given Ocrevus.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Ocrevus. Talk about any health conditions or problems you may have, including if you:

- Think you have an infection. Your doctor will wait until the infection is resolved before giving you Ocrevus.
- Have ever had a type of liver disease called hepatitis B or are a carrier of the hepatitis B virus. This is because medicines similar to Ocrevus can cause the hepatitis B virus to become active again. Before your Ocrevus treatment, your doctor will check if you are at risk of having hepatitis B infection by a blood test. Patients who have had hepatitis B or are carriers of the hepatitis B virus will have a blood test and will be monitored by a doctor for signs of hepatitis B

infection. This is because the virus could become active and may result in serious liver problems.

- Have ever had an allergic reaction to ocrelizumab or any of the other ingredients in Ocrevus.
- Have ever taken, are taking, or plan to take medicines that affect your immune system, or other treatments for MS. These medicines could increase your risk of getting an infection.
- Have depression or a history of depression.
- Have a history of heart disease, heart attack or stroke.
- Have had a recent vaccination or are scheduled to receive any vaccinations. **You should receive any required vaccines at least 6 weeks before you start treatment with Ocrevus.** You should **not receive** certain vaccines (called 'live' or 'live attenuated' vaccines) while you are being treated with Ocrevus and until your healthcare provider tells you that your immune system is no longer weakened.
- Are pregnant, think that you might be pregnant, or plan to become pregnant. It is not known if Ocrevus will harm your unborn baby. You should use birth control (contraception) during treatment with Ocrevus and for 6 months after your last infusion of Ocrevus.
- Are breast-feeding or plan to breast-feed. It is not known if Ocrevus passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take Ocrevus.
- Have cancer or if you have had cancer in the past. Your doctor may decide to delay your treatment with Ocrevus.

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

Other warnings you should know about:

Infusion reactions

- Infusion reactions are the most common side effect of Ocrevus treatment and can be serious and require you to be hospitalized.
- Tell your doctor or nurse straight away if you experience any of these signs or symptoms during or after each infusion: itchy skin, trouble breathing, nausea, shortness of breath, rash, throat irritation or pain, headache, fatigue, hives, feeling faint, swelling of the throat, fast heartbeat, tiredness, fever, dizziness, coughing or wheezing, redness on your face (flushing).
- Infusion reactions can happen during the infusion or up to 24 hours after the infusion.
- To reduce the risk of infusion reaction, your doctor or nurse will give you other medicines before each infusion of Ocrevus and you will be closely monitored during the infusion and for at least one hour after the infusion has been given.
- If you get infusion reactions, your doctor or nurse may need to stop or slow down the rate of your infusion.

Infections

- Ocrevus may increase your risk of getting upper respiratory tract infections, lower respiratory tract infections, and herpes infections.

- Tell your doctor or nurse straight away if you have any of these signs of infection during or after Ocrevus treatment: fever and/or chills, cough which does not go away, herpes (such as cold sore, shingles or genital sores). If you have an active infection, your doctor will delay your treatment with Ocrevus until your infection is gone.
- Progressive multifocal leukoencephalopathy (PML): Tell your doctor or nurse straight away if you or your care-giver think your MS is getting worse or if you notice any new symptoms. This is because of a very rare and life-threatening brain infection, called 'progressive multifocal leukoencephalopathy' (PML), can cause symptoms similar to those of MS. PML can occur in patients taking Ocrevus. Tell your partner or caregiver about your Ocrevus treatment. They might notice symptoms of PML that you do not, such as memory lapses, troubles thinking, difficulty walking, sight loss, changes in the way you talk, weakness on one side of your body, strength, or using your arms or legs.
- Hepatitis B virus (HBV) reactivation: Before starting treatment with Ocrevus, your healthcare provider will do blood tests to check for hepatitis B viral infection. If you have ever had hepatitis B virus infection, the hepatitis B virus may become active again during or after treatment with Ocrevus. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems including liver failure or death. Your healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop receiving Ocrevus.

Vaccinations

- Tell your doctor or nurse if you have recently been given, or might be given in the near future, any sort of vaccine.
- While you are being treated with Ocrevus, you should not be given some types of vaccine, called 'live' or 'live attenuated' vaccines (for example BCG for tuberculosis or vaccines against yellow fever).
- Talk to your doctor before you receive any non-live (inactivated) vaccines, including the seasonal flu vaccine. While you are being treated with Ocrevus, responses to non-live vaccines may be decreased. However, the impact on the effectiveness of the vaccine is not known.
- Your doctor will check if you need any vaccinations before you start treatment with Ocrevus. Any vaccinations should be given at least 6 weeks before you start treatment with Ocrevus.
- If you were pregnant while taking Ocrevus, talk to your doctor before vaccinating your newborn.

Weakened immune system

Ocrevus taken before or after other medicines that weaken the immune system could increase your risk of getting infections. If you have another disease which affects the immune system, you may not be able to receive Ocrevus.

Decreased immunoglobulins

Ocrevus may cause a decrease in some types of immunoglobulins (proteins in your blood that help your immune system fight infection). Your healthcare provider will do blood tests to check your blood immunoglobulin levels.

Depression and suicide

If you develop depression, depressed mood, or suicidal thoughts, contact your doctor right away. Symptoms could include, irritability (getting upset easily), depression (feeling unusually sad, feeling hopeless or bad about yourself), nervousness, anxiety, sleeping a lot more or a lot less than usual, feel tired or sleepy all the time, or thoughts of hurting yourself or suicide.

Others

Heart diseases and serious skin reactions can occur in patients taking other medicines like Ocrevus. Contact your doctor if you develop a wide-spread redness or blistering of the skin and the inside of the mouth.

Children and adolescents

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for children and adolescents under 18 years old.

Pregnancy

- Tell your doctor or nurse before being given Ocrevus if you are pregnant, think that you might be pregnant or are planning to have a baby. This is because Ocrevus may cross the placenta and affect your baby.
- Do not use Ocrevus if you are pregnant unless you have discussed this with your doctor. Your doctor will consider the benefit of you taking Ocrevus against the risk to your baby.

Contraception for women

If you are able to become pregnant (conceive), you must use contraception:

- During treatment with Ocrevus and
- For 6 months after your last infusion of Ocrevus.

Breast-feeding

Do not breast-feed while you are being treated with Ocrevus. This is because Ocrevus may pass into breast milk.

Driving and using machines

It is not known whether Ocrevus can affect you being able to drive or use any tools or machines. Your doctor will tell you whether your MS may affect your ability to drive or use tools and machines safely.

Risk of cancers (malignancies) including breast cancer

Follow your doctor's instructions about standard screening guidelines for breast cancer.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Ocrevus:

Tell your doctor if you are taking, have recently taken or might take any other medicines. In particular, tell your doctor if:

- You have ever taken, are taking or are planning to take medicines which affect your immune system - such as chemotherapy, immuno-suppressants or other treatments for MS. These medicines could affect your ability to fight infections in combination with Ocrevus.

- You are taking medicines for high blood pressure. This is because some people have a decrease in their blood pressure while being given Ocrevus. Your doctor may ask you to stop taking these medicines for 12 hours before each Ocrevus infusion.

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

How to take Ocrevus:

Medicines you will receive before you are given Ocrevus

Before you are given Ocrevus, you will receive other medicines to prevent or reduce possible side effects, such as infusion reactions.

You will receive corticosteroids before each infusion and anti-histamines and you may also receive medicines to reduce fever.

How Ocrevus is given

- Ocrevus will be given to you by a doctor or a nurse. It will be given as an infusion into a vein (called an intra-venous infusion or 'IV' infusion).
- You will be closely monitored while you are being given Ocrevus and for at least 1 hour after the infusion has been given. This is in case you experience any side effects such as infusion reactions. The infusion may be slowed, temporarily stopped or permanently stopped if you have an infusion reaction, depending on how serious it is (see **Other warnings you should know about** and **What are possible side effects from using Ocrevus?** for information about infusion reactions).

Usual dose:

You will be given a total dose of 600 mg of Ocrevus every 6 months.

- The first dose of Ocrevus will be a 300 mg infusion, followed 2 weeks later by a second 300 mg infusion. Each infusion will last about 2 hours and 30 minutes or longer.
- The following doses of Ocrevus will be given as one single 600 mg infusion. Each infusion will either last about 3 hours and 30 minutes or about 2 hours depending on the infusion rate prescribed by your healthcare professional.

Overdose:

If you think you, or a person you are caring for, have taken too much Ocrevus, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

What are possible side effects from using Ocrevus?

Like all medicines, Ocrevus can cause side effects, although not everybody gets them.

These are not all the possible side effects you may have when taking Ocrevus. If you experience any side effects not listed here, tell your healthcare professional. Please also see 7 Warnings and Precautions detailed in the Product Monograph (see **If you want more information about Ocrevus**).

Most side effects are mild to moderate but some may be serious. The following side effects have been reported with Ocrevus:

Infusion reactions

- **Infusion Reaction:** Infusion reactions are the most common side effect of Ocrevus treatment. In most cases, they were mild reactions but some serious reactions can happen.
- **Tell your doctor or nurse right away if you experience any signs or symptoms of an infusion reaction during the infusion or up to 24 hours after the infusion.**
- To reduce the risk of infusion reactions, your doctor or nurse will give you other medicines before each infusion of Ocrevus. Your doctor or nurse will also monitor you during the infusion and for at least one hour after the infusion has been given.

Immune

- Inflammation of the large bowel (colitis): Tell your healthcare professional if you have any symptoms of colitis, such as:
 - diarrhea (loose stools) or more frequent bowel movements than usual
 - stools that have blood or mucus
 - stomach-area (abdomen) pain.

Infections

- You might get infections more easily with Ocrevus. These infections are usually mild infections but serious infections can happen.
- **Tell your doctor or nurse straight away if you have any of these signs of infection during or after Ocrevus treatment.**
- Signs of serious herpes infection include:
 - changes in vision
 - severe or persistent headache
 - confusion
 - eye redness or eye pain
 - stiff neck.
- The following infections have been seen in patients treated with Ocrevus in MS.
 - Very common:** may affect more than 1 in 10 people
 - upper respiratory tract infection
 - common cold
 - flu.

Common: may affect up to 1 in 10 people

- sinus infection
- bronchitis (bronchial tube inflammation)
- infection of the stomach and bowel (gastroenteritis)
- respiratory tract infection
- viral infection
- herpes infection (cold sore or shingles)
- red and inflamed eye (conjunctivitis)
- skin infection (cellulitis).

Uncommon: may affect up to 1 in 100 people

- genital sores.

- Other side effects

Common: may affect up to 1 in 10 people

- problems sleeping
- cough
- a build-up of thick mucus in the nose, throat or chest.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Infections – fever or chills, cough which does not go away, herpes (such as cold sore, shingles and genital sores).		✓	
UNCOMMON			
Infusion Reactions – itchy skin, rash, hives, redness of the skin, flushing, low blood pressure, fever, tiredness, dizziness, headache, throat irritation or pain, shortness of breath, swelling of the throat, feeling sick or nausea, fast heart beat.		✓	
Depression and suicide - getting upset easily, feeling unusually sad, feeling hopeless or bad about yourself, nervousness, anxiety, sleeping a lot more or a lot less than usual, feel tired or sleepy all		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
the time, thoughts of hurting yourself or suicide.			
SEEN WITH OTHER MEDICATIONS SIMILAR TO Ocrevus			
Progressive multifocal leukoencephalopathy (PML), a rare brain infection - progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, changes in thinking, memory and orientation, confusion, personality changes.		✓	
Hepatitis B - mild fever, feeling of sickness, fatigue, loss of appetite, joint and/or abdominal pain and yellowing of whites of the eyes, skin and tongue.		✓	
Severe allergy (hypersensitivity) - itchy skin, rash, hives, redness of the skin, flushing, low blood pressure, fever, tiredness, dizziness, headache, throat irritation or pain, shortness of breath, swelling of the throat, feeling sick or nausea, fast heart beat.		✓	
Skin reactions - wide-spread redness or blistering of the skin and the inside of the mouth.		✓	
Serious heart problems - chest pain, fast heart rate or an irregular or uneven heart rate.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Ocrevus will be stored by the healthcare professionals at the hospital or clinic under the following conditions:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the outer carton and the vial label after 'EXP'. The expiry date refers to the last day of that month.
- Store in a refrigerator (2° - 8°C). Do not freeze. Keep the vials in the outer carton in order to protect from light.

Ocrevus must be diluted before it is given to you. Dilution will be done by a healthcare professional. It is recommended that the product is used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the healthcare professional and would normally not be longer than 24 hours at 2° - 8°C and 8 hours at room temperature.

Do not throw away any medicines via wastewater. This measure will help protect the environment.

If you want more information about Ocrevus:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (www.rochecanada.com), or by calling 1-888-762-4388.

This leaflet was prepared by Hoffmann-La Roche Limited.

Last Revised: JAN 09, 2023

©Copyright 2022, Hoffmann-La Roche Limited

OCREVUS® Registered trade-mark of F. Hoffmann-La Roche AG, used under license

All other trade-marks are the property of their respective owners.



Hoffmann-La Roche Limited
Mississauga, ON L5N 5M8