OCREVUS™ (ocrelizumab) IN MULTIPLE SCLEROSIS (MS)

Media Inquiries:
(650) 467-6800

OCREVUS™
ocrelizumab 300MG/10ML INJECTION FOR IV

About OCREVUS

OCREVUS™ (ocrelizumab) is a therapeutic monoclonal antibody that represents a different scientific approach to treating MS. It targets a type of immune cell called a CD20-positive B cell that plays a key role in the disease. OCREVUS is approved by the FDA to treat relapsing or primary progressive forms of multiple sclerosis (MS). OCREVUS is given once every six months by an intravenous (IV) infusion.[1]

- **FIRST AND ONLY** approved disease-modifying therapy for primary progressive multiple sclerosis (PPMS), a highly disabling form of MS[1,2]
- **FIRST AND ONLY** medicine approved to treat two types of MS: relapsing forms of MS (RMS) and PPMS[1]
- **FIRST AND ONLY** approved MS treatment to target CD20-positive B cells[1]

About Multiple Sclerosis

MS is a chronic neurological disease for which there is no cure, and over time will lead to some level of disability in most people.[3,4] The cause of MS is unknown. In people with MS, the immune system attacks the insulation around nerve cells in the brain, spinal cord and/or optic nerves, causing inflammation and potentially debilitating symptoms.[4] The majority of people living with MS either have a relapsing form or PPMS at the time of diagnosis.[5] Relapsing forms of MS are characterized by episodes of new or worsening symptoms (relapses) followed by periods of recovery.[6] PPMS is a highly disabling form of MS characterized by steadily worsening symptoms, usually without periods of improvement/remission.[6]

Important Safety Information

What is OCREVUS?

OCREVUS is a prescription medicine used to treat adults with relapsing or primary progressive forms of multiple sclerosis.

It is not known if OCREVUS is safe or effective in children.

Who should not receive OCREVUS?

Do not receive OCREVUS if you are a patient that has an active hepatitis B virus (HBV) infection.

Do not receive OCREVUS if you are a patient that has had a life threatening allergic reaction to OCREVUS. Tell your healthcare provider if you have had an allergic reaction to OCREVUS or any of its ingredients in the past.

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Please see the following pages and OCREVUS full Prescribing Information including Most Serious Side Effects for Important Safety Information.

About Multiple Sclerosis

APPROXIMATELY 400,000

PEOPLE IN THE US ARE LIVING WITH MS[7]

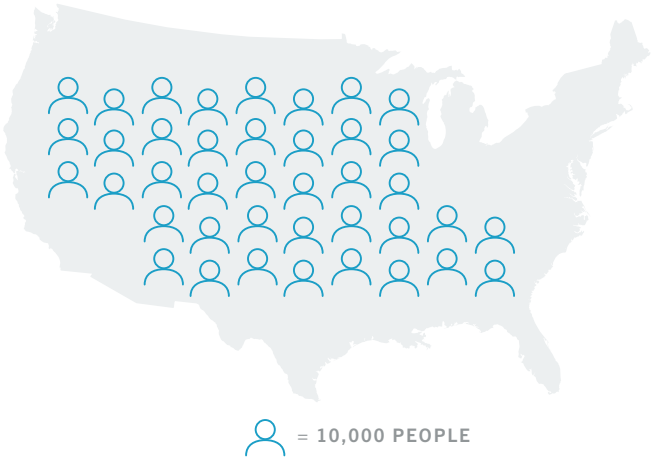
20–40

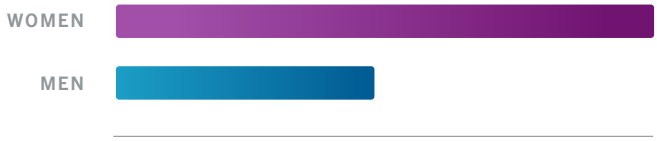
AGE RANGE IN WHICH MS IS COMMONLY DIAGNOSED[4]

RMS OCCURS AT LEAST

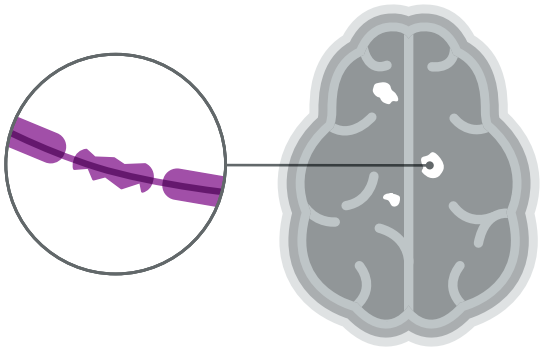
2x

AS FREQUENTLY IN WOMEN AS IN MEN[4]





OCCURRENCE OF RMS BY GENDER



People with all forms of MS experience **disease activity** – inflammation in the nervous system and permanent loss of nerve cells in the brain, spinal cord or optic nerves – even when their clinical symptoms aren't apparent or don't appear to be getting worse.[8]

Disease activity causes **lesions** in the brain, which can be measured with magnetic resonance imaging (MRI).[8]

Most people with MS continue to experience disease activity and worsening disability. An important goal of treating MS is to slow the progression of disability.[6]

Important Safety Information (continued)

What is the most important information I should know about OCREVUS?

OCREVUS can cause serious side effects, including:

- **Infusion reactions:** OCREVUS can cause infusion reactions that can be serious and require a patient to be hospitalized. Patients will be monitored during your infusion and for at least 1 hour after each infusion of OCREVUS for signs and symptoms of an infusion reaction. Patients should tell their healthcare provider or nurse if they get any of these symptoms: itchy skin, rash, hives, tiredness, coughing or wheezing, trouble breathing, throat irritation or pain, feeling faint, fever, redness on the face (flushing), nausea, headache, swelling of the throat, dizziness, shortness of breath, fatigue or fast heart beat.

  These infusion reactions can happen for up to 24 hours after your infusion. It is important that patients call their healthcare provider right away if they get any of the signs or symptoms listed above after each infusion.

  If a patient gets infusion reactions, their healthcare provider may need to stop or slow down the rate of your infusion.

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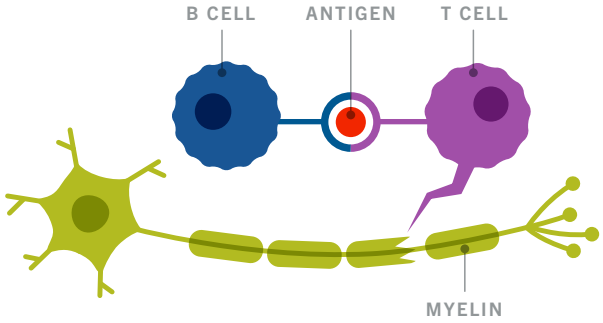
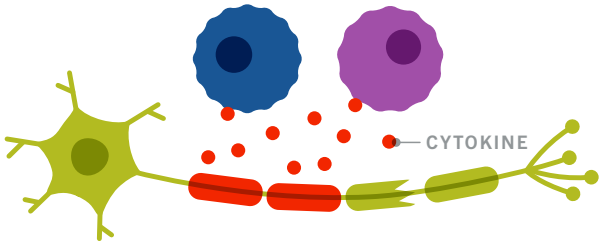
Please see the following pages and OCREVUS full Prescribing Information including Most Serious Side Effects for Important Safety Information.

About B Cells

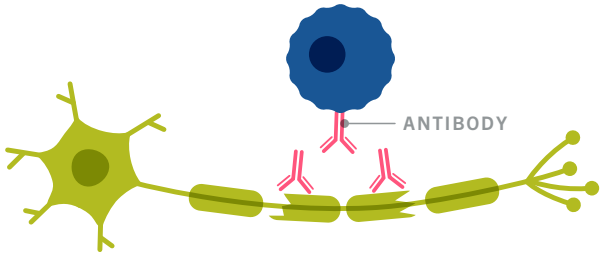
T cells have long been believed to be the culprit in MS. Pioneering science has shown **B cells** may also play a key role in MS in several ways:



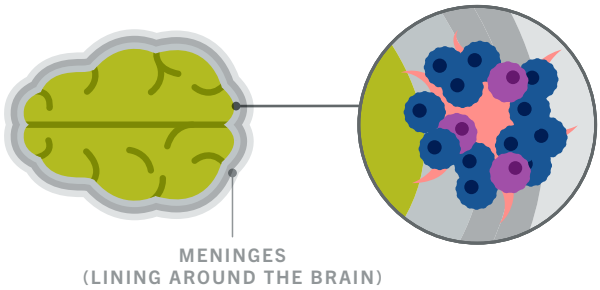
Activate other immune cells to attack the insulation and support around nerve cells (myelin)[9,10]



Release chemicals that stimulate inflammatory activity in the brain and spinal cord[11,12]

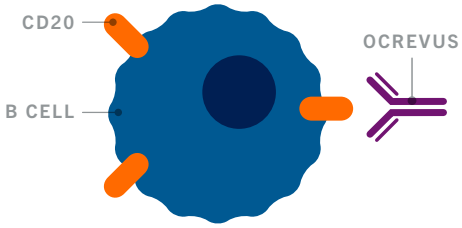


Produce antibodies that attack myelin and recruit other immune cells to attack myelin[13,14]

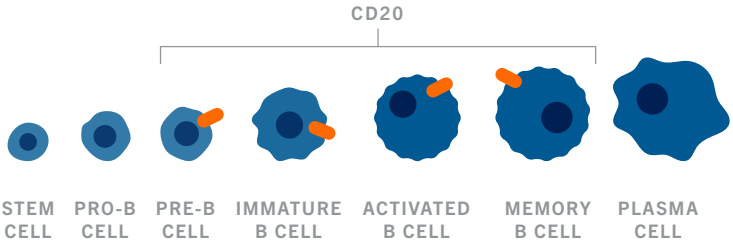


May form structures with other immune cells in the brain that sustain the immune system attack on nerve cells in certain types of MS[15,16]

How OCREVUS May Work (Proposed Mechanism of Action)[1]



OCREVUS is a humanized monoclonal antibody that is designed to target **CD20-positive B cells**.



Although the exact way OCREVUS works is not known, it is thought to work in MS by **decreasing certain B cells which have the CD20 protein on its surface**. Since the CD20 protein is not found on all B cells, other B cells may still be available to help your body fight infection and other illnesses.

Important Safety Information (continued)

- **Infection:**
  - OCREVUS increases a patient's risk of getting upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes infections. Patients should tell their healthcare provider if they have an infection or have any of the following signs of infection including fever, chills, a cough that does not go away, or signs of herpes (such as cold sores, shingles, or genital sores). These signs can happen during treatment or after a patient has received their last dose of OCREVUS. If a patient has an active infection, their healthcare provider should delay treatment with OCREVUS until the infection is gone.

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Please see the following pages and OCREVUS full Prescribing Information including Most Serious Side Effects for Important Safety Information.

OCREVUS Efficacy in MS[1]

The FDA approval of OCREVUS is based on positive results from three Phase III studies (OPERA I and OPERA II in RMS; ORATORIO in PPMS).

In RMS, OCREVUS was proven superior to Rebif®, a commonly used treatment, over two years:

OCREVUS reduced relapses per year by **nearly half**. Relapses were reduced by

46% IN OPERA I

47% IN OPERA II

COMPARED WITH REBIF (P<0.0001 AND P<0.0001)

OCREVUS was better at **slowing disability progression.** People taking OCREVUS were

40% LESS LIKELY

TO HAVE DISABILITY PROGRESSION COMPARED WITH REBIF (P=0.0006)*†

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

†Data prospectively pooled from Study 1 and Study 2.

OCREVUS more effectively reduced signs of **disease activity.** OCREVUS was superior at reducing **T1 gadolinium-enhancing lesions**, a sign of active inflammation, by

94% IN OPERA I

95% IN OPERA II

COMPARED WITH REBIF (P<0.0001 AND P<0.0001)

OCREVUS was superior at reducing total number of new and/or enlarging **T2 hyperintense lesions**, a measure of the total amount of lesions, both old and new, by

77% IN OPERA I

83% IN OPERA II

COMPARED WITH REBIF (P<0.0001 AND P<0.0001)

Important Safety Information (continued)

- **Infection (continued):**
  - **Progressive Multifocal Leukoencephalopathy (PML):** Although no cases have been seen with OCREVUS treatment, PML may happen with OCREVUS. PML is a rare brain infection that usually leads to death or severe disability. Patients should tell their healthcare provider right away if you have any new or worsening neurologic signs or symptoms. These may include problems with thinking, balance, eyesight, weakness on 1 side of your body, strength, or using your arms or legs.
  - **Hepatitis B virus (HBV) reactivation:** Before starting treatment with OCREVUS, a patient's healthcare provider will do blood tests to check for hepatitis B viral infection. If a patient has 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. A patient's healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop receiving OCREVUS.

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Please see the following pages and OCREVUS full Prescribing Information including Most Serious Side Effects for Important Safety Information.

For PPMS, in a clinical study compared with a placebo, OCREVUS was the first and only treatment to:

Significantly slow disability progression over a median treatment duration of three years. People taking OCREVUS were

24% LESS LIKELY

TO HAVE DISABILITY PROGRESSION FOR 3 MONTHS (P=0.0321)‡

‡Defined as an increase of 1.0 point or more from the baseline EDSS score for patients with baseline score of 5.5 or less, or an increase of 0.5 or more when the baseline score is more than 5.5.

Reduce the volume of T2 hyperintense lesion volume, a measure of the total amount of lesions, both old and new, over 120 weeks

.39 REDUCTION

WITH OCREVUS

.79 INCREASE

WITH PLACEBO (P<0.0001)

Reduce the risk of 20 percent worsening on the timed 25-foot walk, a measure of walking speed, confirmed at 12 weeks by

25%

WITH OCREVUS COMPARED WITH PLACEBO

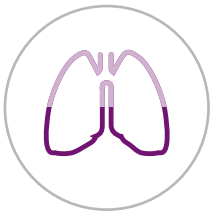
Study-Specific Safety in MS[1]

In the OPERA I and OPERA II studies, OCREVUS adverse reactions in at least 5% of RMS patients and higher than Rebif were:

UPPER RESPIRATORY TRACT INFECTIONS (40%)

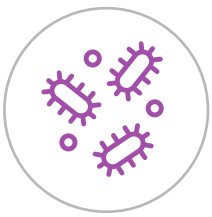
INFUSION REACTIONS (34%)

DEPRESSION (8%)



LOWER RESPIRATORY TRACT INFECTIONS (8%)

BACK PAIN (6%)



HERPES VIRUS ASSOCIATED INFECTIONS (6%)

PAIN IN EXTREMITY (5%)

Important Safety Information (continued)

- **Infection (continued):**
  - **Weakened immune system:** OCREVUS taken before or after other medicines that weaken the immune system could increase your risk of getting infections.

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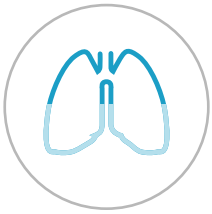
Please see the following pages and OCREVUS full Prescribing Information including Most Serious Side Effects for Important Safety Information.

In the ORATORIO study, OCREVUS adverse reactions in at least 5% of PPMS patients and higher than placebo were:

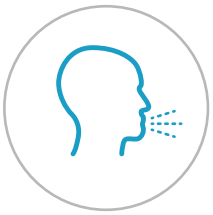


UPPER RESPIRATORY TRACT INFECTIONS (49%)

INFUSION REACTIONS (40%)

SKIN INFECTIONS (14%)

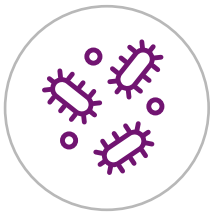
LOWER RESPIRATORY INFECTIONS (10%)



COUGH (7%)

DIARRHEA 6%

SWELLING IN THE LIMBS (EDEMA PERIPHERAL) (6%)



HERPES VIRUS ASSOCIATED INFECTIONS (5%)

Possible serious side effects with OCREVUS include infusion reactions, infections and malignancies.

Important Safety Information (continued)

Before receiving OCREVUS, patients should tell their healthcare provider about all of their medical conditions, including if they:

- have ever taken, take, or plan to take medicines that affect your immune system, or other treatments for MS.
- have ever had hepatitis B or are a carrier of the hepatitis B virus.
- have had a recent vaccination or are scheduled to receive any vaccinations. **A patient should receive any required vaccines at least 6 weeks before you start treatment with OCREVUS**. A patient **should not receive** certain vaccines (called 'live' or 'live attenuated' vaccines) while they are being treated with OCREVUS and until their healthcare provider tells them that their immune system is no longer weakened.
- are pregnant, think that they might be pregnant, or plan to become pregnant. It is not known if OCREVUS will harm an unborn baby. Patients 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. Patients should talk to their healthcare provider about the best way to feed your baby if the patient takes OCREVUS.

What are the possible side effects of OCREVUS?

OCREVUS may cause serious side effects, including:

- Risk of cancers (malignancies) including breast cancer. Follow your healthcare provider's instructions about standard screening guidelines for breast cancer.

Most common side effects include infusion reactions and infections.

These are not all the possible side effects of OCREVUS.

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Please see the following pages and OCREVUS full Prescribing Information including Most Serious Side Effects for Important Safety Information.

Important Safety Information (continued)

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

For more information, go to www.OCREVUS.com or call 1-844-627-3887

For additional safety information, please see the full Prescribing Information and Medication Guide.

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1 OCREVUS (ocrelizumab) Prescribing Information. Genentech, Inc. 2016.
2 National Multiple Sclerosis Society. Treating PPMS. Available at http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Primary-progressive-MS/Treating-Primary-Progressive-MS.
3 MS International Federation. What is MS? Available at http://www.msif.org/about-ms/what-is-ms/.
4 National Institutes of Health-National Institute of Neurological Disorders and Stroke. (2015). Multiple Sclerosis: Hope Through Research. Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Multiple-Sclerosis-Hope-Through-Research.
5 Multiple Sclerosis International Federation. Types of MS. Available at https://www.msif.org/about-ms/types-of-ms/.
6 National Multiple Sclerosis Society. Types of MS. Available at http://www.nationalmssociety.org/What-is-MS/Types-of-MS.
7 Tullman MJ. Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. Am J Manag Care. 2013;19(suppl 2):S15-S20.
8 Erbayat A, et al. (2013). Reliability of classifying multiple sclerosis disease activity using magnetic resonance imaging in a multiple sclerosis clinic. JAMA Neurol, 70(3):338-44.
9 Constant SL. (1999). B lymphocytes as antigen-presenting cells for CD4+ T cell priming in vivo. J Immunol, 162(10):5695-5703.
10 Crawford A, et al. (2006). Primary T cell expansion and differentiation in vivo requires antigen presentation by B cells. J Immunol, 176(6):3498-3506.
11 Bar-Or A, et al. (2010). Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? Ann Neurol, 67(4):452-461.
12 Duddy M, et al. (2007). Distinct effector cytokine profiles of memory and naive human B cell subsets and implication in multiple sclerosis. J Immunol, 178(10):6092-6099.
13 Genain CP, et al. (1999). Identification of autoantibodies associated with myelin damage in multiple sclerosis. Nat Med, 5(2):170-175.
14 Storch MK, et al. (1998). Multiple sclerosis: in situ evidence for antibody- and complement-mediated demyelination. Ann Neurol, 43(4):465-471.
15 Serafini B, et al. (2004). Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. Brain Pathol, 14(2):164-174.
16 Magliozzi R, et al. (2010). A Gradient of neuronal loss and meningeal inflammation in multiple sclerosis. Ann Neurol, 68(4):477-493.