OCREVUS® (ocrelizumab)—**#1** most-prescribed MS DMT in the US[1]

The ONLY aCD20 now available in **two HCP-administered**, 2X-yearly options*: intravenous (IV) infusion and subcutaneous (SC) injection[2,3]

INTRODUCING

OCREVUS ZUNOVO™

ocrelizumab & hyaluronidase-ocsq

Subcutaneous injection 920mg

A **CONVENIENT**† ~10-minute,‡ HCP-administered SC injection[3]

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

*The first dose of OCREVUS® [IV] is split between 2 treatments, for a total of 3 treatments in the first year and OCREVUS ZUNOVO™ (no split first dose).
†Please see the **Dosing and Administration** page for additional information.

aCD20=anti-CD20; DMT=disease-modifying treatment; MS=multiple sclerosis.

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 **12-14**, and click for full OCREVUS **Prescribing Information** and **Medication Guide** and full OCREVUS ZUNOVO **Prescribing Information** and **Medication Guide**.

INTRODUCING OCREVUS ZUNOVO

2X-YEARLY, ~10-MINUTE,* HCP-ADMINISTERED SUBCUTANEOUS INJECTION[3]

***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[3]:

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

- CONSIDER FOR PATIENTS WITH MS WHO[4-6]:

- 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

Can you think of an appropriate patient with MS in your practice who could benefit from **OCREVUS ZUNOVO**?

Only OCREVUS ZUNOVO provides a subcutaneous option for both RMS and PPMS[3]

†Please see the Dosing and Administration page for additional information.

aCD20=anti-CD20; IV=intravenous; MS=multiple sclerosis; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis.

Select Important Safety Information

OCREVUS (ocrelizumab): Infusion Reactions

Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue OCREVUS if a life-threatening or disabling infusion reaction occurs.

OCREVUS ZUNOVO: 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.

Please see additional Important Safety Information on pages 12-14, and click for full OCREVUS Prescribing Information and Medication Guide and full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

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

INTRODUCING OCREVUS ZUNOVO

FDA APPROVAL BASED ON COMPARABILITY IN A PHARMACOKINETIC (PK) BRIDGE STUDY

Efficacy was established with PK bridging study: No clinically significant difference based on PK exposure[3]

PRIMARY ENDPOINT:
Non-inferior PK exposure was based on the first 12 weeks following administration of OCREVUS ZUNOVO (920 mg) vs OCREVUS (ocrelizumab) (600 mg)[3,5]

Mean C_{max} was reached after ~4 days, with 81% estimated bioavailability[3]

WEEK 12 PK ANALYSIS[3,7]			
	OCREVUS ZUNOVO 920 mg* (n=116)	OCREVUS [IV] split 600 mg*† (n=116)	GMR OCREVUS ZUNOVO vs OCREVUS [IV]† (90% CI)
AUC over the first 12 weeks (AUC_{W1-12})	3730 µg/mL·day	2,750 µg/mL·day	**1.29** (1.23-1.35)
Maximum serum concentration (C_{max})	132 µg/mL	137 µg/mL	0.96 (0.92-1.01)

*Estimated mean exposure for AUC or C_{max}.[3]
†For patients in the OCREVUS [IV] arm, completion of a full 600-mg first dose was administered as two 300-mg IV infusions given 14 days apart.[5]
‡GMR and two-sided 90% CI of OCREVUS ZUNOVO vs OCREVUS [IV] between baseline and Week 12. Non-inferiority would be established if the lower end of the two-sided 90% CI is >0.8; the non-inferiority limit of 0.8 corresponds to a maximal 20% loss in AUC for the SC administration compared with IV, as recommended in the regulatory guidance documents for demonstration of bioequivalence for PK bridging.[7]

AUC=area under the concentration-time curve; CI=confidence interval; GMR=geometric mean ratio; IV=intravenous; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis; SC=subcutaneous.

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 ocrelizumab based on the primary PK endpoint of AUC up to Week 12 post injection/infusion (AUC_{W1-12}).[3]

Effectiveness of OCREVUS [IV] was established by pivotal studies in adult RMS and PPMS patients.

Click here for the full OCARINA II study design

Select Important Safety Information

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 administration of ocrelizumab in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with ocrelizumab-containing products and after discontinuation, until B-cell repletion.

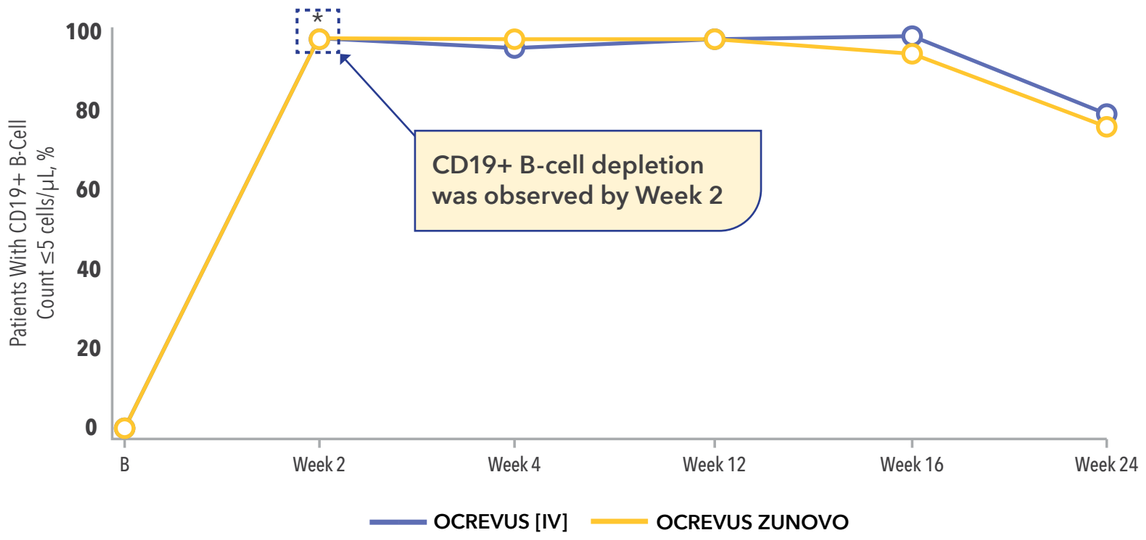
Please see additional Important Safety Information on pages 12-14, and click for full OCREVUS Prescribing Information and Medication Guide and full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

INTRODUCING OCREVUS ZUNOVO

B-CELL DEPLETION COMPARABILITY OBSERVED[3]

Treatment with OCREVUS ZUNOVO resulted in B-cell depletion levels comparable to OCREVUS® (ocrelizumab) as measured up to Week 24[3,7]

PERCENTAGE OF PATIENTS WITH CD19+ B-CELL COUNT ≤5 CELLS/µL[3,5,7]



Limitations
It is unclear to what extent B-cell levels associate with specific clinical outcomes in individual patients. The precise mechanisms through which OCREVUS [IV] exerts its therapeutic clinical effects in RMS and PPMS are not fully understood.

*Completion of first dose for patients in the OCREVUS [IV] arm was at Week 2 due to a split first dose.[5]

IV=intravenous; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis.

Select Important Safety Information

Progressive Multifocal Leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients with MS treated with ocrelizumab in the postmarketing setting. At the first sign or symptom suggestive of PML, withhold ocrelizumab treatment 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 ocrelizumab-containing products should be discontinued.

Please see additional Important Safety Information on pages 12-14, and click for full OCREVUS Prescribing Information and Medication Guide and full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

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

INTRODUCING OCREVUS ZUNOVO

SAFETY PROFILE CONSISTENT WITH OCREVUS (ocrelizumab) WITH THE EXCEPTION OF INJECTION REACTIONS[3,7]

OCREVUS ZUNOVO: All-exposure* safety profile (Week 24)[7]

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

- The most common symptoms reported by patients with local injection reactions included erythema, pain, swelling, and pruritus[3]
- The most common symptoms reported by patients with systemic injection reactions included headache and nausea[3]

OCREVUS [IV]: Established safety profile (based on pivotal studies)[2]

	RMS		PPMS	
Adverse reactions ≥5% and higher than control arm‖	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.[3]

*Patients who had ≥1 dose of OCREVUS ZUNOVO were included regardless of study arm randomization.[7]
†Reported AEs were encoded using MedDRA version 26.1.[7]
‡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 which were judged by the investigator to be related to the OCREVUS ZUNOVO injection.[5,7]
§Standard-of-care treatments were used to treat IRs if needed and included medications such as acetaminophen and oral or topical antihistamines.[7]
¶The first dose was given as two separate 300-mg infusions at Weeks 0 and 2.[5]

AE=adverse event; IR=injection reaction; MedDRA=Medical Dictionary for Regulatory Activities; SC=subcutaneous.

Please see additional Important Safety Information on pages 12-14, and click for full OCREVUS Prescribing Information and Medication Guide and full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

INTRODUCING OCREVUS ZUNOVO

INJECTION REACTION RATES

Among patients who received only OCREVUS ZUNOVO in the OCARINA II study (n=118), all injection reactions were Grade 1 or Grade 2

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.[8]

Local and systemic reactions

Among the 118 patients who received only OCREVUS ZUNOVO throughout the study, the frequency of local and systemic reactions was as follows for first and subsequent doses:

- Common symptoms reported with local and systemic injection reactions included injection site erythema, injection site pain, injection site swelling, injection site pruritus, headache, and nausea
- The most common symptoms included erythema, pain, swelling, and pruritus reported by patients with local injection reactions; headache and nausea reported by patients with systemic injection reactions[3]

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
- 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%)
- Median duration of symptoms were 3 days and 3.5 days for systemic and local injection reactions, respectively
- All patients recovered from injection reactions, of which 26% required symptomatic treatment

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[9]

Summary analysis of injection reactions showed:

- All injection reactions were of mild to moderate severity
- Incidence of injection reactions decreased after the first injection[5]
- All injection reactions that occurred were resolved[5]
- There were no injection reactions that led to treatment discontinuation[5]

Select Important Safety Information

Reduction in Immunoglobulins

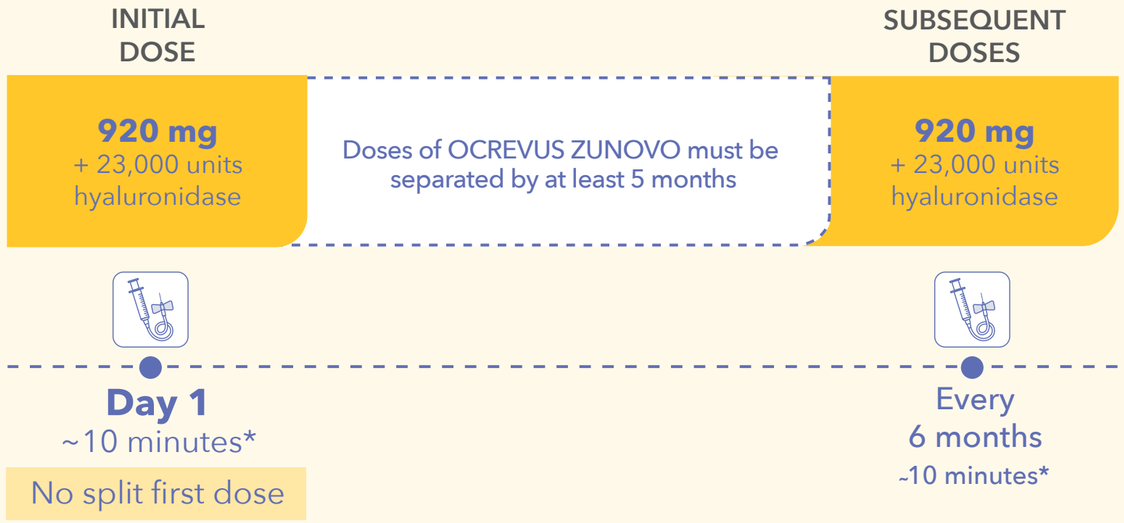
Monitor the level of immunoglobulins at the beginning of treatment. Monitor during and after discontinuation of ocrelizumab treatment, until B-cell repletion, and especially when recurrent serious infections are suspected. Consider discontinuing ocrelizumab treatment in patients with serious opportunistic or recurrent serious infections, and if prolonged hypogammaglobulinemia requires treatment with intravenous immunoglobulins.

Please see additional Important Safety Information on pages 12-14, and click for full OCREVUS Prescribing Information and Medication Guide and full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

ONLY OCREVUS ZUNOVO

2X-YEARLY, HCP-ADMINISTERED SUBCUTANEOUS INJECTION WITH NO SPLIT FIRST DOSE[3]

OCREVUS ZUNOVO 920 mg/23 mL: No reconstitution[3]



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

The active excipient hyaluronidase works in a transient and reversible way to increase the dispersion area and allow larger fluid volumes to be administered subcutaneously[3,10,11]

IMPORTANT ADMINISTRATION INFORMATION

- OCREVUS ZUNOVO is for subcutaneous use in the abdomen only
- OCREVUS ZUNOVO has different dosage and administration instructions than intravenous ocrelizumab
- OCREVUS ZUNOVO should be administered via subcutaneous injection by a healthcare professional

DELAYED OR MISSED DOSE[3]

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. Doses of OCREVUS (ocrelizumab) must be separated by at least 5 months.

IV=intravenous.

Select Important Safety Information

Malignancies
An increased risk of malignancy, including breast cancer, may exist with ocrelizumab.

Please see additional Important Safety Information on pages 12-14, and click for full OCREVUS Prescribing Information and Medication Guide and full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

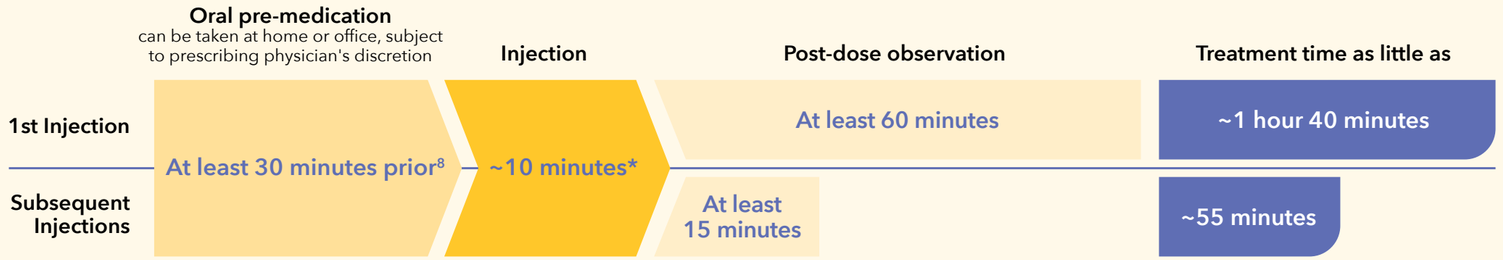
OCREVUS ZUNOVO™
ocrelizumab & hyaluronidase-ocsq
Subcutaneous injection 920mg

ONLY OCREVUS ZUNOVO

THE **ONLY** HCP-ADMINISTERED aCD20 THAT TAKES ~10 MINUTES TO ADMINISTER[3]

Administering OCREVUS ZUNOVO 920 mg/23 mL: No reconstitution[3]

- PRIOR TO FIRST DOSE[3]:
  - 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)
- PRIOR TO EVERY DOSE[3]:
  - Assess for active infection
  - Administer pre-medication: dexamethasone (or an equivalent corticosteroid) and an antihistamine (e.g., desloratadine)
- POST-DOSE OBSERVATION[3]:
  - Monitor patients closely during all injections, for at least 1 hour after the initial injection and for at least 15 minutes after for subsequent doses*



*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.[3]

aCD20=anti-CD20.

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 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 ocrelizumab treatment and evaluate promptly if signs and symptoms such as new or persistent diarrhea or other gastrointestinal signs and symptoms occur.

Please see additional Important Safety Information on pages 12-14, and click for full OCREVUS Prescribing Information and Medication Guide and full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

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

INTRODUCING OCREVUS ZUNOVO

THE CONFIDENCE OF AN HCP-ADMINISTERED SUBCUTANEOUS INJECTION

Manual or via syringe pump[3]*

- For subcutaneous injection in the abdomen only, except for 2 inches (5 cm) around the navel
- Should not be administered into areas where the skin is red, bruised, tender, or hard or where there are moles or scars

Supplies for subcutaneous injection may include[3]:

- 21-gauge transfer needle to draw up solution from vial
- 24–26-gauge butterfly/winged infusion set to administer the drug
- Optional syringe pump† in lieu of manual push

Experiential demonstration of OCREVUS ZUNOVO injection is available

- Designed to build familiarity and confidence in your medical staff to manually administer the injection

Anti-CD20 injection with verifiable subcutaneous administration by an HCP that can help monitor for adherence[3]

*Administer 23 mL of OCREVUS ZUNOVO subcutaneously in the abdomen over approximately 10 minutes. DO NOT administer the remaining priming volume in the SC infusion set to the patient.[3]

†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 infusion pump manufacturer's instructions for the most up-to-date information and to ensure appropriate use of any drug or device.

aCD20=anti-CD20; SC=subcutaneous.

Select Important Safety Information

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.

Please see additional Important Safety Information on pages 12-14, and click for full OCREVUS Prescribing Information and Medication Guide and full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

OCREVUS ZUNOVO™
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Subcutaneous injection 920mg

INTRODUCING OCREVUS ZUNOVO

COMMITTED TO HELPING PATIENTS GET STARTED ON OCREVUS ZUNOVO AFTER IT HAS BEEN PRESCRIBED

THE SAME SUPPORT YOU KNOW ONCE OCREVUS® (ocrelizumab) HAS BEEN PRESCRIBED

PATIENT NAVIGATOR
Your point of contact for assistance throughout your patients' treatment

COVERAGE AND REIMBURSEMENT SUPPORT
A range of support from OCREVUS Access Solutions to help patients begin treatment as soon as possible*

PATIENT FINANCIAL ASSISTANCE
Options are available for eligible patients with commercial insurance, public insurance, or no insurance,† including the OCREVUS Co-pay Program‡

ADDITIONAL SUPPORT TO HELP PATIENTS GET STARTED ON OCREVUS ZUNOVO

STARTER PROGRAM§
May provide free medicine to eligible patients who are waiting >5 business days for a health insurance coverage determination

INJECTION TRAINING
Experiential demonstration of OCREVUS ZUNOVO manual injection for medical staff designed to build familiarity and confidence in appropriate administration

WE ARE READY TO HELP
Contact your Genentech representative or a Patient Navigator at 844-627-3887

*The completion and submission of coverage- or reimbursement-related documentation are the responsibility of the patient and healthcare provider. Genentech makes no representation or guarantee concerning coverage or reimbursement for any service or item.
†Each option has its own eligibility criteria that must be met for patients to receive assistance.
‡Eligibility criteria apply. Not valid for patients using federal or state government programs to pay for their Genentech medicine and/or administration of their Genentech medicine. Patients must be taking the Genentech medicine for an FDA-approved indication. Please visit the Co-pay Program website for the full list of terms and conditions.
§Subject to eligibility requirements and terms and conditions. This program is void where prohibited by law and may not be used in or by residents of restricted states, if applicable.

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 12-14, and click for full OCREVUS Prescribing Information and Medication Guide and full OCREVUS ZUNOVO Prescribing Information and Medication Guide.

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

OCARINA II

- OCARINA II (NCT05232825) 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 non-inferiority 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})[3]

- 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. During the controlled period (Day 0 to Week 24), patients received either a single 920-mg OCREVUS ZUNOVO injection at Study Day 1 or two 300-mg ocrelizumab IV infusions at Study Days 1 and 14. After the controlled period, all patients had the opportunity to receive further injections of 920-mg OCREVUS ZUNOVO at Weeks 24 and 48 (Dose 2 and 3)[3,5]

- Patients were aged 18–65 years with an EDSS between 0 and 6.5 at screening. The demographics were similar and baseline characteristics were well balanced across the two treatment groups. The mean age was 40 years in the OCREVUS ZUNOVO arm and 40 years in the IV arm. 35% of patients were male and 65% were female in the OCREVUS ZUNOVO arm, and 41% of patients were male and 59% were female in the OCREVUS [IV] arm. The mean/median duration since MS diagnosis was 5.7/3.1 years in the OCREVUS ZUNOVO arm and 4.8/2.4 years in the OCREVUS [IV] arm[3]

- Non-inferior PK exposure was based on the first 12 weeks following administration of OCREVUS ZUNOVO (920 mg) versus OCREVUS [IV] (600 mg) was demonstrated based on a non-significant difference in AUC up to Week 12 (AUC_{W1-12}) post-injection. The observed PK non-inferiority is expected to result in a comparable benefit-risk profile[3,7]

AUC=area under concentration curve; EDSS=expanded disability status scale; IV=intravenous; MS=multiple sclerosis; PK=pharmacokinetics; PPMS=primary progressive multiple sclerosis; RMS=relapsing multiple sclerosis; SC=subcutaneous.

Select Important Safety Information

OCREVUS (ocrelizumab): Infusion Reactions
Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue OCREVUS if a life-threatening or disabling infusion reaction occurs.

OCREVUS ZUNOVO: 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.

Please see additional Important Safety Information on pages **12-14**, and click for full OCREVUS **Prescribing Information** and **Medication Guide** and full OCREVUS ZUNOVO **Prescribing Information** and **Medication 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.

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 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.

INTRODUCING

OCREVUS ZUNOVO™

ocrelizumab & hyaluronidase-ocsq

Subcutaneous injection 920mg

THE **ONLY** ~10 MINUTE,* 2X-YEARLY, HCP-ADMINISTERED aCD20 SUBCUTANEOUS INJECTION[3]

***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* subcutaneous injection with[3]:
  - **NO** split first dose
  - **NO** reconstitution
  - **NO** IV infusion–specific supplies needed
- No **CLINICALLY** significant difference vs OCREVUS (ocrelizumab) based on PK exposure[1,3,7]
- **CONSISTENT** safety profile to OCREVUS [IV] with the exception of injection reactions[1,3,7]
- **COMMITTED** to helping patients get started on **OCREVUS ZUNOVO** after it has been prescribed
  - The same patient access and financial assistance programs as OCREVUS [IV]
  - OCREVUS ZUNOVO injection training and Starter Program for eligible patients

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 the Dosing and Administration page for additional information.
aCD20=anti-CD20; IV=intravenous; PK=pharmacokinetics.

Genentech
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