OCREVUS ZUNOVO™
ocrelizumab & hyaluronidase-ocsq
Subcutaneous injection 920mg/23,000 units

The **ONLY** ~10-minute, 2X-yearly, HCP-administered subcutaneous injection[1]

WHAT TO EXPECT WITH **OCREVUS ZUNOVO®**

OCREVUS ZUNOVO for the Treatment of Relapsing Multiple Sclerosis (RMS) and Primary Progressive MS (PPMS)

Indications

OCREVUS ZUNOVO 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

Treatment with OCREVUS ZUNOVO 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 OCREVUS ZUNOVO are injection reactions 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, immune-mediated colitis, and liver injury.

Please see additional safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

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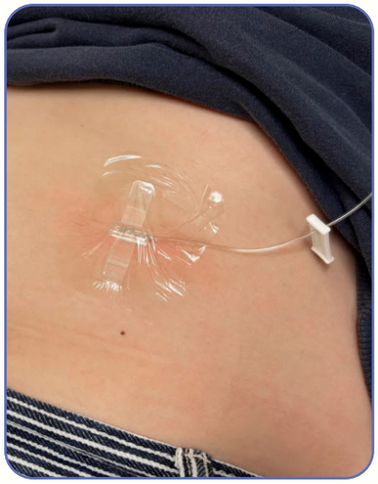
Subcutaneous injection 920mg/23,000 units

OCREVUS ZUNOVO® is a 2X-yearly, ~10-minute injection[1]



Actual OCREVUS ZUNOVO patient, used with permission.

	1st dose **(no split dose)**[1]	All subsequent doses[1]
Oral Premedication	**At least 30 min prior**	**At least 30 min prior**
Injection*	**~10 min**	**~10 min**
Post-Injection Monitoring†	**At least 60 min**	**At least 15 min**
Overall Time	**~1 hr 40 min**	**~55 min**

equal to ~1.5 Tbsp

920-mg ocrelizumab + 23,000 units hyaluronidase
Single 23-mL injection in abdomen with a pump or a syringe for **~10 minutes** every 6 months[1]

*Injection time may take longer if the treatment is interrupted or slowed.[1]
†For all doses, post-injection observation with access to appropriate medical support to manage severe injection reactions after injection is recommended.[1]

PRIOR TO FIRST DOSE[1]:

- Perform hepatitis B virus screening
- Test for quantitative serum immunoglobulins
- Complete necessary vaccinations (≥4 weeks prior for live or live-attenuated vaccines and, when possible, ≥2 weeks prior for non-live vaccines)
- Obtain serum aminotransferases (ALT and AST), alkaline phosphatase, and bilirubin levels

PRIOR TO EVERY DOSE[1]:

- Assess for active infection
- Administer pre-medication: dexamethasone (or an equivalent corticosteroid) and an antihistamine (eg, desloratadine)

Select Important Safety Information

Injection Reactions
OCREVUS ZUNOVO can cause injection reactions. Management recommendations for injection reactions depend on the type and severity of the reaction. Permanently discontinue OCREVUS ZUNOVO if a life-threatening or disabling injection reaction occurs.

Infections
Serious, including life-threatening or fatal, bacterial, viral, parasitic and fungal infections have occurred with ocrelizumab. An increased risk of serious infections has been observed in patients who have received anti-CD20 B-cell depleting therapies. Delay OCREVUS ZUNOVO administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with OCREVUS ZUNOVO and after discontinuation, until B-cell repletion.

Please see additional safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

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Safety profile consistent with OCREVUS® (ocrelizumab) with the exception of injection reactions[1,2]

OCREVUS ZUNOVO: ALL-EXPOSURE* SAFETY PROFILE (WEEK 24)[2]

Patients with ≥1 event, n (%)	RMS/PPMS OCREVUS ZUNOVO 920 mg (n=118)
Adverse events†	87 (73.7)
Serious adverse events	3 (2.5)
Infections	41 (34.7)
Injection reactions‡§ – Local injection reactions – Systemic injection reactions	57 (48.3) 54 (45.8) 13 (11.0)

- The most common symptoms reported by patients with local injection reactions included erythema, pain, swelling, and pruritus[1]
- The most common symptoms reported by patients with systemic injection reactions included headache and nausea[1]

OCREVUS [IV]: ESTABLISHED SAFETY PROFILE (BASED ON PIVOTAL STUDIES)[1]

Adverse reactions ≥5% and higher than control arm	RMS		PPMS	
	OCREVUS [IV] 600 mg every 24 weeks‖ (n=825)	REBIF SC 44 mg 3 times per week (n=826)	OCREVUS [IV] 600 mg every 24 weeks‖ (n=486)	Placebo (n=239)
Upper respiratory tract infections	40	33	49	43
Infusion reactions	34	10	40	26
Skin infections	♦	♦	14	11
Depression	8	7	♦	♦
Lower respiratory tract infections	8	5	10	9
Cough	♦	♦	7	3
Back pain	6	5	♦	♦
Herpes virus-associated infections	6	4	5	4
Diarrhea	♦	♦	6	5
Pain in extremity	5	4	♦	♦
Edema peripheral	♦	♦	6	5

♦Did not meet above criteria of: Adverse reactions ≥5% with OCREVUS [IV] (%) and higher than control arm.

*Patients who had ≥1 dose of OCREVUS ZUNOVO were included regardless of study arm randomization.[2]
†Reported AEs were encoded using MedDRA version 26.0.[3]
‡IRs comprise local injection reactions and/or systemic injection reactions, which may happen concurrently, therefore increasing rates of occurrence of total IRs. IRs are defined by the MedDRA preferred terms injection-related reaction and injection site reaction, which occurred during or within 24 hours after OCREVUS ZUNOVO administration and were judged by the investigator to be related to the OCREVUS ZUNOVO injection.[2,3]
§Standard-of-care treatments were used to treat IRs if needed and included medications such as acetaminophen and oral or topical antihistamines.[2]
‖The first dose was given as two separate 300-mg infusions at Weeks 0 and 2.[3]

AE=adverse event; IR=injection or infusion reaction; IV=intravenous; MedDRA=Medical Dictionary for Regulatory Activities; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis; SC=subcutaneous.

Please see safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

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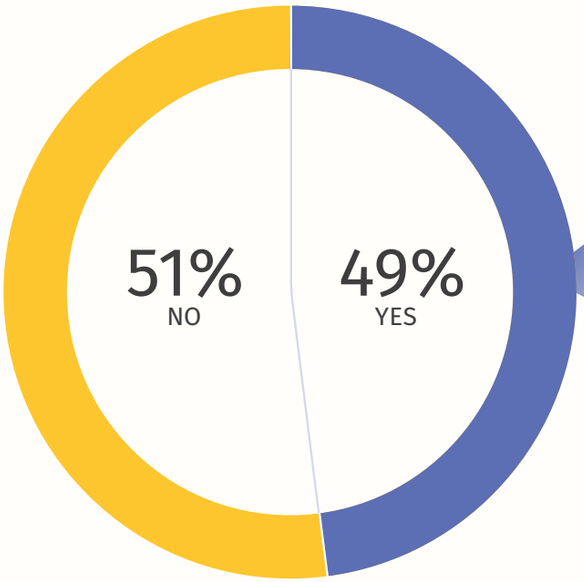
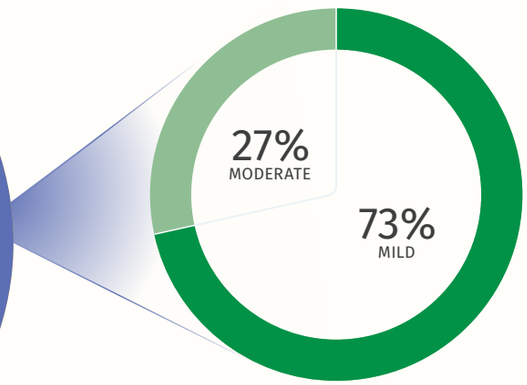
Injection reactions were highest with the first dose[3]

Among the 118 patients who received only OCREVUS ZUNOVO® in the OCARINA II study, 51% of patients did not experience an injection reaction with the first dose[1]

HAD AT LEAST 1 INJECTION REACTION[1]
(n=58/118)



INJECTION REACTIONS WERE MILD (73%) OR MODERATE (27%) IN SEVERITY[1]



- **Grade 1 (Mild)** was defined as tenderness with or without associated symptoms (eg, warmth, erythema, itching)[4]
- **Grade 2 (Moderate)** was defined as pain, lipodystrophy, edema, or phlebitis[4]
- **Grade 3 (Severe)** was defined as ulceration or necrosis, severe tissue damage, or operative intervention indicated[4]
- **Grade 4 (Life-threatening)** was defined as life-threatening consequences, or urgent intervention indicated[4]
- **Grade 5 (Fatal)** was defined as death[4]

INCIDENCE OF INJECTION REACTIONS[1] | (n=58/118)

47% had at least 1 local injection reaction

11% had at least 1 systemic injection reaction

- **Injection reactions occurred within 24 hours for 83% of patients,** and during the injection for 19% of patients[1]
- Median duration of symptoms was **3 days** for systemic injection reactions and **3.5 days** for local injection reactions[1]
- **All patients recovered from injection reactions**, of which 26% required symptomatic treatment[1]
- The most common symptoms reported by patients with local injection reactions included erythema, pain, swelling, and pruritus[1]
- The most common symptoms reported by patients with systemic injection reactions included headache and nausea[1]

Please see safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

Incidence of local and systemic injection reactions decreased after the first injection[3]

Among the 118 patients who received only OCREVUS ZUNOVO® in the OCARINA II study[1]

FIRST INJECTION[1]:

47% had at least 1 local injection reaction

11% had at least 1 systemic injection reaction

SUBSEQUENT INJECTIONS (2 TO 4)[5]:

32%–43% had at least 1 local injection reaction

4%–7% had systemic injection reactions

- For subsequent injections: All injections were of mild (80% to 90%) or moderate (10% to 20%) severity[5]

SUMMARY ANALYSIS OF INJECTION REACTIONS SHOWED:

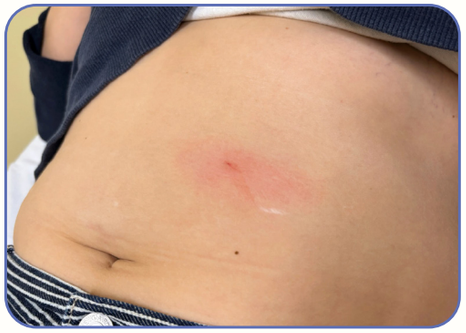
- All injection reactions were mild to moderate in severity[1]
- Incidence of injection reactions decreased after the first injection[3]
- All injection reactions that occurred were resolved[3]
- There were no injection reactions that led to treatment discontinuation[3]

OCARINA II was a multicenter, randomized, open-label, parallel-arm trial conducted to evaluate the pharmacokinetics, pharmacodynamics, safety, and immunogenicity of OCREVUS ZUNOVO compared with intravenous OCREVUS® (ocrelizumab) in patients with either RMS or PPMS. OCARINA II was designed to demonstrate comparative PK of treatment with OCREVUS ZUNOVO versus intravenous ocrelizumab based on the primary PK endpoint of AUC up to Week 12 post-injection/infusion (AUC_{W1-12}). A total of 236 patients with RMS or PPMS (213 patients with RMS, 23 patients with PPMS) were randomized in a 1:1 ratio to the SC arm or IV arm.

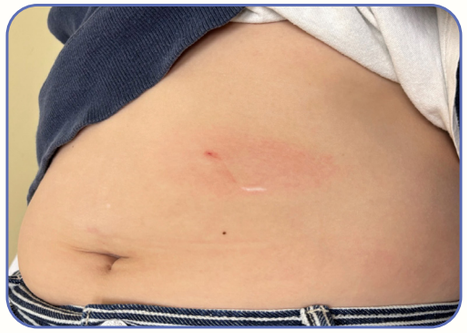
AUC=area under the curve; IV=intravenous; PK=pharmacokinetics; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis; SC=subcutaneous.

Please see safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

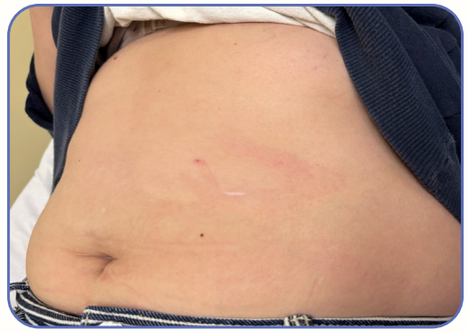
Real-world patient local injection site reactions*†



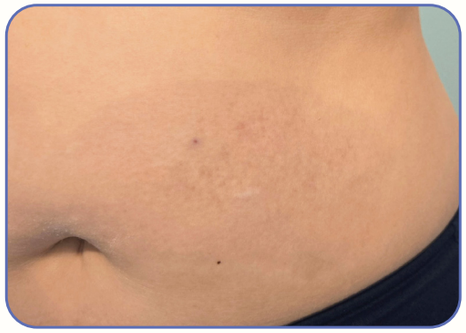
IMMEDIATELY AFTER



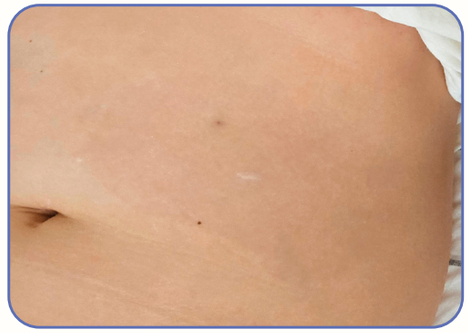
30 MINUTES AFTER



1 HOUR AFTER



24 HOURS AFTER



48 HOURS AFTER

***Images are not indicative of the safety profile for OCREVUS ZUNOVO and do not encompass the full injection reaction experience. Systemic reactions are not shown here.**
†Images unavailable beyond the timepoints shown.

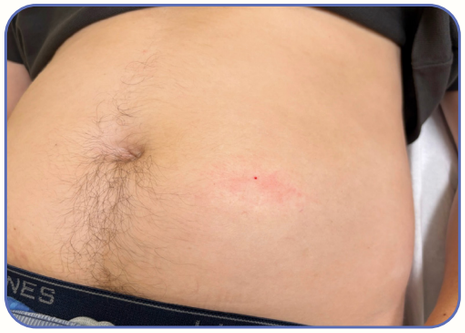
Select Important Safety Information

Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with MS treated with intravenous ocrelizumab in the postmarketing setting. At the first sign or symptom suggestive of PML, withhold OCREVUS ZUNOVO and perform an appropriate diagnostic evaluation. Magnetic resonance imaging (MRI) findings may be apparent before clinical signs or symptoms. 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 OCREVUS ZUNOVO should be discontinued.

Please see additional safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

Real-world patient local injection site reactions*†



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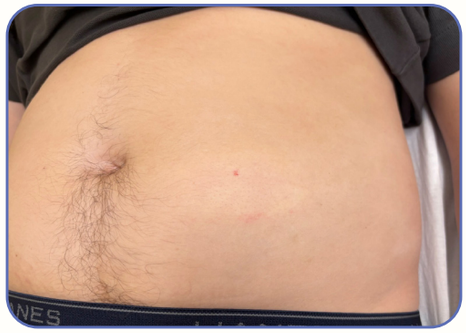

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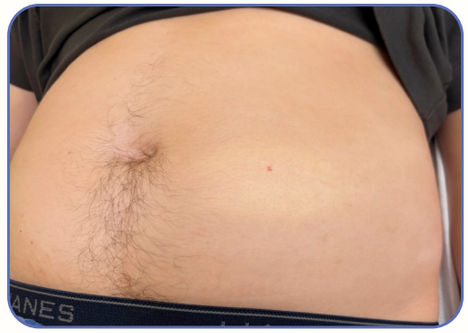

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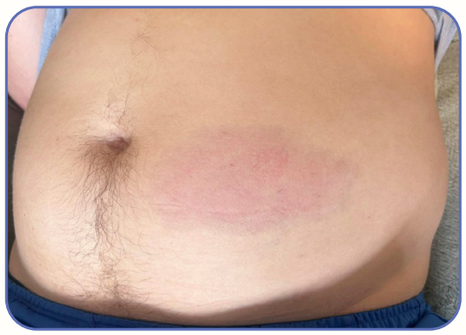
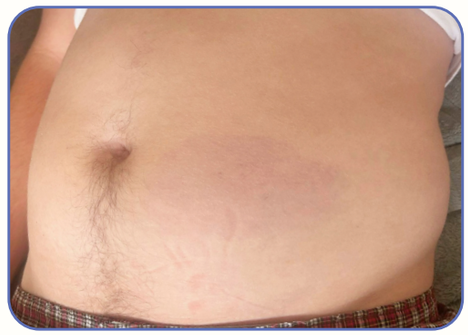


24 HOURS AFTER



48 HOURS AFTER‡

***Images are not indicative of the safety profile for OCREVUS ZUNOVO and do not encompass the full injection reaction experience. Systemic reactions are not shown here.**
†Images unavailable beyond the timepoints shown.
‡Resolution occurred beyond 48 hours.

Select Important Safety Information

Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with OCREVUS ZUNOVO. Monitor during and after discontinuation of treatment with OCREVUS ZUNOVO until B-cell repletion, and especially when recurrent serious infections are suspected. Consider discontinuing OCREVUS ZUNOVO in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Please see additional safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

Patient preference

Patient Preference Questionnaire (PPQ) responses from OCARINA II clinical trial at Week 48, safety evaluable (n=102)[6,7]

80.4%
Preferred OCREVUS ZUNOVO® method of delivery (SC) (n=82)

10.8%
Preferred OCREVUS® (ocrelizumab) method of delivery (IV) (n=11)

8.8%
Had no preference (n=9)

PPQ data at Week 48 are described here. At Week 48, patients initially randomized to OCREVUS ZUNOVO had received up to a maximum of 3 OCREVUS injections, while patients initially randomized to OCREVUS IV had received up to a maximum of 2 OCREVUS injections.[8]

QUESTIONNAIRE DESIGN[7]

The survey included 3 questions that captured:

- A patient's preference for mode of administration (IV, SC, no preference)
- The strength of their preference (very strong, fairly strong, not very strong)
- The reasons for their preference (feels less emotionally distressing, requires less time in the clinic, lower level of injection-site pain, feels more comfortable during administration, other reason)*

The response options in the survey did not include all clinically relevant attributes that could have inhibited patients from carrying out a comprehensive trade-off analysis.

LIMITATIONS:

- This was an exploratory endpoint
- The impact of switch order was not explored due to lack of crossover design, and only reflects data from IV>SC arm
- The response options in the survey did not include all clinically relevant attributes that could have inhibited patients from carrying out a comprehensive trade-off analysis
- Questions were asked in a clinical trial setting, and responses may not be generalizable in the real-world setting

*Patients were to select 2 options.[7]
IV=intravenous; SC=subcutaneous.

Select Important Safety Information

Malignancies

An increased risk of malignancy, including breast cancer, may exist with OCREVUS ZUNOVO.

Please see additional safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

Commonly asked questions

Q ***"What were the most common injection site reactions seen with OCREVUS ZUNOVO®?"***

A Overall, OCREVUS ZUNOVO was shown to have a safety profile that was consistent to OCREVUS® [IV], apart from injection reactions.[1,2]

- Injection reactions occurred in 49% of patients taking OCREVUS ZUNOVO[1]
- The most common local reactions were erythema, pain, swelling, and pruritus at the site of the injection. In OCARINA II, the most common systemic reactions were headache and nausea; no adverse event led to discontinuation[1,3]

Q ***"Are more infections seen with OCREVUS ZUNOVO vs OCREVUS [IV]?"***

A In OCARINA II, infections seen after the first injection with OCREVUS ZUNOVO occurred at a rate of 37.3% and were similar to OCREVUS [IV] (28%).[9]

Q ***"What can I share with patients to prepare them in the event that they experience a reaction during their injection?"***

A

- For 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. If there are signs of life-threatening injection reactions, immediately and permanently stop treatment. The patient should receive appropriate supportive treatment[1]
- Oral premedications are recommended at least 30 minutes before each injection to mitigate injection reactions. Start with an oral corticosteroid and an antihistamine[1]
- A post-dose observation of at least 60 minutes for the first injection and at least 15 minutes for subsequent injections is recommended[1]

Select Important Safety Information

Immune-Mediated Colitis

Immune-mediated colitis, which can present as a severe and acute-onset form of colitis, has been reported in patients receiving intravenous 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. Monitor patients for immune-mediated colitis during OCREVUS ZUNOVO treatment and evaluate promptly if signs and symptoms such as new or persistent diarrhea or other gastrointestinal signs and symptoms occur.

Please see additional safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

Commonly asked questions

Q ***"What do I tell my patients to look out for — and who and when to call — if they have an ISR after leaving the office?"***

A

- OCREVUS ZUNOVO can cause injection reactions, which can be local or systemic[1]
- 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[1]

Please refer to the OCREVUS ZUNOVO Medication Guide for the full list of possible signs and symptoms.

- Follow practice guidelines in instructing your patients on who to contact and how to reach them in the event of an injection reaction

Q ***"Does OCREVUS ZUNOVO contain a higher volume of ocrelizumab than the IV formulation?"***

A

- Yes, OCREVUS ZUNOVO is administered in doses of 920 mg of ocrelizumab and 23,000 units of hyaluronidase every 6 months. The IV formulation—OCREVUS—is administered in a split initial dose of 300 mg ocrelizumab each and subsequent doses of 600 mg every 6 months[1,10]
- The hyaluronidase in OCREVUS ZUNOVO works in a transient and reversible way to increase the drug dispersion area of the subcutaneous layer and allow larger fluid volumes to be administered subcutaneously[1,11,12]

Q ***"Does Genentech provide education and support to prepare patients and practices for what to expect with OCREVUS ZUNOVO subcutaneous administration?"***

A

- Genentech is committed to providing resources that educate and support patients and clinicians about the signs and symptoms of injection reactions
- Resources are available to prepare both clinicians and patients for what to expect when administering OCREVUS ZUNOVO including Clinical Education Manager (CEM) support

Click here to access OCREVUS ZUNOVO resources

Select Important Safety Information

Liver Injury

Clinically significant liver injury, without findings of viral hepatitis, has been reported in the postmarketing setting in patients with treated anti-CD20 B-cell depleting therapies approved for the treatment of MS, including ocrelizumab. Signs of liver injury, including markedly elevated serum hepatic enzymes with elevated total bilirubin, have occurred from weeks to months after administration.

Obtain liver function tests prior to initiating treatment with OCREVUS ZUNOVO, and monitor for signs and symptoms of any hepatic injury during treatment. Measure serum aminotransferases, alkaline phosphatase, and bilirubin levels promptly in patients who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, nausea, vomiting, right upper abdominal discomfort, dark urine, or jaundice. If liver injury is present and an alternative etiology is not identified, discontinue OCREVUS ZUNOVO.

Please see additional safety information on pages 11-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

Indications and Important Safety Information

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Subcutaneous injection 920mg/23,000 units

Indications

OCREVUS ZUNOVO 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

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.

Warnings and Precautions

Injection Reactions

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 where ocrelizumab was administered intravenously, 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 patients during and after injections. Inform patients that injection reactions can occur during or within 24 hours of the injection.

Reducing the Risk of Injection Reactions and Managing Injection Reactions

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.

Management recommendations for injection reactions depend on the type and severity of the reaction. For life-threatening injection reactions, immediately and permanently stop OCREVUS ZUNOVO and administer appropriate supportive treatment. For 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.

Infections

Serious, including life-threatening or fatal, bacterial, viral, parasitic and fungal infections have been reported in patients receiving intravenous 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 intravenous ocrelizumab-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of intravenous ocrelizumab-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of intravenous ocrelizumab-treated patients experienced one or more infections compared to 68% of patients on placebo. Intravenous ocrelizumab 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 OCREVUS ZUNOVO administration in patients with an active infection until the infection has resolved.

Respiratory Tract Infections

A higher proportion of intravenous ocrelizumab-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of intravenous ocrelizumab-treated patients experienced upper respiratory tract infections compared to 33% of REBIF-treated patients, and 8% of intravenous ocrelizumab-treated patients experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PPMS trial, 49% of intravenous ocrelizumab-treated patients experienced upper respiratory tract infections compared to 43% of patients on placebo, and 10% of intravenous ocrelizumab-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.

Please see additional safety information on pages 12-13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

Important Safety Information (cont.)

Herpes

In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in intravenous ocrelizumab-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 intravenous ocrelizumab-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 OCREVUS ZUNOVO. Some cases were life-threatening.

If serious herpes infections occur, OCREVUS ZUNOVO 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-containing products. Do not administer ocrelizumab-containing products 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 ZUNOVO after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS ZUNOVO, consider the potential for increased immunosuppressive effect. OCREVUS ZUNOVO 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. OCREVUS ZUNOVO may interfere with the effectiveness of non-live vaccines. The safety of immunization with live or live-attenuated vaccines following treatment with OCREVUS ZUNOVO 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 ZUNOVO During Pregnancy

In infants of mothers exposed to OCREVUS ZUNOVO 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 OCREVUS ZUNOVO 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 OCREVUS ZUNOVO should be discontinued.

Please see additional safety information on pages 11 and 13 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

Important Safety Information (cont.)

Reduction in Immunoglobulins

As expected with any B-cell depleting therapy, decreased immunoglobulin levels are observed with OCREVUS ZUNOVO. The pooled data of intravenous ocrelizumab 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 ZUNOVO treatment and after discontinuation of treatment, until B-cell repletion, and especially in the setting of recurrent serious infections. Consider discontinuing OCREVUS ZUNOVO 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 ZUNOVO may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in patients treated with intravenous ocrelizumab. Breast cancer occurred in 6 of 781 females treated with intravenous ocrelizumab 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 treatment with ocrelizumab-containing products 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.

Liver Injury

Clinically significant liver injury, without findings of viral hepatitis, has been reported in the postmarketing setting in patients treated with anti-CD20 B-cell depleting therapies approved for the treatment of MS, including ocrelizumab. Signs of liver injury, including markedly elevated serum hepatic enzymes with elevated total bilirubin, have occurred from weeks to months after administration.

Patients treated with OCREVUS ZUNOVO found to have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 3x the upper limit of normal (ULN) with serum total bilirubin greater than 2x ULN are potentially at risk for severe drug-induced liver injury.

Obtain liver function tests prior to initiating treatment with OCREVUS ZUNOVO, and monitor for signs and symptoms of any hepatic injury during treatment. Measure serum aminotransferases, alkaline phosphatase, and bilirubin levels promptly in patients who report symptoms that may indicate liver injury, including new or worsening fatigue, anorexia, nausea, vomiting, right upper abdominal discomfort, dark urine, or jaundice. If liver injury is present and an alternative etiology is not identified, discontinue OCREVUS ZUNOVO.

Use in Specific Populations

Pregnancy

There are no adequate data on the developmental risk associated with use of OCREVUS ZUNOVO in pregnant women. There are no data on B-cell levels in human neonates following maternal exposure to OCREVUS ZUNOVO or ocrelizumab. 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 OCREVUS ZUNOVO and any potential adverse effects on the breastfed infant from OCREVUS ZUNOVO or from the underlying maternal condition.

Females and Males of Reproductive Potential

Women of childbearing potential should use effective contraception while receiving OCREVUS ZUNOVO and for 6 months after the last administration of OCREVUS ZUNOVO. Instruct patients that if they are pregnant or plan to become pregnant while taking 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 see additional safety information on pages 11-12 and click here for full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

OCREVUS ZUNOVO™

ocrelizumab & hyaluronidase-ocsq

Subcutaneous injection 920mg/23,000 units

Click here to watch how to administer **OCREVUS ZUNOVO®**

Genentech is committed to enhancing the patient experience. Please contact your representative if you have any questions.

References: 1. OCREVUS ZUNOVO [prescribing information]. South San Francisco, CA: Genentech, Inc. 2025. **2.** Newsome SD, Krzystanek E, Selmaj K, et al. Subcutaneous ocrelizumab in patients with multiple sclerosis: results of the phase III OCARINA II study. Poster presented at: 9th Joint ECTRIMS-ACTRIMS Meeting; October 11-13, 2023; Milan, Italy. Poster P370. **3.** Data on file. Genentech, Inc. August 2023. **4.** Data on file. Genentech, Inc. March 2023. **5.** Data on file. Genentech, Inc. December 2023. **6.** Newsome SD, Goldstick L, Selmaj K, et al. Ocrelizumab subcutaneous administration: further characterization of the benefit-risk profile from the OCARINA II study and patient preferences. Poster presented at: ACTRIMS Forum 2025; February 27-March 1, 2025; West Palm Beach, Florida, USA and virtual. Poster P089. **7.** Data on file. Genentech, Inc. April 2024. **8.** Newsome SD, Krzystanek E, Selmaj K, et al. Ocrelizumab administered subcutaneously: results from the clinical development program. Presented at: 2024 Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting; May 29–June 1, 2024; Nashville, TN, USA. **9.** Newsome SD, Krzystanek E, Selmaj KW, et al. Subcutaneous ocrelizumab in patients with multiple sclerosis: results of the phase 3 OCARINA II study. *Neurology*. 2025;104(9):e213574. doi:10.1212/WNL.0000000000213574 **10.** OCREVUS [prescribing information]. South San Francisco, CA: Genentech, Inc. 2025. **11.** Connor RJ, Taverna DM, Thrall K, LaBarre MJ, Kang DW. Use of computed tomography to assess subcutaneous drug dispersion with recombinant human hyaluronidase PH20 in a swine model. *J Pharmacol Toxicol Methods*. 2020;106:106936. doi:10.1016/j.vascn.2020.106936 **12.** Bookbinder LH, Hofer A, Haller MF, et al. A recombinant human enzyme for enhanced interstitial transport of therapeutics. *J Control Release*. 2006;114(2):230-241. doi:10.1016/j.jconrel.2006.05.027

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