OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

OCREVUS ZUNOVO™ ocrelizumab & hyaluronidase-ocsq Subcutaneous injection 920mg

DOSING and ADMINISTRATION GUIDE

Indications

OCREVUS and OCREVUS ZUNOVO are 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

Treatment with ocrelizumab is contraindicated in patients with active hepatitis B virus infection and in patients with a history of life-threatening administration reactions to ocrelizumab. OCREVUS ZUNOVO is also contraindicated in patients with a history of hypersensitivity to ocrelizumab, hyaluronidase, or any component of OCREVUS ZUNOVO.

Select Important Safety Information

The warnings and precautions for ocrelizumab are infusion reactions (OCREVUS) or injection reactions (OCREVUS ZUNOVO) and infections, which include respiratory tract infections, herpes, hepatitis B virus (HBV) reactivation, and a warning for progressive multifocal leukoencephalopathy (PML). Additional warnings are possible increased risk of immunosuppressant effects with other immunosuppressants, reduction in immunoglobulins, malignancies, and immune-mediated colitis.

Please see additional Important Safety Information on pages 25-27, and for additional safety information, please click here for full OCREVUS Prescribing Information and Medication Guide. For OCREVUS ZUNOVO, click here for full Prescribing Information and Medication Guide.

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ABOUT OCREVUS [IV] AND OCREVUS ZUNOVO

2X-yearly HCP-administered OCREVUS—now with the choice and flexibility of 2 route-of-administration options

OCREVUS
(ocrelizumab) injection, for intravenous use

The first dose of OCREVUS [IV] is split between 2 treatments, for a total of 3 treatments in the first year.[1]

OCREVUS ZUNOVO
(ocrelizumab & hyaluronidase-ocsq) injection, for subcutaneous use

OCREVUS ZUNOVO has no split first dose.[2]

Genentech is committed to helping ensure your practice is prepared to administer OCREVUS [IV] and OCREVUS ZUNOVO.

Following the prescribing decision, there are clinical and logistical differences to keep in mind when administering these medicines. Refer to the OCREVUS [IV] ADMINISTRATION and OCREVUS ZUNOVO ADMINISTRATION sections of this guide for specific information on dosing and administration logistics.

OCREVUS ZUNOVO has different dosage and administration instructions than intravenous ocrelizumab.

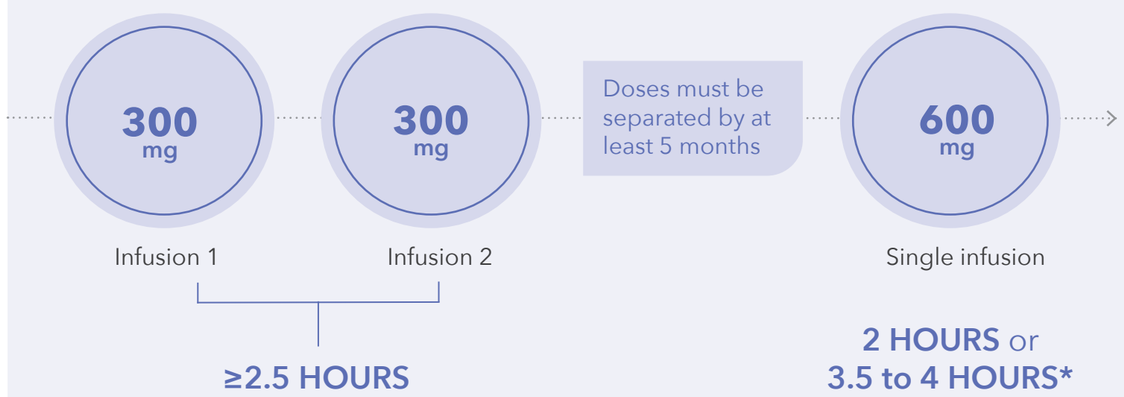
OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

OCREVUS ZUNOVO™ ocrelizumab & hyaluronidase-ocsq Subcutaneous injection 920mg

OCREVUS [IV] DOSE & DOSING SCHEDULE[1]

OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

Shorter 2-hour infusion option after initial dose*



***Infusion time may take longer if the infusion is interrupted or slowed.**

Shorter 2-hour infusion is available after the initial dose for patients who have not experienced serious infusion reactions with any previous OCREVUS [IV] infusion.†

Administering OCREVUS[1]

Premedication (IV)	Infusion	Post-dose monitoring‡
30 to 60 minutes	2 hours or 3.5 to 4 hours*	60 minutes

*Infusion time may take longer if the infusion is interrupted or slowed. No change in premedication, dose, formulation, or post-treatment monitoring between infusion timing options.

†Per the ENSEMBLE Plus study protocol, serious infusion reactions included those that were fatal or life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability, or were deemed to be medically significant by the trial investigator.[1]

‡For all doses, post-infusion monitoring with access to appropriate medical support to manage severe infusion reactions for at least one hour after infusion is recommended.

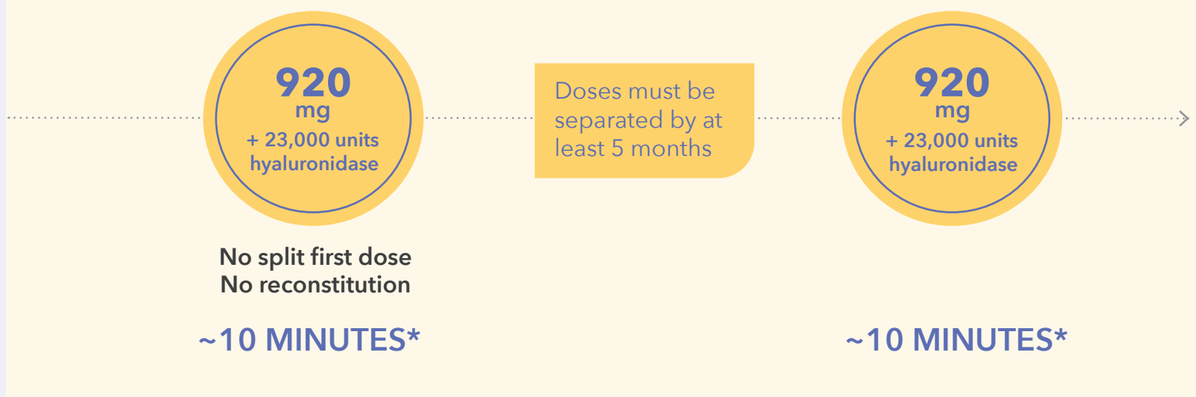
Keep in mind the differences in the initial dose and overall administration time when scheduling your patients.

Please see additional Important Safety Information on pages 25-27, and for additional safety information, please click here for full OCREVUS Prescribing Information and Medication Guide. For OCREVUS ZUNOVO, click here for full Prescribing Information and Medication Guide.

OCREVUS ZUNOVO DOSE & DOSING SCHEDULE[2]

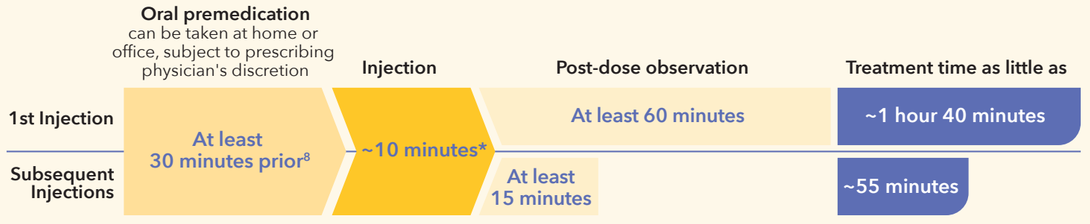
OCREVUS ZUNOVO™ ocrelizumab & hyaluronidase-ocsq Subcutaneous injection 920mg

~10-minute, HCP-administered subcutaneous injection in the abdomen only[2]



The active excipient hyaluronidase works in a transient and reversible way to increase the dispersion area and allow large fluid volumes to be administered subcutaneously.[2]

Administering OCREVUS ZUNOVO



DELAYED OR MISSED DOSES OF OCREVUS [IV] OR OCREVUS ZUNOVO

If a planned infusion of OCREVUS [IV] or injection of OCREVUS ZUNOVO is missed, administer it 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.[2]

***Injection time may take longer if the injection is interrupted.**

†For all doses, it is recommended that post-injection monitoring with access to appropriate medical support to manage severe injection reactions for at least 1 hour after the first injection and at least 15 minutes after subsequent injections.[2]

HOW OCREVUS (ocrelizumab) IS SUPPLIED AND STORED

HOW OCREVUS IS **SUPPLIED**[1]

	OCREVUS infusion is a **preservative-free**, sterile, clear or slightly opalescent, and colorless to pale brown solution.
	OCREVUS is supplied as a carton containing one 300-mg/10-mL (30 mg/mL) **single-dose vial**.

HOW OCREVUS IS **STORED**

	Store OCREVUS vials at 2°C to 8°C (36°F to 46°F).
	Keep the vial in the outer carton to protect from light.
	Do not freeze or shake.

PATIENT PREINFUSION COUNSELING[1]

Advise the patient to read the FDA-approved Medication Guide. Inform patients of the following:

CONTRACEPTION AND PREGNANCY

Females of childbearing potential should **use effective contraception** while receiving OCREVUS (ocrelizumab) and for 6 months after the last injection. If they are pregnant or plan to become pregnant, they should **inform their healthcare provider**.

INFUSION REACTIONS

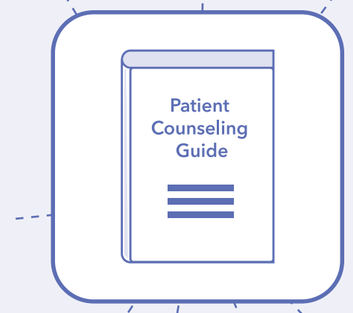
Inform patients about the signs and symptoms of infusion reactions and that **infusion reactions can occur up to 24 hours after infusion**. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion reactions.

MALIGNANCIES

Advise patients that an increased risk of malignancy, including breast cancer, may exist with OCREVUS. Advise patients that they should **follow standard breast cancer screening guidelines**.

IMMUNE-MEDIATED COLITIS

Advise patients to promptly **contact their healthcare provider if they experience any signs and symptoms of colitis**, including diarrhea, abdominal pain, and blood in stool.



INFECTION

Advise patients to contact their healthcare provider for any signs of infection during treatment or after the last dose. Signs include fever, chills, constant cough, dysuria, or signs of herpes, such as cold sores, shingles, or genital sores.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Inform patients that PML has occurred in patients who received OCREVUS and that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. **Inform the patient of the importance of contacting their healthcare provider if they develop any symptoms suggestive of PML** and inform the patient that 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.

VACCINATION

Patients should complete necessary **live or live-attenuated vaccinations at least 4 weeks prior to initiation of OCREVUS** and, when possible, **at least 2 weeks prior for non-live vaccines**. Administration of live-attenuated or live vaccines is not recommended during OCREVUS treatment and until B-cell recovery.

REDUCTION IN IMMUNOGLOBULINS

Inform patients that **OCREVUS may cause a decrease in immunoglobulins** and that their healthcare provider will do blood tests to check their blood immunoglobulin levels.

OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

Please see additional Important Safety Information on pages 25-27, and for additional safety information, please click here for full OCREVUS Prescribing Information and Medication Guide. For OCREVUS ZUNOVO, click here for full Prescribing Information and Medication Guide.

ASSESSMENTS AND RECOMMENDED PREMEDICATION[1]

PRIOR TO THE FIRST DOSE OF OCREVUS (ocrelizumab)

- Perform **hepatitis B virus screening**
- Test for **quantitative serum immunoglobulins**
- **Complete necessary vaccinations** (at least 4 weeks prior to live or live-attenuated vaccines and, when possible, at least 2 weeks prior for non-live vaccines)

BEFORE EACH OCREVUS INFUSION

- **Determine whether there is an active infection.** In case of active infection, delay infusion of OCREVUS until the infection resolves

RECOMMENDED PREMEDICATION

	Premedicate 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.
	Premedicate with an **antihistamine (eg, diphenhydramine) approximately 30-60 minutes prior to each OCREVUS infusion** to further reduce the frequency and severity of infusion reactions. The addition of an antipyretic (eg, acetaminophen) may also be considered.

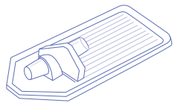
PREPARATION AND STORAGE OF THE DILUTE SOLUTION FOR INFUSION[1]

	OCREVUS (ocrelizumab) must be prepared by a healthcare professional using **aseptic technique**.
	Visually inspect for particulate matter and discoloration prior to administration. **Do not use the solution if discolored 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.
	Prior to the start of the intravenous infusion, the content of the **infusion bag should be at room temperature**.
	Use the prepared solution immediately. **If not used immediately, store up to 24 hours in the refrigerator** at 2°C to 8°C (36°F to 46°F) and 8 hours at room temperature up to 25°C (77°F), which includes infusion time. In the event an intravenous infusion cannot be completed the same day, discard the remaining solution.
	No incompatibilities between OCREVUS and **polyvinyl chloride (PVC) or polyolefin (PO) bags** and intravenous administration sets have been observed.

Please see additional Important Safety Information on pages 25-27, and for additional safety information, please click here for full OCREVUS Prescribing Information and Medication Guide. For OCREVUS ZUNOVO, click here for full Prescribing Information and Medication Guide.

ADMINISTRATION[1]

OCREVUS (ocrelizumab) is administered as an intravenous infusion through a dedicated line

	**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.
	Administer the diluted infusion solution through a dedicated line using an infusion set with a **0.2 or 0.22 micron in-line filter**.
	Observe patients for **at least one hour** after the completion of the infusion.
	Inform patients that infusion reactions can occur **up to 24 hours** after infusion.

See page 13 for information about what to do in the event of infusion reactions.

INFUSION RATE TABLES[1]

INITIAL DOSE (600 MG) ADMINISTERED AS 2 INFUSIONS

Infusion 1
Day 1
300 mg in 250 mL

2.5-HOUR INFUSION: Start at a rate of 30 mL/hr. Thereafter, increase the rate by **30 mL/hr** every 30 minutes to a maximum of 180 mL/hr. **Each infusion will last 2.5 hours or longer.***

Infusion 2
Day 15
300 mg in 250 mL

Start	at 30 min	at 60 min	at 90 min	at 120 min	at 150 min
30 mL/hr	60 mL/hr	90 mL/hr	120 mL/hr	150 mL/hr	180 mL/hr

SUBSEQUENT DOSES† (600 MG) ONCE EVERY 6 MONTHS

Single infusion
600 mg in 500 mL

3.5- TO 4-HOUR INFUSION: Start at a rate of 40 mL/hr. Thereafter, increase the rate by **40 mL/hr** every 30 minutes to a maximum of 200 mL/hr. **Each infusion will last 3.5 hours or longer.***

Start	at 30 min	at 60 min	at 90 min	at 120 min	after 120 min
40 mL/hr	80 mL/hr	120 mL/hr	160 mL/hr	200 mL/hr	continue 200 mL/hr

2-HOUR SHORTER INFUSION
Available for patients without prior serious infusion reactions with any OCREVUS infusion. See page 12 for the definition of serious infusion reactions.

Start at a rate of 100 mL/hr. Thereafter, increase the rate as shown below to a maximum of 300 mL/hr. **Each infusion will last 2 hours or longer.***

Start	at 15 min	at 30 min	at 60 min	after 60 min
100 mL/hr	200 mL/hr	250 mL/hr	300 mL/hr	continue 300 mL/hr

*Infusion time may be longer if the infusion is interrupted or slowed.

Solutions of OCREVUS for intravenous infusion are prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride injection to a final drug concentration of approximately 1.2 mg/mL.

†Administer the first subsequent dose 6 months after infusion 1 of the initial dose.

OCREVUS® ocrelizumab 300MG/10ML INJECTION FOR IV

INFUSION REACTIONS ASSOCIATED WITH OCREVUS

In pooled data from OPERA I/II for OCREVUS, the rate of infusion reactions was 34.9%

Symptoms of infusion reactions include, but are not limited to:

Skin
- Pruritus
- Rash
- Urticaria
- Erythema

Circulatory system
- Hypotension
- Flushing
- Tachycardia

Respiratory system
- Bronchospasm
- Dyspnea
- Pharyngeal or laryngeal edema
- Throat irritation
- Oropharyngeal pain

Other
- Pyrexia
- Fatigue
- Headache
- Dizziness
- Nausea
- Anaphylaxis

Severity of infusion reactions[3]

- **Mild** infusion reactions are asymptomatic or have mild symptoms
- **Moderate** infusion reactions are minimal, local, and do not require invasive intervention
- **Severe** infusion reactions are medically significant but not immediately life-threatening
- **Life-threatening** infusion reactions put a patient at immediate risk of death at the time of the event. Urgent intervention is needed

Infusion reactions can occur up to 24 hours after infusion.

RATE MODIFICATIONS IN THE EVENT OF INFUSION REACTIONS[1]

Modify the infusion rate in response to the severity of the reaction

For infusion reactions that are not life-threatening, **the change in infusion rate will increase the duration of the infusion but not the total dose**.

Mild to Moderate	**Reduce the infusion rate to half the rate at the onset of the infusion reaction and maintain the reduced rate for at least 30 minutes.** If this rate is tolerated, increase the rate as described in the Infusion Rate Tables on page 11. This change in rate will increase the total duration of the infusion but not the total dose.
Severe	**Immediately interrupt the infusion and administer appropriate supportive treatment, as necessary.** 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. If this rate is tolerated, increase the rate as described in the Infusion Rate Tables on page 11. This change in rate will increase the total duration of the infusion but not the total dose.
Life-Threatening	**Immediately stop and permanently discontinue OCREVUS** if there are signs of a life-threatening or disabling infusion reaction. Provide appropriate supportive treatment.

Reminder: Premedication can reduce the frequency and severity of infusion reactions.

INFUSION REACTIONS IN THE OPERA AND ORATORIO TRIALS (controlled period)

3.5- to 4-hour infusion of OCREVUS (ocrelizumab): 99.7% of patients did not experience a serious infusion reaction (IR) in the OPERA and ORATORIO studies (controlled period)[1]

- IRs were highest with the first infusion. Of the IRs that occurred, most were mild to moderate in severity[4]
- 0.3% of patients with multiple sclerosis (MS) treated with OCREVUS experienced infusion reactions that were serious, some requiring hospitalization

OPERA I and II Relapsed Multiple Sclerosis (RMS)[1]

Two randomized, double-blind, double-dummy, active comparator–controlled clinical trials of identical design vs Rebif® in 1656 patients (OCREVUS: OPERA I [n=410], OPERA II [n=417]; Rebif: OPERA I [n=411], OPERA II [n=418]) with RMS treated for 96 weeks. Both studies included patients who had experienced ≥1 relapse within the prior year, or 2 relapses within the prior 2 years, and had an Expanded Disability Status Scale (EDSS) score between 0 and 5.5. The primary outcome of both studies was the annualized relapse rate.

ORATORIO[5]

A randomized, double-blind, placebo-controlled clinical trial in patients with primary progressive multiple sclerosis. Patients were randomized 2:1 to receive either OCREVUS 600 mg (n=488) or placebo (n=244) as two 300-mg intravenous infusions 2 weeks apart every 24 weeks for at least 120 weeks. Selection criteria required a baseline EDSS of 3 to 6.5 and a score of 2 or greater for the EDSS pyramidal functional system due to lower extremity findings. Neurological assessments were conducted every 12 weeks. A magnetic resonance imaging scan was obtained at baseline and at Weeks 24, 48, and 120.

INFUSION REACTIONS IN THE ENSEMBLE PLUS STUDY

No life-threatening, fatal, or serious infusion reactions occurred with OCREVUS in the ENSEMBLE PLUS sub-study[1]

The proportions of patients with infusion reactions were similar between the 2 infusion protocols[1]

24.4%
2-HOUR INFUSION

23.3%
3.5- TO 4-HOUR INFUSION

- 2-hour infusion is available for patients **who have not experienced serious infusion reactions** with any previous OCREVUS infusion[1]
- Overall, in randomized doses, 27.1% of the patients in the 2-hour infusion group and 25.0% of the patients in the 3.5-hour infusion group reported mild or moderate infusion reactions; two infusion reactions were severe in intensity, with 1 severe infusion reaction (0.3%) reported in 1 patient in each group in this sub-study[1]

ENSEMBLE PLUS evaluated the safety of OCREVUS 2-hour infusion

A prospective, multicenter, randomized, double-blind, controlled, parallel-arm sub-study of 580 patients with early relapsing remitting multiple sclerosis (RRMS). 81% (469/579) of treated patients received a single randomized infusion of OCREVUS for the primary analysis.[1]

Per the ENSEMBLE protocol, serious infusion reactions included those that were fatal or life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability, or were deemed to be medically significant by the trial investigator.[6]

Please see additional Important Safety Information on pages **25-27**, and for additional safety information, please click here for full OCREVUS **Prescribing Information** and **Medication Guide**. For OCREVUS ZUNOVO, click here for full **Prescribing Information** and **Medication Guide**.

OCREVUS ZUNOVO: THE ONLY ~10-MINUTE,* 2X-YEARLY, HCP-ADMINISTERED aCD20 SUBCUTANEOUS INJECTION[2]

***Does not include all aspects of the treatment. Actual injection time may vary.**

Provides additional CHOICE and FLEXIBILITY to help meet the needs of your practice and patients

Convenient ~10-minute,* 2X-yearly, HCP-administered injection with[2]:

- **NO** split first dose
- **NO** reconstitution
- **NO** IV infusion–specific supplies needed

Consider for patients with MS who[7-9]:

- Want a non-IV option or have poor venous access
- Prefer a ~10-minute* injection
- Could benefit from an HCP-administered aCD20 to help monitor adherence

Experiential demonstration of OCREVUS ZUNOVO injection for medical staff available to build familiarity and confidence in appropriate administration.

aCD20=anti-CD20; IV=intravenous; MS=multiple sclerosis.

Please see additional Important Safety Information on pages 25-27, and for additional safety information, please click here for full OCREVUS Prescribing Information and Medication Guide. For OCREVUS ZUNOVO, click here for full Prescribing Information and Medication Guide.

HOW OCREVUS ZUNOVO IS SUPPLIED AND STORED[2]

HOW OCREVUS ZUNOVO IS **SUPPLIED**

	OCREVUS ZUNOVO injection for subcutaneous use is a **preservative-free**, sterile, clear to slightly opalescent, and colorless to pale brown solution.
	OCREVUS ZUNOVO is supplied in a carton containing one vial of 920-mg ocrelizumab and 23,000-units/mL hyaluronidase per 23-mL (40 mg and 1,000 units/mL) **no-reconstitution required, single-dose vial. Do not dilute**.

HOW OCREVUS ZUNOVO IS **STORED**

	Store OCREVUS ZUNOVO vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.
	Do not freeze or shake.
	If necessary, OCREVUS ZUNOVO can be removed and placed back into the refrigerator. **The total combined time out of the refrigerator of the unopened OCREVUS ZUNOVO vial must not exceed 12 hours at 25°C (77°F)**.

OCREVUS ZUNOVO™
ocrelizumab & hyaluronidase-ocsq
Subcutaneous injection 920mg

PREADMINISTRATION CHECKLIST[2]

Before administering OCREVUS ZUNOVO subcutaneous injection, do the following:

PERFORM/VERIFY **ASSESSMENTS**

Prior to the first dose:

- Perform **hepatitis B virus screening**
- Test for **quantitative serum immunoglobulins**
- **Complete necessary vaccinations** (4 weeks prior to OCREVUS ZUNOVO administration for live or live-attenuated vaccines and, when possible, 2 weeks prior for non-live vaccines)

Prior to every dose:

- **Determine whether there is an active infection.** In case of active infection, delay injection of OCREVUS ZUNOVO until the infection resolves

CONDUCT **PREINJECTION PATIENT COUNSELING**

See page 19 for more information.

CHECK THAT **SUPPLIES** ARE AVAILABLE

Supplies for subcutaneous injection may include:

- 21-gauge transfer needle to draw up solution from vial
- 24-26-gauge butterfly/winged subcutaneous infusion set to administer the drug
- Optional syringe pump in lieu of manual push. See page 21 for more information

NOTE: OCREVUS ZUNOVO is compatible with polypropylene, polycarbonate, polyethylene, stainless steel, polyvinylchloride, and polyurethane.

INSPECT MEDICATION

- **Check the vial labels** to ensure that the drug being prepared and administered is OCREVUS ZUNOVO and not OCREVUS (ocrelizumab)
- Visually inspect for particulate matter and discoloration prior to administration. **Do not use the vial if particulates or discoloration is present. Do not shake.** Discard any unused portion remaining in the vial

ADMINISTER/VERIFY RECOMMENDED PREMEDICATION

- Oral premedications are recommended at least 30 minutes before each injection with 20 mg of dexamethasone (or an equivalent corticosteroid) and an antihistamine (eg, desloratadine). Additionally, a post-dose observation of at least 60 minutes for the first injection and at least 15 minutes for subsequent injections is recommended to reduce the risk of local and systemic reactions
- The **addition of an antipyretic** (eg, acetaminophen) may also be considered

Please see additional Important Safety Information on pages 25-27, and for additional safety information, please click here for full OCREVUS Prescribing Information and Medication Guide. For OCREVUS ZUNOVO, click here for full Prescribing Information and Medication Guide.

PATIENT PREINJECTION COUNSELING[2]

Advise the patient to read the FDA-approved Medication Guide. Inform patients of the following:

CONTRACEPTION AND PREGNANCY

Females of childbearing potential should use **effective contraception** while receiving OCREVUS ZUNOVO and for 6 months after the last injection. If they are pregnant or plan to become pregnant, they should **inform their healthcare provider**.

INJECTION REACTIONS

Inform patients that the signs and symptoms of injection reactions can be local or systemic, and that **injection reactions can occur up to 24 hours after the injection**. Advise patients to contact their healthcare provider immediately for signs or symptoms of injection reactions.

MALIGNANCIES

Advise patients that an increased risk of malignancy, including breast cancer, may exist with OCREVUS ZUNOVO. Advise patients that they should **follow standard breast cancer screening guidelines**.

IMMUNE-MEDIATED COLITIS

Advise patients to promptly **contact their healthcare provider if they experience any signs and symptoms of colitis**, including diarrhea, abdominal pain, and blood in stool.

INFECTION

Advise patients **to contact their healthcare provider for any signs of infection** during treatment or after the last dose. Signs include fever, chills, constant cough, or signs of herpes, such as cold sores, shingles, or genital sores.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Inform patients that PML has occurred in patients who received intravenous ocrelizumab and may happen with OCREVUS ZUNOVO. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. **Instruct the patient of the importance of contacting their healthcare provider if they develop any symptoms suggestive of PML** and inform the patient that 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.

VACCINATION

Patients should complete necessary **live or live-attenuated vaccinations at least 4 weeks** prior to initiation of OCREVUS ZUNOVO and, when possible, **at least 2 weeks prior for non-live vaccines**. Administration of live-attenuated or live vaccines is not recommended during OCREVUS ZUNOVO treatment and until B-cell recovery.

PML=progressive multifocal leukoencephalopathy; SC=subcutaneous.

OCREVUS ZUNOVO™
ocrelizumab & hyaluronidase-ocsq
Subcutaneous injection 920mg

PREPARATION AND STORAGE[2]

PREPARING THE SYRINGE FOR SUBCUTANEOUS INJECTION

Immediate use is recommended.

	Remove the vial from refrigerated storage and **allow the solution to acclimate to room temperature (25°C [77°F]).**
	**Attach the transfer needle to the syringe.**
	**Withdraw the entire contents of OCREVUS ZUNOVO solution from the vial** with a syringe and transfer needle. A 21-gauge needle is recommended.
	Remove the transfer needle from the syringe and **attach the 24-26–gauge winged/butterfly set**. Use a subcutaneous (SC) infusion set with a priming volume **NOT to exceed 0.8 mL** for administration.
	**Prime the SC infusion line** with the OCREVUS ZUNOVO solution to eliminate the air in the infusion line. Stop before the fluid reaches the needle.
	**Ensure the syringe contains exactly 23 mL** of OCREVUS ZUNOVO solution. Expel any excess volume from the syringe.
	**Administer immediately** to avoid needle clogging. **DO NOT store the prepared syringe that has been attached to the already-primed SC infusion set.**

STORING THE SYRINGE IF DOSE IS NOT USED IMMEDIATELY

	Use aseptic technique to withdraw the entire OCREVUS ZUNOVO contents from the vial into the syringe to account for the dose volume (23 mL) plus the priming volume. Replace the transfer needle with a syringe closing cap. **DO NOT attach a winged SC infusion set.**
	**The closed syringe can be refrigerated (2°C to 8°C [36°F to 46°F]) for up to 72 hours** followed by 8 hours at ambient temperatures ≤25°C (77°F) in diffuse daylight.
	If the prepared syringe was stored at 2°C to 8°C (36°F to 46°F), **allow the syringe to acclimate to room temperature prior to administration**.

OCREVUS ZUNOVO contains no preservative. Immediate use is recommended.

ADMINISTRATION

ADMINISTERING OCREVUS ZUNOVO FOR SUBCUTANEOUS INJECTION

OCREVUS ZUNOVO should be administered via subcutaneous injection by a healthcare professional. **Do not administer OCREVUS ZUNOVO intravenously**.

	Administer 23 mL of OCREVUS ZUNOVO subcutaneously in the abdomen in approximately 10 minutes. **DO NOT administer the remaining priming volume in the SC infusion set to the patient.**
	The recommended injection site should be the abdomen, **except for 2 inches (5 cm) around the navel**.
	OCREVUS ZUNOVO injections **should not be administered into areas where the skin is red, bruised, tender, or hard or areas where there are moles or scars.**

Administration with syringe pump in lieu of manual injection (optional).[10]

Information on syringe pump from OCARINA II clinical trial

Syringe pump:

- The B. Braun Perfusor® Space Syringe Pump was used in the OCARINA II clinical trial
- Genentech does not endorse or recommend any particular pumps
- Please refer to the syringe pump manufacturer's instructions for the most up-to-date information and to ensure appropriate use of any drug or device

Syringe pump specifications:

- Occlusion limit compatible with **30-mL to 60-mL** syringe size
- Flow rate capability of **1 mL to 5 mL/min**

In the OCARINA II study, the instructions for programming the pump called for the occlusion alarm to be set to greater than 6 psi, **high**, or the **least sensitive** equivalent setting.

Please see additional Important Safety Information on pages 25-27, and for additional safety information, please click here for full OCREVUS Prescribing Information and Medication Guide. For OCREVUS ZUNOVO, click here for full Prescribing Information and Medication Guide.

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INJECTION REACTIONS ASSOCIATED WITH OCREVUS ZUNOVO[2]

OCREVUS ZUNOVO can cause injection reactions, which can be either local or systemic

Common symptoms of local injection reactions at the injection site include:

- Erythema
- Pain
- Swelling
- Pruritus

Common symptoms of systemic injection reactions include:

- Headache
- Nausea

In case of injection reactions:

- **Life-threatening injection reactions:** Immediately and permanently stop OCREVUS ZUNOVO treatment. **The patient should receive appropriate supportive treatment**
- **Less severe injection reactions:** The injection should be interrupted immediately, and the patient should receive symptomatic treatment. **The injection should be completed at the healthcare provider's discretion and only after all symptoms have resolved**

Incidence of injection reactions decreased after first injection.

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RATE OF INJECTION REACTIONS IN OCARINA II

Local and systemic reactions

- AMONG THE 118 PATIENTS WHO RECEIVED ONLY OCREVUS ZUNOVO THROUGHOUT THE STUDY[2,8]:
  - All injection reactions were of mild to moderate severity
  - Incidence of injection reactions decreased after the first injection[8]
  - All injection reactions that occurred were resolved[8]
  - There were no injection reactions that led to treatment discontinuation[8]

FIRST INJECTION:

47% had at least 1 local injection reaction

11% had at least 1 systemic injection reaction

- 49% (58/118) of patients exhibited injection reactions
- All injection reactions were mild (73%) or moderate (27%) severity[2]
- The majority of patients with injection reactions (83%) had injection reactions occur within 24 hours after the end of the injection rather than during the injection (19%)[2]
- Median duration of symptoms were 3 days and 3.5 days for systemic and local injection reactions, respectively[2]
- All patients recovered from injection reactions, of which 26% required symptomatic treatment[2]

SUBSEQUENT INJECTIONS (DOSE 2 TO 4):

32%-43% had local injection reactions

4%-7% had systemic injection reactions

- All injection reactions were of mild (80% to 90%) or moderate (10% to 20%) severity[11]

- GRADES OF **INJECTION REACTIONS**[12]
  - Grade 1 was defined as tenderness with or without associated symptoms (eg, warmth, erythema, itching); Grade 2 was defined as pain, lipodystrophy, edema, phlebitis; Grade 3 was defined as ulceration or necrosis, severe tissue damage, or operative intervention indicated; Grade 4 was defined as life-threatening consequences or urgent intervention indicated; Grade 5 was defined as death

OCARINA II is a multicenter, randomized, open-label, parallel-arm trial conducted to evaluate the pharmacokinetics (PK), pharmacodynamics, safety and immunogenicity of OCREVUS ZUNOVO compared with intravenous ocrelizumab and designed to demonstrate noninferiority of treatment with OCREVUS ZUNOVO vs intravenous ocrelizumab based on the primary PK endpoint of area under the concentration-time curve (AUC) up to Week 12 post-injection/infusion (AUC_{W1-12}).[2]

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THE PROPOSED MECHANISM OF ACTION FOR OCRELIZUMAB

Directed against CD20-expressing B cells[1,2,13-15]

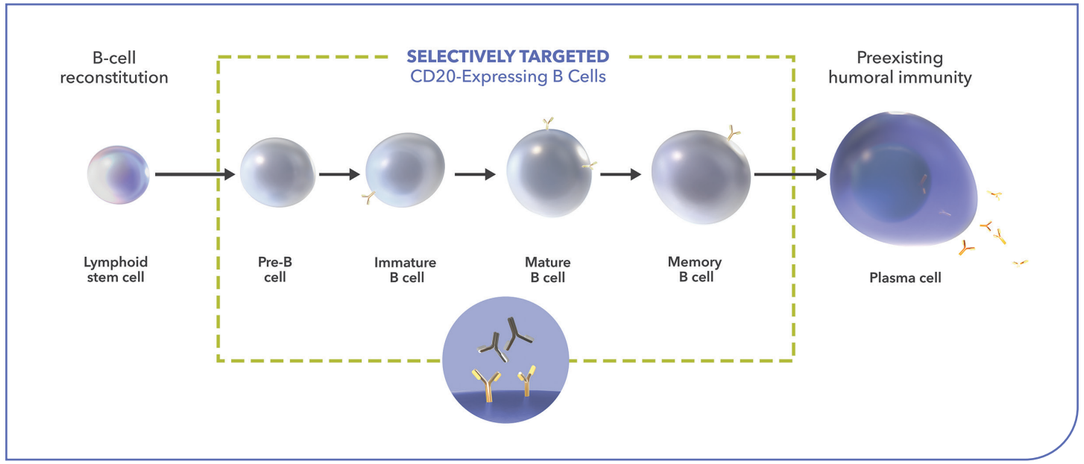

Image adapted from Krumbholz M et al. *Nat Rev Neurol*. 2012;8(11):613-623.[15]

OCREVUS (ocrelizumab) and OCREVUS ZUNOVO contain ocrelizumab, a recombinant **humanized monoclonal antibody directed against CD20-expressing B cells**. Lymphoid stem cells and plasma cells do not express CD20 and therefore are not directly targeted by OCREVUS [IV] or OCREVUS ZUNOVO.[13]

The precise mechanisms through which OCREVUS [IV] and OCREVUS ZUNOVO exert their therapeutic clinical effects in relapsing multiple sclerosis (RMS) and relapsing remitting multiple sclerosis (RRMS) are not fully elucidated but are presumed to involve immunomodulation through **selective binding to CD20-expressing B cells**. Following cell surface binding to B lymphocytes, OCREVUS [IV] and OCREVUS ZUNOVO result in antibody-dependent cellular cytolysis and complement-mediated lysis.[1,2]

OCREVUS ZUNOVO also contains hyaluronidase, an active excipient that works in a transient and reversible way to increase the dispersion area and allow large fluid volumes to be administered subcutaneously.[2]

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IMPORTANT SAFETY INFORMATION

Indications

OCREVUS and OCREVUS ZUNOVO are 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

Treatment with ocrelizumab is contraindicated in patients with active hepatitis B virus infection and in patients with a history of life-threatening administration reactions to ocrelizumab. OCREVUS ZUNOVO is also contraindicated in patients with a history of hypersensitivity to ocrelizumab, hyaluronidase, or any component of OCREVUS ZUNOVO.

Important Safety Information

Warnings and Precautions

Injection Reactions (OCREVUS ZUNOVO) OR Infusion Reactions (OCREVUS)

OCREVUS ZUNOVO can cause injection reactions, which can be local or systemic. Common symptoms of local injection reactions reported by patients treated with OCREVUS ZUNOVO in multiple sclerosis (MS) clinical trials included erythema, pain, swelling, and pruritus. Common symptoms of systemic injection reactions reported by patients included headache and nausea. In an open-label, active-controlled trial, injection reactions were more frequently reported with the first injection; 49% of patients experienced an injection reaction with the first injection.

In OCREVUS MS clinical trials, the incidence of infusion reactions in patients [who received methylprednisolone (or an equivalent steroid) and possibly other pre-medication to reduce the risk of infusion reactions prior to infusion] was 34% to 40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of intravenous ocrelizumab-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization. Symptoms of infusion reactions 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.

Monitor OCREVUS ZUNOVO patients during and after injections. 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 administration reactions can occur during or within 24 hours of treatment.

Reducing the Risk and Managing Injection or Infusion Reactions

For OCREVUS ZUNOVO, administer oral pre-medication (e.g., dexamethasone or an equivalent corticosteroid, and an antihistamine) at least 30 minutes prior to each OCREVUS ZUNOVO injection to reduce the risk of injection reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered.

For OCREVUS, 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.

Management recommendations depend on the type and severity of the reaction. For life-threatening reactions, immediately and permanently stop OCREVUS ZUNOVO or OCREVUS and administer appropriate supportive treatment. For less severe OCREVUS ZUNOVO injection reactions, the injection should be interrupted immediately, and the patient should receive symptomatic treatment. The injection should be completed at the healthcare provider's discretion and only after all symptoms have resolved. For less severe OCREVUS infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

Infections

Serious, including life-threatening or fatal, bacterial, viral, parasitic and fungal infections have been reported in patients receiving ocrelizumab. An increased risk of infections (including serious and fatal bacterial, fungal, and new or reactivated viral infections) has been observed in patients during and following completion of treatment with anti-CD20 B-cell depleting therapies.

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 was not associated with an increased risk of serious infections in MS patients in controlled trials.

Ocrelizumab increases the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections. Delay administration of ocrelizumab in patients with an active infection until the infection has 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

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IMPORTANT SAFETY INFORMATION (continued)

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

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 ocrelizumab. Serious herpes virus infections may occur at any time during treatment with ocrelizumab. Some cases were life-threatening.

If serious herpes infections occur, treatment with ocrelizumab should be discontinued or withheld until the infection has resolved, and appropriate treatment should be administered.

Hepatitis B Virus Reactivation
Hepatitis B virus (HBV) reactivation has been reported in MS patients treated with ocrelizumab 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 ocrelizumab. Do not administer ocrelizumab 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 treatment with ocrelizumab after an immunosuppressive therapy or initiating an immunosuppressive therapy after ocrelizumab-containing products, consider the potential for increased immunosuppressive effect. Treatment with ocrelizumab has not been studied in combination with other MS therapies.

Vaccinations
Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ocrelizumab treatment for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ocrelizumab treatment for non-live vaccines. Ocrelizumab may interfere with the effectiveness of non-live vaccines. The safety of immunization with live or live-attenuated vaccines following treatment with ocrelizumab 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 Ocrelizumab Products During Pregnancy
In infants of mothers exposed to ocrelizumab 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 you should consider assessing vaccine immune responses, including consultation with a qualified specialist, to assess whether a protective immune response was mounted.

Progressive Multifocal Leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with MS treated with ocrelizumab in the postmarketing setting. PML is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically occurs only in patients who are immunocompromised, and that usually leads to death or severe disability. PML has occurred in ocrelizumab-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 risk of PML prior to or concomitantly with ocrelizumab and did not have any known ongoing systemic medical conditions resulting in compromised immune system function.

JCV infection resulting in PML has also been observed in patients treated with other anti-CD20 antibodies and other MS therapies.

At the first sign or symptom suggestive of PML, withhold treatment with ocrelizumab-containing products and perform an appropriate diagnostic evaluation. 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.

Magnetic resonance imaging (MRI) findings may be apparent before clinical signs or symptoms of PML. Monitoring with MRI for signs consistent with PML may be useful, and any suspicious findings should lead to further investigation to allow for an early diagnosis of PML, if present. If PML is confirmed, treatment with ocrelizumab should be discontinued.

Reduction in Immunoglobulins
As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with ocrelizumab 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 treatment with ocrelizumab and after discontinuation of treatment, until B-cell repletion, and especially in the setting of recurrent serious infections. Consider discontinuing treatment with ocrelizumab 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 ocrelizumab 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.

Immune-Mediated Colitis
Immune-mediated colitis, which can present as a severe and acute-onset form of colitis, has been reported in patients receiving ocrelizumab in the postmarketing 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 ocrelizumab 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.

Use in Specific Populations

Pregnancy
There are no adequate data on the developmental risk associated with use of ocrelizumab in pregnant women. There are no data on B-cell levels in human neonates following maternal exposure to ocrelizumab-containing products. However, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. Ocrelizumab is a humanized monoclonal antibody of an immunoglobulin G1 subtype and immunoglobulins are known to cross the placental barrier.

Lactation
There are no data on the presence of ocrelizumab or hyaluronidase 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 ocrelizumab and any potential adverse effects on the breastfed infant from ocrelizumab or from the underlying maternal condition.

Females and Males of Reproductive Potential
Women of childbearing potential should use effective contraception while receiving ocrelizumab and for 6 months after the last dose of ocrelizumab. Instruct patients that if they are pregnant or plan to become pregnant while taking OCREVUS or OCREVUS ZUNOVO, they should inform their healthcare provider.

Most Common Adverse Reactions
In patients treated with OCREVUS:

- **RMS:** The most common adverse reactions (≥10% and >REBIF): upper respiratory tract infections and infusion reactions.
- **PPMS:** The most common adverse reactions (≥10% and >placebo): upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.

The most common adverse reaction observed with OCREVUS ZUNOVO in patients with RMS and PPMS was injection reactions (incidence of 49%).

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please click here for full OCREVUS Prescribing Information and Medication Guide. For OCREVUS ZUNOVO, click here for full Prescribing Information and Medication Guide.

References: 1. OCREVUS [prescribing information]. South San Francisco, CA: Genentech, Inc. 2024. **2.** OCREVUS ZUNOVO [prescribing information]. South San Francisco, CA: Genentech, Inc. 2024. **3.** Hauser SL, Bar-Or A, Comi G, et al; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. Supplementary Appendix. *N Engl J Med*. 2017;376(3):221-234. doi:10.1056/NEJMoa1601277 **4.** De Seze J, Arnold DJ, Bar-Or A, et al; OPERA I, OPERA II and ORATORIO clinical investigators. Infusion-related reactions with ocrelizumab in relapsing multiple sclerosis and primary progressive multiple sclerosis. Poster presented at: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); September 14-17, 2016; London, United Kingdom. Poster P720. **5.** Montalban X, Hauser SL, Kappos L, et al; ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209-220. doi:10.1056/NEJMoa1606468 **6.** Data on file. Genentech, Inc. October 2020. **7.** Armenteros-Yeguas V, Gárate-Echenique L, Tomás-López MA, et al. Prevalence of difficult venous access and associated risk factors in highly complex hospitalised patients. *J Clin Nurs*. 2017;26(23-24):4267-4275. doi:10.1111/jocn.13750 **8.** Data on file. Genentech, Inc. March 2023. **9.** Gold R, Schmidt S, Deisenhammer F, et al. Real-world evidence and patient preference for subcutaneous versus intravenous natalizumab in the treatment of relapsing-remitting multiple sclerosis—initial results from the observational SISTER study. *Ther Adv Neurol Disord*. 2024;77:1-19. doi:10.1177/17562864241241382 **10.** Data on file. Genentech, Inc. November 2023. **11.** Data on file. Genentech, Inc, September 2024. **12.** Data on file. Genentech, Inc. March 2023. **13.** Hauser SL, Bar-Or A, Comi G, et al; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med*. 2017;376(3):221-234. doi:10.1056/NEJMoa1601277 **14.** Baker D, Marta M, Pryce G, Giovannoni G, Schmierer K. Memory B cells are major targets for effective immunotherapy in relapsing multiple sclerosis. *EBioMedicine*. 2017;16:41-50. doi:10.1016/j.ebiom.2017.01.042 **15.** Krumbholz M, Derfuss T, Hohlfeld R, Meinl E. B cells and antibodies in multiple sclerosis pathogenesis and therapy. *Nat Rev Neurol*. 2012;(8):613-632. doi:10.1038/nrneurol.2012.203

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No matter which formulation you choose, you can expect the same commitment to patient support.

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Select Important Safety Information

The warnings and precautions for ocrelizumab are infusion reactions (OCREVUS) or injection reactions (OCREVUS ZUNOVO) and infections, which include respiratory tract infections, herpes, hepatitis B virus (HBV) reactivation, and a warning for progressive multifocal leukoencephalopathy (PML). Additional warnings are possible increased risk of immunosuppressant effects with other immunosuppressants, reduction in immunoglobulins, malignancies, and immune-mediated colitis.

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