PDL DRUG REVIEW

Proprietary Name: Enspryng®
Common Name: satralizumab
PDL Category: Immunosuppressants

Comparable Products	Preferred Drug List Status
Soliris	Medical Coverage
Uplizna	Medical Coverage

Summary

Pharmacology/Usage: Satralizumab-mwge, the active ingredient of Enspryng®, is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody based on a human IgG2 framework. It is produced by recombinant DNA technology in Chinese hamster ovary cells. Its exact mechanism of action is not known but it is presumed to involve inhibition if IL-6 mediated signaling through binding to soluble and membrane-bound IL-6 receptors.

Indication: For the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adults who are anti-aquaporin-4 (AQP4) antibody positive.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate data on the developmental risk associated with the use in pregnant women. There are clinical considerations, as monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses. The largest amount transferred during pregnancy is 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. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Injection, a solution in a single-dose prefilled syringe: 120mg/ml. Prior to use, remove the prefilled syringe from the refrigerator and allow to sit at room temperature for 30 minutes.

Recommended Dosage: Prior to initiating Enspryng®,

- Perform Hepatitis B virus (HBV) screening. Use 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®.
- Assess 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 starting Enspryng® treatment.

- Assess liver transaminases and serum bilirubin. Caution should be used when considering initiation of Enspryng® treatment in patients whose AST or ALT levels are greater than 1.5 times the upper limit of normal.
- Administer all immunizations per immunization guidelines at least 4 weeks prior to the start of Enspryng® for live or live-attenuated vaccines, and whenever possible, at least 2 weeks prior to the start of Enspryng® for non-live vaccines.

Enspryng® is for subcutaneous use only. A patient may self-inject or the patient's caregiver may administer after proper training in subcutaneous injection technique, if the health care provider determines appropriate. Administer by SC injection in the abdomen or thigh, rotating the injection sites with each administration. Prior to every use, advise patients to consult with their healthcare professional if they suspect an active infection, including localized infections. Delay the use of Enspryng® in case of active infection until the infection is resolved.

The recommended loading dose for the first 3 administrations is 120mg SC injection at weeks 0, 2, and 4, followed by a maintenance dose of 120mg every 4 weeks. Refer to the prescribing information for specific information regarding dosage for delayed or missed doses.

ALT and AST levels must be monitored every 4 weeks for the first 3 months of Enspryng® treatment, followed by every 3 months for one year, and thereafter as clinically indicated. Refer to the prescribing information for when to discontinue treatment due to elevated levels and the process of restarting treatment.

Monitor neutrophil counts 4 to 8 weeks after the start of therapy and thereafter at regular clinically determined intervals. If the neutrophil count is below 1.0 X 10^9/L and confirmed by repeat testing, Enspryng® should be interrupted until the neutrophil count is > 1.0 X 10^9/L.

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

Drug Interactions: There are no drug interactions reported with this product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Enspryng®) minus reported % incidence for placebo for maintenance. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included rash (17%), arthralgia (17%), pain in extremity (6%), fatigue (11%), nausea (6%), nasopharyngitis (8%), pruritus (10%), depression (10%), cellulitis (10%), neutropenia (6%), blood creatine phosphokinase increased (6%), and fall (6%). Other reported adverse events included injection-related reactions (1%) and body weight increases of at least 7% from baseline (22%). The rate of infections in study 1 was 51 patients/100 patient-years in patients treated with Enspryng® compared with 108 patients/100 patient-years in patients receiving placebo. The rate of infections in study 2 was 168 patients/100 patient-years in patients treated with Enspryng® as compared with 143 patients/100 patient-years in patients treated with placebo.

An increased risk of infections has been observed in patients treated with IL-6 receptor antagonists, including Enspryng®. Delay administration of Enspryng® in patients with an active infection, including localized infections, until the infection is resolved. Patients with chronic hepatitis B virus infection were excluded from clinical trials, and thus perform hepatitis B virus screening in all patients before the start of Enspryng® treatment. Do not administer Enspryng® to patients with active hepatitis. In addition, patients should be assessed for tuberculosis risk factors and tested for latent infection prior to starting Enspryng®. Consider anti-tuberculosis therapy prior to the start 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. Monitor for the development of symptoms and signs of tuberculosis with Enspryng®, even if the initial tuberculosis testing is negative.

Mild and moderate elevations of liver enzymes have been observed in patients treated with Enspryng®, at a higher incidence than in patients receiving placebo. 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.

Decreases in neutrophil counts were observed in patients treated with Enspryng® at a higher incidence than placebo. Neutrophil counts should be monitored 4 to 8 weeks after the start of Enspryng®, and thereafter at regular clinically determined intervals.

Contraindications: In patients with:

- A known hypersensitivity to satralizumab or any of the active ingredients
- Active Hepatitis B infection
- Active or untreated latent tuberculosis

Manufacturer: Genentech Inc

Analysis: The safety and efficacy of Enspryng® for the treatment of NMOSD were established in 2 studies. Study 1 was a randomized, placebo-controlled trial that included adults (N=95) without concurrent immunosuppressive therapy (IST), in which 64 patients were anti-AQP4 antibody positive and 31 patients were anti-AQP4 antibody negative. Patients met the following criteria to be eligible for the study 1, including clinical evidence of 1 relapse in the previous 12 months and EDSS score of 0 to 6.5, and patients were excluded if previously treated with IST within an interval specified for each such therapy.

In this study, 41 anti-AQP4 antibody positive adults 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 mean age of the anti-AQP4 antibody positive adults was 44 years, while 50% were White and the mean EDSS (expanded disability status scale) score was 3.8.

Study 2 was a randomized, placebo-controlled trial that included adults (N=76) with concurrent IST, of which 52 adult patients were anti-AQP4 antibody positive and 24 adult patients were anti-AQP4 antibody negative. Patients met the following criteria to be eligible for study 2, including clinical evidence of at least 2 relapses in the previous 2 years (at least one of which must have occurred in the previous year), had an EDSS score of 0 to 6.5, and one of the following baseline treatments at a stable dose as a monotherapy for 8 weeks prior to baseline to include azathioprine, mycophenolate mofetil, or oral corticosteroids.

In this study, 26 anti-AQP4 antibody positive adults 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. Females accounted for 100% of this study population, while 46% were White, the mean age was 46 years, and the mean EDSS score was 4.0.

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

Results suggested that in study 1, the time to the first CEC-confirmed relapse was significantly longer in the Enspryng®-treated patients compared to those who received placebo (risk reduction (RR) 55%, hazard ratio (HR) 0.45; p=0.0184). In the anti-AQP4 antibody positive population, there was a 74% RR (HR 0.26; p=0.0014). There was no evidence of a benefit in the anti-AQP4 antibody negative patients.

Results suggested that 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 (RR 62%, HR 0.38; p=0.0184). In the anti-AQP4 antibody positive population, there was a 78% RR (HR 0.22, p=0.0143). There was no evidence of a benefit in the anti-AQP4 antibody negative patients.

Specific results of both studies can be found in the table below, which was adapted from the prescribing information. These are results in anti-AQP4 antibody positive 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 endpoint)				
Number (%) of patients with Relapse	9 (22%)	13 (56.5%)	3 (11.5%)	11 (42.3%)
Hazard Ratio	0.26		0.22	
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%

Place in Therapy: Enspryng® is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. Use is contraindicated with active Hepatitis B infection or active or untreated latent tuberculosis. In two placebo-controlled trials, the time to the first Clinical Endpoint Committee (CEC)-confirmed relapse was significantly longer with the Enspryng® group compared to placebo. In addition, significantly more in the Enspryng® group than placebo group were relapse-free at 96 weeks. While there are 3 treatments available for NMOSD, Enspryng® is the only product that can be self-administered by the patient.

A 2020 meta-analysis by Xue et al[2] included 4 randomized controlled trials to assess the safety and efficacy of monoclonal antibodies (rituximab, eculizumab [Soliris®], inebilizumab-cdon [Uplizna®], and satralizumab [Enspryng®]) in NMOSD. Pooled results suggested that the monoclonal antibodies reduced annualized relapse rate (mean -0.27, p<0.0001), on-trial relapse rate (RR 0.25, p=0.0003), EDSS score (mean -0.51, p=0.01), and serious adverse events (RR 0.59, p=0.03). In a subgroup analysis comparing with other monoclonal antibodies, eculizumab might be more effective in decreasing on-trial relapse risk for AQP4 positive patients (p=0.002). Note that the other three treatments included both AQP+ and AQP- patients while the eculizumab trial included only AQP4+ patients. The authors concluded that monoclonal antibody therapy was safe and effective in NMOSD treatment. Further studies are needed.

It is recommended that Enspryng® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Enspryng [package insert]. South San Francisco, CA: Genentech, Inc, A member of the Roche Group 2020.
[2] Xue T, Yang Y, Lu Q, et al. Efficacy and safety of monoclonal antibody therapy in neuromyelitis optica spectrum disorders: Evidence from randomized controlled trials. *Mult Scler Relat Disord*. 2020; 43:102166.