

Latest information as of November 2021

COVID-19 VACCINES AND OCREVUS

Immune response to vaccines and timing of non-live vaccine administration

Patient safety is Genentech's highest priority.

We are closely monitoring the evolving situation to best understand how COVID-19 and vaccines will affect people who are treated with OCREVUS. While there are no conclusive data to answer all the possible questions and concerns, we are committed to actively reporting any findings and ensure information is shared in an accurate and timely manner.

Genentech is dedicated to studying COVID-19 and vaccines in patients treated with OCREVUS and providing information as it becomes available.

**You may reach out to your Genentech Representative or
Medical Science Liaison for more information.**

Important Safety Information

Indications

OCREVUS is indicated for the treatment of:

- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- Primary progressive MS, in adults.

Contraindications

OCREVUS is contraindicated in patients with active hepatitis B virus infection and in patients with a history of life-threatening infusion reaction to OCREVUS.

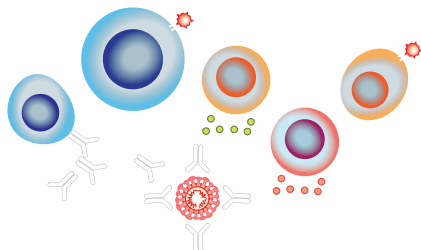
For additional safety information, please [click here](#) for full Prescribing Information and Medication Guide.



Immune response to COVID-19 vaccines^{1,2}

Immune response to COVID-19 vaccines in patients taking OCREVUS is currently being studied.

Immune response for COVID-19 vaccines rely on both B- and T-cell responses



- **Memory B cells** (humoral immunity) interact with T cells to produce antibodies and help establish memory cells
- **T cells** (cellular immunity) help to activate the immune response and clear infected cells

The immune response to COVID-19 vaccines is composed of a complex interaction between B and T cells.

Limitations of serological measurements³⁻⁵

Current methods of B-cell and T-cell activity measurement have limitations

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| <ul style="list-style-type: none">• B cell: COVID-19 antibody tests—there are a variety of tests with different sensitivities and that detect different antibodies | <ul style="list-style-type: none">• T cell: T-cell assays—not widely accessible outside of research environments |
| <ul style="list-style-type: none">• Tests were developed for diagnostic purposes, not to detect immune status• There is no agreed upon B- or T-cell assay or response cutoff that is associated with protection | |

CDC does not currently recommend antibody testing to evaluate immunity from COVID-19 vaccination, the need for vaccination, or the need to quarantine after a close contact with someone who has COVID-19. In addition, while the available vaccines are effective in protecting people from getting infected and severely ill, breakthrough cases are expected in the general population.

Please visit [cdc.gov](https://www.cdc.gov) for more information.

Important Safety Information

Warnings and Precautions

Infusion Reactions

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, 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 34-40%, 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.

For additional safety information, please [click here](#) for full Prescribing Information and Medication Guide.



Vaccine response in OCREVUS patients: the VELOCE study^{6,7}

The VELOCE study examined the effects of OCREVUS on humoral responses to selected non-live vaccines in RMS patients.

Study design

- Phase IIIb, randomized, open-label study
- Studied 102 patients with RMS (18 to 55 years of age)
- 2:1 randomization
- **Non-live vaccines and neoantigen studied:** tetanus toxoid (TT)-containing vaccine, 23-valent pneumococcal polysaccharide vaccine (23-PPV) (Pneumovax[®]), 13-valent pneumococcal conjugate vaccine (13-PCV) (Pevnar[®]), seasonal influenza (inactivated), keyhole limpet hemocyanin (KLH)

Vaccine administration in OCREVUS arm*

- Vaccinations were administered at various timepoints (depending on vaccine type)[†] starting 12 weeks after OCREVUS initiation and ending 4 weeks prior to the next scheduled OCREVUS dose
- The study was not designed to identify the optimal time point for vaccination, and different vaccines may have different optimal times for administration

The OCREVUS Prescribing Information states that OCREVUS may interfere with the effectiveness of non-live vaccines.

Conclusions

- Patients could mount a humoral response, although attenuated, to clinically relevant non-live vaccines and the neoantigen, KLH
- The clinical significance of this attenuation for vaccine effectiveness and durability of response requires further study
- Vaccination with non-live vaccines even after OCREVUS initiation is likely to generate a vaccine response in most patients and may be considered when vaccination is deemed useful
- Whenever possible, vaccination requirements should be completed before the initiation of OCREVUS

Limitations

- Did not study cell-mediated response, only antibody response
- Did not study the safety and effectiveness of live or live-attenuated vaccines
- Did not study COVID-19 vaccines

*Vaccinations were administered on Day 1 in the control arm.

[†]All patients in the OCREVUS arm received TT-containing vaccine at Week 12, 23-PPV vaccine at Week 16, and a 3-dose course of neoantigen KLH vaccine at Weeks 12, 16, and 20. In addition, 33 OCREVUS patients (OCR1 treatment group) received a 13-PCV vaccine at Week 20 and 35; OCREVUS patients (OCR2 treatment group) received seasonal influenza vaccine at various timepoints between Weeks 12 and 20 based on regional recommendations.

Important Safety Information

Warnings and Precautions

Infusion Reactions continued

Observe 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.

For additional safety information, please [click here](#) for full Prescribing Information and Medication Guide.



Timing of non-live vaccine administration⁶

OCREVUS PI non-live vaccine guidance



- Whenever possible, vaccines should be administered at least 2 weeks prior to starting OCREVUS
- OCREVUS may interfere with the effectiveness of non-live vaccines

NMSS COVID-19 vaccine guidance⁸

- The National MS Society (NMSS) has issued COVID-19 vaccine guidance that is generally consistent with the timing of non-live vaccine administration in the VELOCE study and the OCREVUS Prescribing Information
- The NMSS has also issued guidance on additional doses of COVID-19 vaccines for immunocompromised patients

For the latest NMSS COVID-19 vaccine guidance, please visit [nationalmssociety.org](https://www.nationalmssociety.org).

Vaccination decisions, including timing, should be made between a patient and HCP.

Important Safety Information

Warnings and Precautions

Infusion Reactions (continued)

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. 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.

Infections

A higher proportion of OCREVUS-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of OCREVUS-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of OCREVUS-treated patients experienced one or more infections compared to 68% of patients on placebo. OCREVUS increased the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections. OCREVUS was not associated with an increased risk of serious infections in MS patients. Delay OCREVUS administration in patients with an active infection until the infection is resolved.

Respiratory Tract Infections

A higher proportion of OCREVUS-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 33% of REBIF-treated patients, and 8% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PPMS trial, 49% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 43% of patients on placebo and 10% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 9% of patients on placebo. The infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections and bronchitis.

For additional safety information, please [click here](#) for full Prescribing Information and Medication Guide.



Important Safety Information

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in OCREVUS-treated patients than in REBIF-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 to moderate in severity. In the placebo-controlled (PPMS) clinical trial, oral herpes was reported more frequently in the OCREVUS-treated patients than in the patients on placebo (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 postmarketing 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.

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. Although no cases of PML were identified in OCREVUS clinical trials, JC virus infection resulting in PML has been observed in patients treated with other anti-CD20 antibodies and other MS therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). 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 (per USPI).

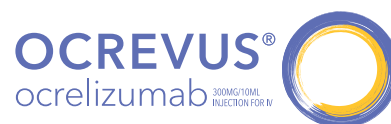
Hepatitis B Virus (HBV) Reactivation

Hepatitis B reactivation has been reported in MS patients treated with OCREVUS in the postmarketing setting. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with OCREVUS. Do not administer OCREVUS to patients with active HBV confirmed by positive results for HBsAg and anti-HB 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.

Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants

When initiating OCREVUS after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS, consider the potential for increased immunosuppressive effect. OCREVUS has not been studied in combination with other MS therapies.

For additional safety information, please [click here](#) for full Prescribing Information and Medication Guide.



Important Safety Information

Vaccinations

Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of OCREVUS for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of OCREVUS for non-live vaccines. OCREVUS may interfere with the effectiveness of non-live vaccines. 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.

Vaccination of Infants Born to Mothers Treated with OCREVUS During Pregnancy

In infants of mothers exposed to OCREVUS during pregnancy, do not administer live or live-attenuated vaccines before confirming the recovery of B-cell counts as measured by CD19+ B-cells. Depletion of B-cells in these infants may increase the risks from live or live-attenuated vaccines.

You may administer non-live vaccines, as indicated, prior to recovery from B-cell depletion, but should consider assessing vaccine immune responses, including consultation with a qualified specialist, to assess whether a protective immune response was mounted.

Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with OCREVUS treatment. The pooled data of OCREVUS clinical studies (RMS and PPMS) and their open-label extensions (up to approximately 7 years of exposure) have shown an association between decreased levels of immunoglobulin G (IgG<LLN) and increased rates of serious infections. Monitor the levels of quantitative serum immunoglobulins during OCREVUS treatment and after discontinuation of treatment, until B-cell repletion, and especially in the setting of recurrent serious infections. Consider discontinuing OCREVUS therapy in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

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 and none of 668 females treated with REBIF or placebo. Patients should follow standard breast cancer screening guidelines.

Use in Specific Populations

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to OCREVUS during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-872-4370 or visiting www.ocrevuspregnancyregistry.com.

There are no adequate data on the developmental risk associated with use of OCREVUS in pregnant women. There are no data on B-cell levels in human neonates following maternal exposure to OCREVUS. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. OCREVUS is a humanized monoclonal antibody of

For additional safety information, please [click here](#) for full Prescribing Information and Medication Guide.



Important Safety Information

Lactation

There are no data on the presence of ocrelizumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. 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.

Females and Males of Reproductive Potential

Women of childbearing potential should use effective contraception while receiving OCREVUS and for 6 months after the last infusion of OCREVUS.

Most Common Adverse Reactions

RMS: The most common adverse reactions ($\geq 10\%$ and $> \text{REBIF}$): upper respiratory tract infections and infusion reactions.

PPMS: The most common adverse reactions ($\geq 10\%$ and $> \text{placebo}$): upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.

Please report cases of OCREVUS patients who have experienced adverse events to one of the following:

- our US Drug Safety group at **888-835-2555**
- FDA's MedWatch program at www.FDA.gov/medwatch or **(800) FDA-1088**

For additional safety information, please [click here](#) for full Prescribing Information and Medication Guide.

References: **1.** Flanagan KL, et al. *Front Immunol.* 2020;11:579250. **2.** Abbas AK, Lichtman AH, Pillai S, eds. *Cellular and Molecular Immunology.* 10th ed. Elsevier; 2021. **3.** Centers for Disease Control and Prevention. Interim guidelines for COVID-19 antibody testing. <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html>. Accessed October 2021. **4.** Malipiero G, et al. *Immunol Res.* 2021;1-8. **5.** Centers for Disease Control and Prevention. COVID-19 vaccine breakthrough case investigation and reporting. <https://www.cdc.gov/vaccines/covid-19/health-departments/breakthrough-cases.html>. Accessed October 2021. **6.** OCREVUS [prescribing information]. South San Francisco, CA: Genentech, Inc; 2021. **7.** Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. *Neurology.* 2020;95(14):e1999-2009. **8.** National MS Society. <https://www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/covid-19-vaccine-guidance/Timing-MS-Medications-with-COVID-19-Vaccines>.