HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ENSPRYNG safely and effectively. See full prescribing information for ENSPRYNG.

ENSPRYNG® (satralizumab-mwge) injection, for subcutaneous use
Initial U.S. Approval: 2020

INDICATIONS AND USAGE

ENSPRYNG is an interleukin-6 (IL-6) receptor antagonist indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. (1)

DOSAGE AND ADMINISTRATION

- Hepatitis B virus, tuberculosis, and liver transaminase screening is required before the first dose. (2.1)
- Prior to every use, determine if there is an active infection. (2.2)
- The recommended loading dosage of ENSPRYNG for the first three administrations is 120 mg by subcutaneous injection at Weeks 0, 2, and 4, followed by a maintenance dosage of 120 mg every 4 weeks. (2.2)
- See Full Prescribing Information for important preparation and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL in a single-dose prefilled syringe (3)

CONTRAINDICATIONS

- Known hypersensitivity to satralizumab or any of the inactive ingredients (4)
- Active Hepatitis B infection (4)
- Active or untreated latent tuberculosis (4)

WARNINGS AND PRECAUTIONS

- Infections: Delay ENSPRYNG administration in patients with an active infection until the infection is resolved. Vaccination with live or live-attenuated vaccines is not recommended during treatment. (5.1)
- Elevated Liver Enzymes: Monitor ALT and AST levels during treatment; interruption of ENSPRYNG may be required. (5.2)
- Decreased Neutrophil Counts: Monitor neutrophils during treatment. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 15%) are nasopharyngitis, headache, upper respiratory tract infection, gastritis, rash, arthralgia, extremity pain, fatigue, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2022

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ENSPRYNG is indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to the First Dose of ENSPRYNG

Hepatitis B Virus Screening

Prior to initiating ENSPRYNG, perform Hepatitis B virus (HBV) screening. ENSPRYNG is contraindicated in patients with active HBV confirmed by positive results for surface antigen [HBsAg] and anti-HBV tests. For patients who are negative for HBsAg and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment with ENSPRYNG *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Tuberculosis Screening

Prior to initiating ENSPRYNG, evaluate for active tuberculosis and test for latent infection. For patients with active tuberculosis or positive tuberculosis screening without a history of appropriate treatment, consult infectious disease experts before initiating treatment with ENSPRYNG *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Liver Transaminase Screening

Liver transaminases and serum bilirubin should be assessed prior to initiation of treatment with ENSPRYNG *[see Warnings and Precautions (5.2)]*.

Caution should be exercised when considering initiation of ENSPRYNG treatment in patients whose aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels are greater than 1.5 times the upper limit of normal (ULN).

Vaccinations

Because vaccination with live-attenuated or live vaccines is not recommended during treatment with ENSPRYNG, administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ENSPRYNG for non-live vaccines *[see Warnings and Precautions (5.1).*

2.2 Recommended Dosage

For subcutaneous use only.

Prior to every use of ENSPRYNG, advise patients to consult with their healthcare professional (HCP) if they suspect an active infection, including localized infections. In case of active infection, delay use of ENSPRYNG until the infection is resolved *[see Warnings and Precautions (5.1)]*.

The recommended loading dosage of ENSPRYNG for the first three administrations is 120 mg by subcutaneous injection at Weeks 0, 2, and 4, followed by a maintenance dosage of 120 mg every 4 weeks.

Missed Dose

If a dose of ENSPRYNG is missed for any reason other than increases in liver enzymes *[see Dosage and Administration (2.4)]*, administer as described in Table 1.

Table 1 Recommended Dosage for Delayed or Missed Doses

Last Dose Administered	Recommended Dosage for Delayed or Missed Doses
Less than 8 weeks during the maintenance period or missed a loading dose	Administer 120 mg by subcutaneous injection as soon as possible, and do not wait until the next planned dose. Maintenance period After the delayed or missed dose is administered, reset the dose schedule to every 4 weeks. Loading period If the second loading dose is delayed or missed, administer as soon as possible and administer the 3rd and final loading dose 2 weeks later. If the third loading dose is delayed or missed, administer as soon as possible and administer the 1st maintenance dose 4 weeks later.
8 weeks to less than 12 weeks	120 mg by subcutaneous injection at 0* and 2 weeks, followed by 120 mg every 4 weeks.
12 weeks or longer	120 mg by subcutaneous injection at 0*, 2, and 4 weeks followed by 120 mg every 4 weeks.

* "0 weeks" refers to time of the first administration after the missed dose.

2.3 Important Administration Instructions

- ENSPRYNG is intended for patient self-administration by subcutaneous injection under the guidance of a health care professional (HCP). After proper training in subcutaneous injection technique, a patient may self-inject ENSPRYNG or the patient's caregiver may administer ENSPRYNG, if the HCP determines that it is appropriate. See ENSPRYNG "Instructions for Use" (IFU) for more detailed instructions on the preparation and administration of ENSPRYNG.
- Patients or caregivers should seek immediate medical attention if the patient develops symptoms of a serious allergic reaction and should not administer further doses until evaluated by a HCP *[see Contraindications (4) and Warning and Precautions (5.4)]*.
- Prior to use, remove the prefilled syringe from the refrigerator and allow to sit at room temperature outside of the carton for 30 minutes. Do not warm ENSPRYNG in any other way.
- Inspect visually for particulate matter and discoloration prior to administration. ENSPRYNG solution should be clear and colorless to slightly yellow. Do not use ENSPRYNG if the solution is cloudy, discolored, or contains particles, or if any part of the prefilled syringe appears to be damaged.
- Instruct patients to inject the full amount in the syringe (1 mL), which provides 120 mg of ENSPRYNG, according to the directions provided in the IFU.
- Administer ENSPRYNG by subcutaneous injection in the abdomen or thigh. Rotate injection sites with each administration. Do not give injection into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

2.4 Safety Monitoring During Treatment

Liver Transaminases

Monitor ALT and AST levels every 4 weeks for the first 3 months of treatment with ENSPRYNG, followed by every 3 months for one year, and thereafter as clinically necessary *[see Warnings and Precautions (5.2)]*.

If an ALT or AST elevation of greater than 5 times the ULN occurs, discontinue ENSPRYNG as follows:

- If associated with any bilirubin elevation, discontinue ENSPRYNG, and reinitiation is not recommended.
- If not associated with any bilirubin elevation above the ULN, when the ALT or AST level has returned to the normal range and following a benefit-risk assessment of the patient, treatment with ENSPRYNG can be restarted per the schedule in Table 2.

Table 2 Recommended Dosage for Restart of Treatment After Liver Transaminase Elevation

Last Dose Administered	Recommended Dosage for Restart of Treatment
Less than 12 weeks	Restart at a dosage of 120 mg by subcutaneous injection every 4 weeks.
12 weeks or longer	Restart at a dose of 120 mg by subcutaneous injection at Weeks 0*, 2, and 4, followed by a dosage of 120 mg every 4 weeks.

* "0 weeks" refers to time of the first administration after the missed dose.

If treatment is restarted, the liver parameters must be closely monitored, and if any subsequent increase in ALT/AST and/or bilirubin above the ULN is observed, ENSPRYNG should be discontinued, and another reinitiation is not recommended.

Neutrophil Counts

Monitor neutrophils 4 to 8 weeks after initiation of therapy and thereafter at regular clinically determined intervals. If the neutrophil count is below 1.0×10^9/L and confirmed by repeat testing, ENSPRYNG should be interrupted until the neutrophil count is $> 1.0 \times 10^9$/L *[see Warnings and Precautions (5.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/mL clear, and colorless to slightly yellow solution in single-dose prefilled syringe.

4 CONTRAINDICATIONS

ENSPRYNG is contraindicated in patients with:

- A known hypersensitivity to satralizumab or any of the inactive ingredients *[see Warnings and Precautions (5.4)]*
- Active Hepatitis B infection *[see Warnings and Precautions (5.1)]*
- Active or untreated latent tuberculosis *[see Warnings and Precautions (5.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Infections

An increased risk of infections, including serious and potentially fatal infections, has been observed in patients treated with IL-6 receptor antagonists, including ENSPRYNG.

The most common infections reported in a randomized clinical trial of patients treated with ENSPRYNG who were not on other chronic immunosuppressant therapies (Study 1), and that occurred more often than in patients receiving placebo, were nasopharyngitis (12%) and cellulitis (10%). The most common infections in patients who were on an additional concurrent immunosuppressant, and that occurred more often than in patients receiving placebo, were nasopharyngitis (31%), upper respiratory infection (19%), and pharyngitis (12%).

Delay ENSPRYNG administration in patients with an active infection, including localized infections, until the infection is resolved.

Hepatitis B Virus (HBV) Reactivation

Risk of HBV reactivation has been observed with other immunosuppressant therapies. Patients with chronic HBV infection were excluded from clinical trials. Perform HBV screening in all patients before initiation of treatment with ENSPRYNG. Do not administer ENSPRYNG to patients with active hepatitis. For patients who are chronic carriers of HBV [HBsAg+] or are negative for HBsAg and positive for HB core antibody [HBcAb+], consult liver disease experts before starting and during treatment with ENSPRYNG.

Tuberculosis

Tuberculosis has occurred in patients treated with other interleukin-6 receptor antagonists. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating ENSPRYNG. Consider anti-tuberculosis therapy prior to initiation of ENSPRYNG in patients with a history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consult infectious disease experts regarding whether initiating anti-tuberculosis therapy is appropriate before starting treatment. Patients should be monitored for the development of symptoms and signs of tuberculosis with ENSPRYNG, even if initial tuberculosis testing is negative.

Vaccinations

Live or live-attenuated vaccines should not be given concurrently with ENSPRYNG because clinical safety has not been established. Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of ENSPRYNG for live or live-attenuated vaccines and, whenever possible, at least 2 weeks prior to initiation of ENSPRYNG for non-live vaccines.

5.2 Elevated Liver Enzymes

Mild and moderate elevations of liver enzymes have been observed in patients treated with ENSPRYNG at a higher incidence than in patients receiving placebo *[see Adverse Reactions (6.1)]*.

ALT and AST levels should be monitored every 4 weeks for the first 3 months of treatment, followed by every 3 months for one year, and thereafter, as clinically indicated *[see Dosage and Administration (2.4)]*.

5.3 Decreased Neutrophil Counts

Decreases in neutrophil counts were observed in patients treated with ENSPRYNG at a higher incidence than placebo *[see Adverse Reactions (6.1)]*.

Neutrophil counts should be monitored 4 to 8 weeks after initiation of therapy, and thereafter at regular clinically determined intervals *[see Dosage and Administration (2.4)]*.

5.4 Hypersensitivity Reactions

Hypersensitivity reactions, including rash, urticaria, and fatal anaphylaxis, have occurred with other interleukin-6 receptor antagonists.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infections *[see Warnings and Precautions (5.1)]*
- Elevated Liver Enzymes *[see Warnings and Precautions (5.2)]*
- Decreased Neutrophil Counts *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

The safety of ENSPRYNG was evaluated in two randomized, placebo-controlled clinical trials [Study 1 evaluated ENSPRYNG without concurrent immunosuppressive therapy (IST) and Study 2 evaluated ENSPRYNG with concurrent IST], which included 41 anti-AQP4 seropositive patients treated with ENSPRYNG in Study 1 and 26 anti-AQP4 seropositive patients treated with ENSPRYNG in Study 2 *[see Clinical Studies (14)]*. In the double-blind, controlled period, the median exposure time on ENSPRYNG treatment was approximately 2 years in Study 1 and approximately 3 years in Study 2. The median exposure time on placebo treatment was approximately 1 year in both Study 1 and Study 2.

Adverse reactions that occurred in Study 1 and Study 2 in more than 5% of patients treated with ENSPRYNG, and at a greater incidence than in patients who received placebo, are shown in Table 3 and Table 4, respectively. The most common adverse reactions (15% or greater with ENSPRYNG in either) were nasopharyngitis, headache, upper respiratory tract infection, gastritis, rash, arthralgia, extremity pain, fatigue, and nausea.

Table 3 Adverse Reactions Occurring in 4 or More Patients Treated with ENSPRYNG and Greater Incidence than Placebo in Study 1

Adverse Reaction	ENSPRYNG (N = 41) %	PLACEBO (N = 23) %
Rash	17	0
Arthralgia	17	0
Pain in extremity	15	9
Fatigue	15	4
Nausea	15	9
Nasopharyngitis	12	4
Pruritus	10	0
Depression	10	0
Cellulitis	10	0
Neutropenia	10	4
Blood creatine phosphokinase increased	10	4
Fall	10	4

Wash your hands

10. Wash your hands with soap and water. **(See Figure H)**.

Figure H

Choose the injection site

11. Choose your injection site in either:
    - the lower part of your stomach (abdomen) or
    - the front and middle of your thighs. **(See Figure I)**.

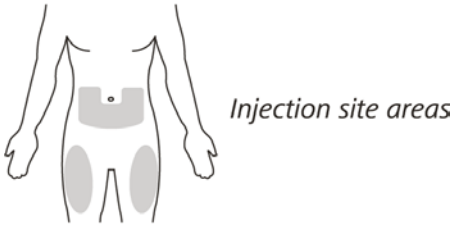

Figure I

- **Do not** inject into the 2-inch (5 cm) area around your belly button.
- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard or broken.

Choose a different injection site for **each new injection. Choose a different place to inject which is at least 1 inch (2.5 cm) away from the place where you last injected.**

Clean the injection site

12. Wipe the injection site with an alcohol pad and let it air dry.

    Do not:

    - fan or blow on the area which you have cleaned.
    - touch the injection site again before you give the injection.

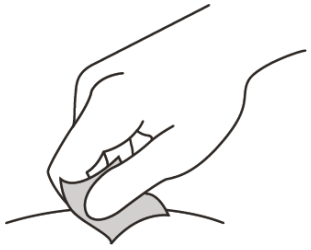

Figure J

Inject ENSPRYNG

13. Hold the barrel of the syringe between your thumb and index finger. With your other hand, pull the needle cap straight off. You may see a drop of liquid at the end of the needle. This is normal and will not affect your dose **(See Figure K)**.

    - **Use the syringe within 5 minutes of removing the cap or the needle may clog.**

    Do not:

    - take the needle cap off until you are ready to inject ENSPRYNG.
    - put the needle cap back on after it has been removed as this may damage the needle.
    - touch the needle or let it touch any surfaces after removing the needle cap.

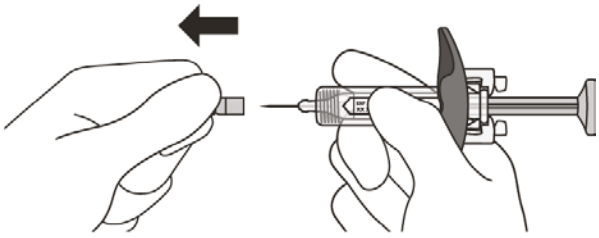

Figure K

14. Throw away the needle cap in a puncture-resistant sharps container immediately. See Step 21 “Disposing of ENSPRYNG”.
15. Hold the barrel of the syringe using your thumb and index finger. With your other hand, pinch the area of skin you have cleaned **(See Figure L).**

16. Use a quick, dart-like motion to insert the needle at an angle between 45° to 90° **(See Figure L).**

    Do not:

    - insert the needle through clothing.
    - change the angle of the injection.
    - insert the needle again.

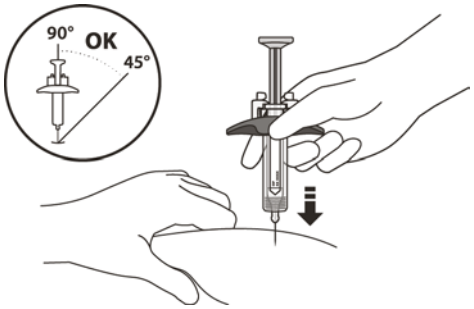

Figure L

17. After the needle is inserted, let go of the pinched skin.
18. Slowly inject all of the medicine by gently pushing the plunger all the way down until it touches the activation guards **(See Figure M).**

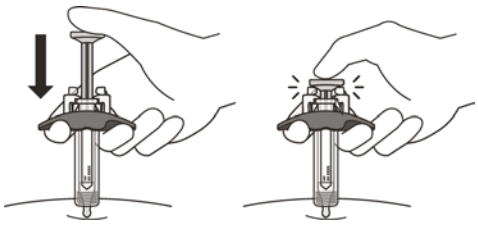

Figure M

19. Gently release the plunger and allow the needle to come out of the skin at the same angle it was inserted **(See Figure N)**.

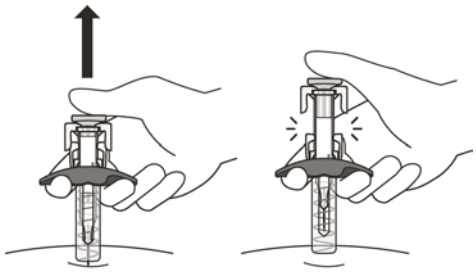

Figure N

- **The needle will now be covered by the needle-shield.** If the needle is not covered, carefully place the syringe into a puncture-resistant sharps container to avoid injury. See Step 21 “Disposing of ENSPRYNG”.

Taking care of the injection site

20. There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site but **do not** rub it. If needed, you may also cover the area you injected with a small bandage. If the medicine gets into contact with your skin, wash the area with water.

Disposing of ENSPRYNG

21. Put your used syringe in an FDA-cleared sharps disposal container immediately after use **(See Figure O)**. **Do not** throw away (dispose of) the syringe in your household trash.

Figure O

- If you **do not** have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
  - upright and stable during use
  - leak-resistant
  - properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- **Do not** dispose of your used sharps disposal container in trash unless your community guidelines permit this.
- **Do not** recycle your used sharps disposal container.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
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Approved: 8/2020

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