

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.

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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 (5.2)*].

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) and Clinical Pharmacology (12.2)*].

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. <u>Maintenance period</u> After the delayed or missed dose is administered, reset the dose schedule to every 4 weeks. <u>Loading period</u> If the second loading dose is delayed or missed, administer as soon as possible and administer the 3 rd and final loading dose 2 weeks later. If the third loading dose is delayed or missed, administer as soon as possible and administer the 1 st 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 $1.0 \times 10^9/L$ 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 (5.1)*]
- 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

Table 4 Adverse Reactions Occurring in 3 or More Patients Treated with ENSPRYNG and Greater Incidence than Placebo in Study 2

Adverse Reaction	ENSPRYNG + IST (N = 26) %	PLACEBO + IST (N = 26) %
Nasopharyngitis	31	15
Headache	27	12
Upper respiratory tract infection	19	12
Gastritis	15	0
Arthralgia	12	0
Pharyngitis	12	8

Injection-Related Reactions

In Study 1 and Study 2, injection-related reactions were reported in 9% of patients treated with ENSPRYNG compared with 8% in patients receiving placebo. These reactions in the ENSPRYNG-treated patients were predominantly mild to moderate in severity, and most occurred within 24 hours after the injection. The most commonly reported systemic symptom was diarrhea. The reported local injection site reactions were pruritus, injection site reaction, and skin mass.

Infections

In Study 1, the rate of infections was 51 patients/100 patient-years (95% CI: 32, 78) in patients treated with ENSPRYNG compared with 108 patients/100 patient-years (95% CI: 52, 199) in patients receiving placebo. The rate of serious infections was 5 patients/100 patient-years (95% CI: 1, 14) in patients treated with ENSPRYNG compared with 4 patients/100 patient-years (95% CI: 0, 21) in patients receiving placebo.

In Study 2, the rate of infections was 168 patients/100 patient-years (95% CI: 100, 265) in patients treated with ENSPRYNG compared with 143 patients/100 patient-years (95% CI: 83, 229) in patients treated with placebo. The rate of serious infections was 4 patients/100 patient-years (95% CI: 1, 15) in patients treated with ENSPRYNG compared with 10 patients/100 patient-years (95% CI: 2, 28) in patients receiving placebo.

Laboratory Abnormalities

Decreased Neutrophil Count

Of the patients treated with ENSPRYNG, 10% had neutrophils below $1 \times 10^9/L$ compared to 9% in placebo in Study 1. In Study 2, 15% patients had neutrophils below $1 \times 10^9/L$ compared to 4% in placebo. There was one patient in Study 1 treated with ENSPRYNG with neutrophil counts $< 0.5 \times 10^9/L$, and one patient in Study 2 discontinued ENSPRYNG because of neutropenia.

Decreased Platelet Count

In Study 1, a shift in platelet count decreases from normal at baseline to below the lower limit of normal (LLN) occurred in 26% of patients treated with ENSPRYNG compared to 5% of patients receiving placebo. In Study 2, decreases in platelet counts from normal at baseline to below the LLN occurred in 35% of patients treated with ENSPRYNG and in 17% of patients receiving placebo. None of the patients had a decrease in platelet count to less than $50 \times 10^9/L$.

Elevated Liver Enzymes

In Study 1, increases from normal at baseline to above ULN in ALT or AST occurred in 43% and 25% of patients treated with ENSPRYNG, respectively, compared to 13% and 9% of patients receiving placebo. In Study 2, increases from normal at baseline to above the ULN in ALT or AST occurred in 8% and 8% of patients treated with ENSPRYNG, respectively, compared to 12% and 19% of patients receiving placebo.

In Study 1 and Study 2 combined, elevations of ALT or AST greater than 3 times the ULN occurred in 3% of patients treated with ENSPRYNG, compared to no patients treated with placebo. These elevations were not associated with increases in total bilirubin. One patient receiving ENSPRYNG in Study 2 had an elevation of ALT above 5 times the ULN, which was observed 4 weeks after initiation of therapy, normalizing 78 days after discontinuation of ENSPRYNG.

Lipid Abnormalities

In Study 1 and Study 2, elevations in total cholesterol above 7.75 mmol/L (300 mg/dl) occurred in 12% and 15% of patients treated with ENSPRYNG, respectively, compared to no patients receiving placebo.

Elevations in triglycerides above 3.42 mmol/L (300 mg/dl) occurred in 27% and 12% of patients treated with ENSPRYNG in Study 1 and Study 2, respectively, compared to 13% and 8% of patients receiving placebo.

Fibrinogen Levels

In Study 1, the median percent reduction in fibrinogen was 38% in patients treated with ENSPRYNG compared to 5% in patients receiving placebo. In Study 2, the median percent reduction in fibrinogen level was 33% in patients treated with ENSPRYNG compared to 0% in patients receiving placebo.

Complement Levels

In Study 1, the median percent reduction in the C3 and C4 components of complement was 23% and 50% in patients treated with ENSPRYNG, respectively, compared to 0% and 1% patients receiving placebo. In Study 2, the median percent reduction in the C3 and C4 components of complement was 20% and 53% in patients treated with ENSPRYNG, respectively, compared to 0% and 1% in patients receiving placebo.

Body Weight

In the pool of Studies 1 and 2, body weight increases of at least 7% from baseline occurred in 30% of patients treated with ENSPRYNG compared to 8% of patients receiving placebo.

Body weight increases of at least 15% from baseline occurred in 6% of patients treated with ENSPRYNG compared to 4% of patients receiving placebo.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of anti-satralizumab-mwge antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In Study 1 and Study 2, anti-drug-antibodies (ADAs) were observed in 73% and 38% of patients receiving ENSPRYNG in the double-blind period, respectively. The ability of these ADAs to neutralize satralizumab-mwge binding is unknown. Patients with higher body weight and lower exposure were more likely to develop ADAs (irrespective of treatment with IST). Exposure was lower in ADA positive patients. Although anti-satralizumab-mwge antibody development was not found to affect the efficacy of ENSPRYNG in these patients, the available data are too limited to make definitive conclusions. Immunogenicity does not have a clinically-relevant impact on safety. Based on the available information, neither dose interruption nor modification is warranted in those patients who develop ADAs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of ENSPRYNG in pregnant women. In an animal reproduction study, no adverse effects on maternal animals or fetal development were observed in pregnant monkeys and their offspring, with administration of satralizumab-mwge at doses up to 50 mg/kg/week (*see Data*).

In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Fetal/neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to ENSPRYNG in utero [*see Warnings and Precautions (5.1)*].

Data

Animal Data

Weekly subcutaneous administration of satralizumab-mwge (0, 2, or 50 mg/kg) to monkeys throughout pregnancy resulted in no adverse effects on postnatal development of the offspring; however, immune function was impaired in offspring at both doses. Plasma exposures (C_{ave}) in dams at the low and high doses were approximately 3 and 100 times, respectively, that in humans at the recommended monthly maintenance dose of 120 mg.

8.2 Lactation

Risk Summary

No information is available on the presence of satralizumab-mwge in human milk, the effects of the satralizumab-mwge on the breastfed infant, or the effects of the satralizumab-mwge on milk production. Satralizumab-mwge was excreted in the milk of lactating monkeys administered satralizumab-mwge throughout pregnancy. Human IgG is excreted in human milk and the potential for absorption in the infant is unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ENSPRYNG and any potential adverse effects on the breastfed infant from ENSPRYNG or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ENSPRYNG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients. However, population pharmacokinetic analyses in patients with NMOSD did not show that age affected the pharmacokinetics of satralizumab-mwge [see *Clinical Pharmacology (12.3)*]. In general, caution should be used when dosing the elderly, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant diseases or other drug therapy.

11 DESCRIPTION

Satralizumab-mwge is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody based on a human IgG2 framework. Each light chain and heavy chain consists of 214 and 443 amino acids, respectively. Satralizumab-mwge is a glycoprotein with an approximate molecular weight of 143 kDa and is produced by recombinant DNA technology in Chinese hamster ovary cells. The binding of satralizumab-mwge to the IL-6 receptor is pH-sensitive.

ENSPRYNG (satralizumab-mwge) injection for subcutaneous administration is supplied as a sterile, clear, colorless to slightly yellow solution with no preservative with an approximate pH of 6. ENSPRYNG is supplied in a single-dose prefilled syringe. Each syringe delivers 1 mL of solution containing 120 mg of satralizumab-mwge, L-arginine (26.1 mg), L-histidine (3.1 mg), poloxamer 188 (0.5 mg), L-aspartic acid (pH adjustment), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which satralizumab-mwge exerts therapeutic effects in NMOSD is unknown but is presumed to involve inhibition of IL-6-mediated signaling through binding to soluble and membrane-bound IL-6 receptors.

12.2 Pharmacodynamics

The relationship between any of the pharmacodynamic effects of ENSPRYNG and clinical outcomes in NMOSD is unknown.

12.3 Pharmacokinetics

The pharmacokinetics of ENSPRYNG have been characterized both in Japanese and Caucasian healthy volunteers, and in NMOSD patients. The pharmacokinetics in NMOSD patients using the recommended dose were characterized using population pharmacokinetic analysis methods based on a database of 154 patients.

The concentration-time course of ENSPRYNG in patients with NMOSD was accurately described by a two-compartment population pharmacokinetic model with parallel linear and target-mediated (Michaelis-Menten) elimination and first-order subcutaneous absorption. ENSPRYNG clearance and volume parameters allometrically scaled by body weight (through power function with the fixed power coefficient of 0.75 and 1 for clearance and volume parameters, respectively). Body weight was shown to be a significant covariate, with clearance and V_c for patients weighing 123 kg (97.5th percentile of the weight distribution) increased by 71.3% and 105%, respectively, compared to a patient weighing 60 kg.

Steady state pharmacokinetics were achieved after the loading period (8 weeks) as follows [mean (\pm SD)]: C_{min} : 19.7 (12.2) mcg/mL, C_{max} : 31.5 (14.9) mcg/mL, and AUC: 737 (386) mcg.mL/day.

Absorption

The bioavailability of satralizumab-mwge was 85%.

Distribution

Satralizumab-mwge undergoes biphasic distribution. The central volume of distribution was 3.46 L and the peripheral volume of distribution was 2.07 L. The inter-compartmental clearance was 0.336 L/day.

Elimination

The total clearance of satralizumab-mwge is concentration-dependent. Linear clearance (accounting for approximately half of the total clearance at steady state using the recommended dose in NMOSD patients) is estimated to be 0.0601 L/day. The associated terminal $t_{1/2}$ is approximately 30 days (range 22 – 37 days) based on data pooled from Study 1 and Study 2.

Metabolism

The metabolism of satralizumab-mwge has not been directly studied, as antibodies are cleared principally by catabolism.

Excretion

Monoclonal antibodies, including satralizumab-mwge, are not eliminated via renal or hepatic pathways.

Specific Populations

Population pharmacokinetic analyses in patients with NMOSD showed that age, gender, and race did not meaningfully influence the pharmacokinetics of satralizumab-mwge.

Patients with Renal or Hepatic Impairment

No formal studies of the effect of renal impairment or hepatic impairment on the pharmacokinetics of satralizumab-mwge were conducted.

Drug Interaction Studies

No formal drug-drug interaction studies have been performed with ENSPRYNG.

Based on population pharmacokinetic analyses of the available data, the impact of commonly used small molecule drugs on the pharmacokinetics of satralizumab-mwge remains inconclusive.

Suppression of IL-6 signaling by treatment with ENSPRYNG, from the low baseline levels seen in Study 1 and Study 2, is expected to have a minor impact on exposure of concomitant medications metabolized by CYP450 enzymes. The clinical significance of this is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies of satralizumab-mwge were not conducted.

Mutagenesis

Genetic toxicology studies of satralizumab-mwge were not conducted. As an antibody, satralizumab-mwge is not expected to interact directly with DNA.

Impairment of Fertility

In monkeys administered satralizumab-mwge (0, 2, 10, or 50 mg/kg) weekly by subcutaneous injection for 26 weeks, no effects on sperm, estrus cycle, or male and female reproductive organs were observed. At the high dose, plasma exposures (C_{ave}) were approximately 100 times that in humans at the recommended monthly maintenance dose of 120 mg.

14 CLINICAL STUDIES

The efficacy of ENSPRYNG for the treatment of NMOSD in adult patients was established in two studies. Study 1 was a randomized (2:1), placebo-controlled trial in 95 patients without

concurrent IST (Study 1, NCT02073279) in which 64 patients were anti-AQP4 antibody positive and 31 patients were anti-AQP4 antibody negative.

Study 2 was a randomized (1:1), placebo-controlled trial in 76 adult patients with concurrent IST (Study 2, NCT02028884). Of these, 52 adult patients were anti-AQP4 antibody positive and 24 adult patients were anti-AQP4 antibody negative.

Patients met the following eligibility criteria:

1. Study 1: Clinical evidence of 1 relapse in the previous 12 months
2. Study 2: Clinical evidence of at least 2 relapses in the previous 2 years, at least one of which must have occurred in the previous year
3. EDSS score of 0 to 6.5 (both studies)
4. Study 1: Patients were excluded if previously treated with IST within an interval specified for each such therapy
5. Study 2: One of the following baseline treatments at a stable dose as a monotherapy for 8 weeks prior to baseline: azathioprine, mycophenolate mofetil, oral corticosteroids

In Study 1, 41 anti-AQP4 antibody positive adult patients were randomized to and received ENSPRYNG and 23 received placebo. Females accounted for 76% of the ENSPRYNG group and 96% of the placebo group. The remaining baseline demographic characteristics were balanced between the treatment groups. The mean age was 44 years. Fifty percent were White, 22% were Black or African-American, and 20% were Asian. The mean EDSS score was 3.8.

In Study 2, 26 anti-AQP4 antibody positive adult patients were randomized to and received ENSPRYNG and 26 received placebo. All patients were receiving either concurrent azathioprine (42%), oral corticosteroids (52%), or mycophenolate mofetil (6%) during the trial. The baseline demographic and disease characteristics were balanced between the treatment groups. Females accounted for 100% of the study population. Forty-six percent of patients were White and 52% were Asian. The mean age was 46 years. The mean EDSS score was 4.0.

All potential relapses were adjudicated by a blinded Clinical Endpoint Committee (CEC). The primary efficacy endpoint for both studies was the time to the first CEC-confirmed relapse.

In Study 1, the time to the first CEC-confirmed relapse was significantly longer in ENSPRYNG-treated patients compared to patients who received placebo (risk reduction 55%; hazard ratio 0.45; $p = 0.0184$). In the anti-AQP4 antibody positive population, there was a 74% risk reduction; hazard ratio 0.26; $p = 0.0014$ (Table 5; Figure 1). There was no evidence of a benefit in the anti-AQP4 antibody negative patients.

In Study 2, the time to the first CEC-confirmed relapse was significantly longer in patients treated with ENSPRYNG compared to patients who received placebo (risk reduction 62%; hazard ratio 0.38; $p = 0.0184$). In the anti-AQP4 antibody positive population, there was a 78% risk reduction; hazard ratio 0.22; $p = 0.0143$ (Table 5; Figure 2). There was no evidence of a benefit in the anti-AQP4 antibody negative patients.

Table 5 Efficacy Results from Study 1 and Study 2 in anti-AQP4 Antibody Positive NMOSD Patients

	Study 1		Study 2	
	ENSPRYNG N=41	Placebo N=23	ENSPRYNG + IST* N= 26	Placebo + IST N=26
Time to Clinical Endpoint Committee (CEC)-Determined Relapse (Primary Efficacy Endpoint)				
Number (%) of Patients with Relapse	9 (22)	13 (56.5)	3 (11.5)	11 (42.3)
Hazard Ratio (95% CI)	0.26 (0.11, 0.63)		0.22 (0.06, 0.82)	
p-value	0.0014		0.0143	
Risk Reduction	74%		78%	
Proportion of Protocol Defined Relapse-Free Patients at 96 Weeks	76.5%	41.1%	91.1%	56.8%

* IST = immunosuppressant therapy

Figure 1 Study 1: Time to First CEC-Determined NMOSD Relapse in the Randomized Controlled Period in the ITT Population Anti-AQP4 Antibody Positive Patients

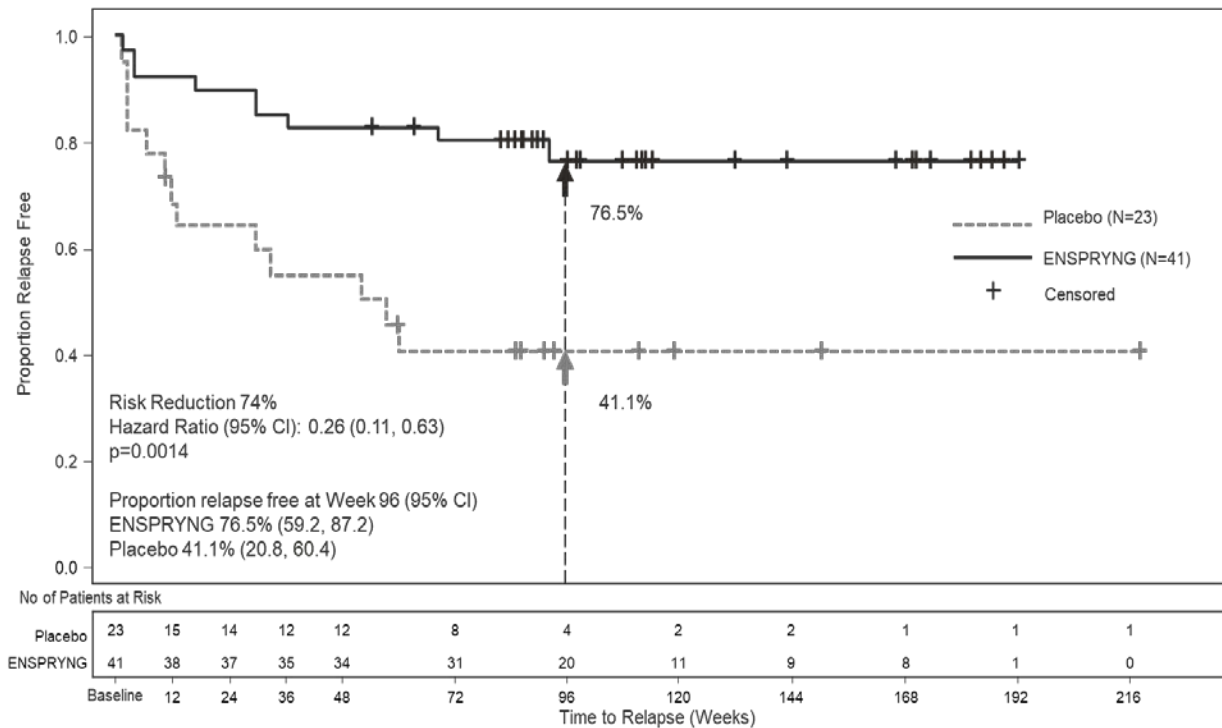
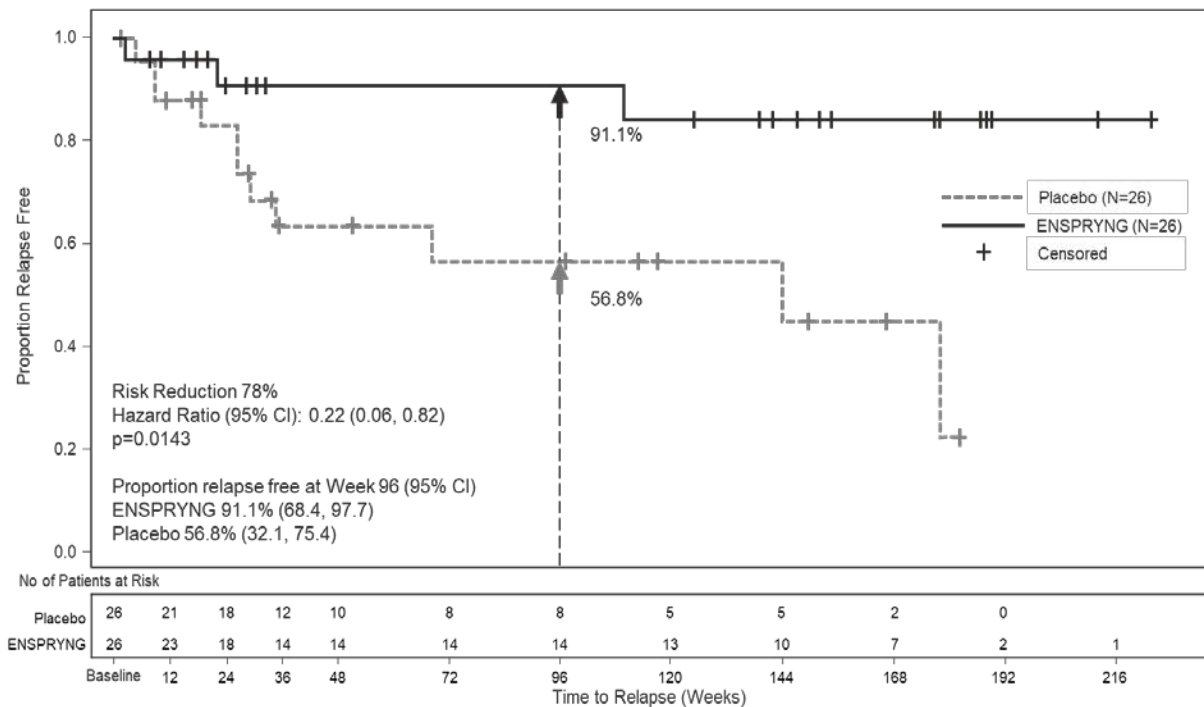


Figure 2 Study 2: Time to First CEC-Determined NMOSD Relapse in the Randomized Controlled Period in the ITT Population Anti-AQP4 Antibody Positive Patients



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ENSPRYNG (satralizumab-mwge) injection is available as a sterile, preservative-free, clear, colorless to slightly yellow solution in single-dose prefilled syringe (PFS) with needle safety device.

ENSPRYNG PFS is not made with natural rubber latex. Each ENSPRYNG carton contains one single-dose 120 mg/mL prefilled syringe (NDC 50242-007-01).

16.2 Storage and Handling

- Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.
- Prior to administration, ENSPRYNG, if unopened, can be removed from and returned to the refrigerator, if necessary. The total combined time out of refrigeration should not exceed 8 days at a temperature that does not exceed 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that an increased risk of infections, including serious and potentially fatal infections, has been observed in patients treated with IL-6 receptor antagonists, including ENSPRYNG. Instruct patients to contact their healthcare provider immediately when symptoms suggesting infection (e.g., fever, chills, constant cough, or sore throat) appear during treatment [see Warning and Precautions (5.1)].

Vaccinations

Advise patients to complete any required vaccinations 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*].

Elevated Liver Enzymes

Inform patients on the importance of liver enzyme testing [*see Warnings and Precautions (5.2)*].

Decreased Neutrophil Counts

Inform patients on the importance of neutrophil count testing [*see Warnings and Precautions (5.3)*].

Hypersensitivity Reactions

Inform patients about the signs and symptoms of hypersensitivity reactions and anaphylaxis and advise them to contact their healthcare provider immediately if these symptoms occur [*see Warnings and Precautions (5.4)*].

Instruction on Injection Technique

Instruct patients and caregivers to read the Instructions for Use before the patient starts using ENSPRYNG, and each time the patient gets a refill as there may be new information they need to know.

Perform the first injection under the guidance of a qualified healthcare professional. If a patient or caregiver is to administer subcutaneous ENSPRYNG, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous ENSPRYNG and the suitability for home use [*see Dosage and Administration (2.3) and Instructions for Use*].

Instruct patients to remove the prefilled syringe from the refrigerator prior to use and allow to sit at room temperature outside of the carton for 30 minutes. Do not warm ENSPRYNG in any other way.

Advise patients to consult their healthcare provider if the full dose is not received.

A puncture-resistant container for disposal of syringes should be used and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper prefilled syringe disposal, and caution against reuse of these items.

ENSPRYNG™ [satralizumab-mwge]

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

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MEDICATION GUIDE
ENSPRYNG™ (en-spryng)
(satralizumab-mwge)
injection, for subcutaneous use

What is the most important information I should know about ENSPRYNG?

ENSPRYNG may cause serious side effects including:

1. Infections. ENSPRYNG can increase your risk of serious infections some of which can be life-threatening. Talk to your healthcare provider if you are being treated for an infection or call them right away if you think you have signs of an infection, with or without a fever, such as:

- chills, feeling tired, muscle aches, cough that will not go away or a sore throat
- skin redness, swelling, tenderness, pain or sores on your body
- diarrhea, belly pain, or feeling sick
- burning when you urinate or urinating more often than usual

Your healthcare provider will check if you have an infection and treat it if needed before you start or continue to take ENSPRYNG.

- Your healthcare provider should test you for hepatitis and tuberculosis (TB) before you start taking ENSPRYNG.
- All required vaccinations should be completed before starting ENSPRYNG. People using ENSPRYNG should not be given 'live' or 'live-attenuated' vaccines. 'Live' or 'live-attenuated' vaccines should be given at least 4 weeks before you start ENSPRYNG. Your healthcare provider may recommend that you get a 'non-live' (inactivated) vaccine, such as some of the seasonal flu vaccines. If you plan to get a 'non-live' (inactivated) vaccine, it should be given, whenever possible, at least 2 weeks before you start ENSPRYNG.

2. Increased liver enzymes.

Your healthcare provider should order blood tests to check your liver enzymes before and while you are taking ENSPRYNG. Your healthcare provider will tell you how often you will need to have these blood tests. Make sure you get all of your follow-up blood tests as ordered by your healthcare provider. Your healthcare provider will tell you if you need to wait to start ENSPRYNG if your liver enzymes are increased.

3. Low neutrophil count.

ENSPRYNG can cause a decrease in your neutrophil counts in your blood. Neutrophils are white blood cells that help the body fight off bacterial infections. Your healthcare provider should order blood tests to check your neutrophil count while you are taking ENSPRYNG.

See **“What are the possible side effects with ENSPRYNG?”**

What is ENSPRYNG?

ENSPRYNG is a prescription medicine used to treat neuromyelitis optica spectrum disorder (NMOSD) in adults who are aquaporin-4 (AQP4) antibody positive.

It is not known if ENSPRYNG is safe and effective in children.

Do not take ENSPRYNG if you:

- are allergic to satralizumab-mwge or any of the ingredients in ENSPRYNG. See **“What are the ingredients in ENSPRYNG?”** at the end of this Medication Guide for a complete list of ingredients in ENSPRYNG.
- have an active hepatitis B infection.
- have active or untreated inactive (latent) TB.

Before you take ENSPRYNG, tell your healthcare provider about all of your medical conditions, including if you:

- have or think you have an infection. See **“What is the most important information I should know about ENSPRYNG?”**
- have liver problems.
- have ever had hepatitis B or are a carrier of the hepatitis B virus.
- have had or have been in contact with someone with tuberculosis.
- have had a recent vaccination or are scheduled to receive any vaccination.
- are pregnant, think that you might be pregnant, or plan to become pregnant. It is not known if ENSPRYNG will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if ENSPRYNG passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ENSPRYNG.

Tell your healthcare provider about all the medicines you are taking, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take ENSPRYNG?

- ENSPRYNG is provided as a solution in a single-dose, prefilled syringe of 120 mg/mL of satralizumab-mwge.
- See the **Instructions for Use** inside the carton for complete instructions for the right way to prepare and inject ENSPRYNG.

- ENSPRYNG is given by an injection under the skin (subcutaneously). If your healthcare provider decides that you or your caregiver can give your injections of ENSPRYNG, you or your caregiver should receive training on the right way to prepare and inject ENSPRYNG.
- Always inject all of the medicine in the syringe.
- The first 3 injections (loading period) of ENSPRYNG are taken 1 time every 2 weeks.
- After this, injection of ENSPRYNG is taken every 4 weeks (maintenance period). Keep taking ENSPRYNG 1 time every 4 weeks for as long as your healthcare provider tells you to.
- If you miss a dose of ENSPRYNG, talk to your health care provider about restarting dosing.

What are the possible side effects of ENSPRYNG?

ENSPRYNG may cause serious side effects, including:

- See “**What is the most important information I should know about ENSPRYNG?**”
- **Serious allergic reactions.** Serious allergic reactions that may be life-threatening have happened with other medicines like ENSPRYNG. Tell your healthcare provider before taking your next dose if you had hives, rash, or flushing after your injection. Seek medical attention right away if you have any symptoms of a serious allergic reaction, such as:
 - shortness of breath or trouble breathing
 - swelling of your lips, face, or tongue
 - dizziness or feeling faint
 - moderate or severe stomach (abdominal) pain or vomiting
 - chest pain
- The most common side effects of ENSPRYNG include:
 - sore throat, runny nose (nasopharyngitis)
 - headache
 - rash
 - upper respiratory tract infection
 - fatigue
 - nausea
 - extremity pain
 - inflammation of the stomach lining (gastritis)
 - joint pain

These are not all the possible side effects of ENSPRYNG.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Genentech at 1-888-835-2555.

How should I store ENSPRYNG?

- Store ENSPRYNG in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton.
- Protect from light.
- **Do not** freeze or use the syringe if it has been frozen.
- **Do not** shake.
- ENSPRYNG, if unopened, can be removed from and returned to the refrigerator, if needed. The total combined time out of the refrigerator should not be more than 8 days at a temperature that does not go above 86°F (30°C).

General information about the safe and effective use of ENSPRYNG.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ENSPRYNG for a condition for which it was not prescribed. Do not give ENSPRYNG to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ENSPRYNG that is written for health professionals.

What are the ingredients in ENSPRYNG?

Active ingredient: satralizumab-mwge

Inactive ingredients: L-arginine, L-histidine, poloxamer 188, L-aspartic acid, and Water for Injection.

Manufactured by: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

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For more information, go to www.ENSPRYNG.com or call 1-844-NSPRYNG.