PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrOCREVUS®

Ocrelizumab for injection

Concentrate for intravenous infusion

300 mg/10 mL (30 mg/mL)

Selective Immunomodulator

OCREVUS® has been issued marketing authorization **without conditions** for the treatment of:

- adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features

OCREVUS® has been issued marketing authorization **with conditions**, pending the generation of additional data to further support the promising evidence of clinical benefit demonstrated in the PPMS pivotal study WA25046. 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 website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

- 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.

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.

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Date of Approval:
April 9, 2019

Submission Control No: 215767

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) policy for one of its indicated uses.

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 approved 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.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION
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.

OCREVUS® has been issued marketing authorization **without conditions** for the treatment of:

- adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical and imaging features.

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.

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 (alphabetical order): 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 30mg/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 breastfeeding or plan to breastfeed. 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.
- You 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 increases 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 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), which can cause symptoms similar to those of MS. PML can occur in patients taking other medicines like OCREVUS, including medicines used for treating MS. Tell your partner or care giver 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 which your doctor may need to investigate these symptoms.
- 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.

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
OCREVUS is not intended to be used in children and adolescents under 18 years old. This is because it has not yet been studied in this age group.

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 sections on **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 30 minutes or longer.
- The following doses of OCREVUS will be given as one single 600 mg infusion. Each infusion will last about 3 hours 30 minutes or longer.

Overdose:

If you think you have taken too much OCREVUS, contact your 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 feel when taking OCREVUS. If you experience any side effects not listed here, contact your healthcare professional. Please also see 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.

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.**
- 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)
  - **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. If you cannot reach your doctor seek immediate medical attention.	
	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 the time, thoughts of hurting yourself or suicide.		✓

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional. If you cannot reach your doctor seek immediate medical attention.	
	Only if severe	In all cases
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, talk to 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 (http://www.hc-sc.gc.ca/dhpmps/medeff/report-declaration/index-eng.php) 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^{o} - 8^{o}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.

Keep out of reach and sight of children.

If you want more information about OCREVUS:

- Talk to your healthcare professional
- Refer to the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information, available on the Health Canada website (http://hc-sec.gc.ca/index-eng.php); the manufacturer's website (www.rochecanada.com), or by calling 1-888-762-4388.

This leaflet was prepared by Hoffmann-La Roche Limited.

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