Satralizumab-mwge (Enspryng™) New Drug Update

September 2020

Nonproprietary Name	satralizumab-mwge
Brand Name	Enspryng
Manufacturer	Genentech
Form	Prefilled syringe
Strength	120 mg/mL
FDA Approval	August 14, 2020
Market Availability	Available
FDA Approval Classification	Breakthrough Therapy, Orphan Drug
FDB Classification- Specific Therapeutic Class (HIC3)	Cytokine and CAM Antagonists (Z2V)

INDICATION[1]

Satralizumab-mwge (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.

PHARMACOKINETICS

Satralizumab-mwge demonstrates first-order absorption with a bioavailability of 85%. Distribution is shown to be biphasic with a central volume of distribution of 3.46 L and a peripheral volume of distribution of 2.07 L. Antibodies, such as satralizumab-mwge, are primarily cleared through catabolic processes. Satralizumab-mwge undergoes Michaelis-Menten elimination in the body, demonstrating concentration dependent clearance. Notably, satralizmab-mwge does not undergo hepatic or renal elimination.

CONTRAINDICATIONS/WARNINGS

Satralizumab-mwge is contraindicated in patients with a known hypersensitivity to satralizumab or any of the inactive drug components. Additionally, satralizumab-mwge is contraindicated in persons with active hepatitis B infection or active or untreated latent tuberculosis.

IL-6 receptor antagonists, including satralizumab-mwge, have been associated with an increased risk of infections. This risk includes serious and potentially fatal infections. The most common infections seen in clinical trial were nasopharyngitis, upper respiratory infections, pharyngitis, and cellulitis. Any patient with an active infection should not receive satralizumab-mwge therapy until the infection has resolved.

Other immunosuppressant therapies have shown to increase the risk of hepatitis B virus (HBV) reactivation. All patients considered for satralizumab-mwge therapy should be tested for HBV prior to initiating therapy. Any person with active hepatitis should not receive satralizumab-mwge. Consultation with a liver disease expert is recommended prior to initiating and throughout therapy in any persons who are chronic carriers of HBV (HBsAg+) or are HBsAg negative but HB core antibody positive (HBcAb+).

Other IL-6 receptor antagonists have been associated with tuberculosis (TB) infection. Prior to initiating satralizumab-mwge therapy, patients should be assessed for TB risk factors and receive TB testing for latent infections. All patients should be monitored for signs and symptoms of TB throughout satralizumab therapy.

Live or live-attenuated vaccines should be given ≥ 4 weeks prior to starting satralizumab therapy as the safety of concurrent administration has not been evaluated. Non-live vaccines should be given ≥ 2 weeks prior to therapy initiation, if possible.

Patients receiving satralizumab-mwge have experienced mild and moderate liver enzyme elevations. Throughout the first 3 months of therapy, alanine aminotransferase (ALT) and aspartate transaminase (AST) laboratory values should be monitored every 4 weeks with subsequent monitoring every 3 months thereafter for 1 year. ALT and AST monitoring following 1 year should be performed as clinically indicated.

Satralizumab-mwge treated patients also have experienced decreases in neutrophil counts and should therefore have their neutrophil count monitored between 4 to 8 weeks after starting therapy. After this initial period, neutrophil monitoring should be performed at regular intervals.

Other IL-6 receptor antagonists have been associated with hypersensitivity reactions (e.g., rash, urticaria, fatal anaphylaxis). Monitor satralizumab-mwge patients closely for signs of hypersensitivity.

DRUG INTERACTIONS

Satralizumab-mwge has no known drug interactions

COMMON ADVERSE EFFECTS

Adverse effects of satralizumab-mwge were evaluated in 2 randomized controlled trials. The most common adverse effects reported with satralizumab-mwge, occurring at an incidence of > 5% and occurring at a greater incidence relative to placebo, respectively, in trial 1, were rash (17% versus 0%), arthralgia (17% versus 0%), pain in extremity (15% versus 9%), fatigue (15% versus 4%), nausea (15% versus 9%), nasopharyngitis (12% versus 4%), pruritis (10% versus 0%), depression (10% versus 0%), cellulitis (10% versus 0%), neutropenia (10% versus 4%), blood creatine phosphokinase increases (10% versus 4%), and falls (10% versus 4%). Additional adverse effects occurring in study 1 for satralizumab-mwge versus placebo, respectively, included infections (51 patients/100 patient-years versus 108 patients/100 patient-years), decreased neutrophil count (10% versus 9%), decreased platelet count (26% versus 5%), elevated liver enzymes (ALT, 43% versus 13%; AST, 25% versus 9%), elevated total cholesterol (12% versus 0%), elevated triglycerides (27% versus 13%), and median reduction in fibrinogen (38% versus 5%).

The most common adverse effects reported with satralizumab-mwge, occurring at an incidence of > 5% and at a greater incidence than placebo, respectively, in study 2, were nasopharyngitis (31% versus 15%),

headache (27% versus 12%), upper respiratory infection (19% versus 12%), gastritis (15% versus 0%), arthralgia (12% versus 0%), and pharyngitis (12% versus 8%). Additional adverse effects occurring in study 2 for satralizumab-mwge versus placebo, respectively, included infections (168 patients/100 patient-years versus 143 patients/100 patient-years), decreased neutrophil count (15% versus 4%), decreased platelet count (35% versus 17%), elevated liver enzymes (ALT, 8% versus 12%; AST, 8% versus 19%), elevated total cholesterol (15% versus 0%), elevated triglycerides (12% versus 8%), and median reduction in fibrinogen (33% versus 0%).

Pooled data from studies 1 and 2 demonstrated additional adverse effects for satralizumab-mwge compared to placebo and included injection-related reactions (9% versus 8%, respectively) and increases in body weight of ≥ 7% from baseline (30% versus 8%, respectively). Additionally, anti-drug-antibodies (ADA) were detected in 73% of patients receiving satralizumab-mwge in study 1 and 38% of patients in study 2. It is unknown if these ADA have the ability to affect satralizumab-mwge binding. Definitive conclusions cannot be made regarding the impact of ADA on efficacy, but it does not appear the antibodies impacted efficacy. Furthermore, antibody development does not seem to result in clinical impact on product safety.

SPECIAL POPULATIONS

Pregnancy

Data for satralizumab-mwge in pregnancy are inadequate to advise of maternal or fetal risk. However, monoclonal antibodies can be transferred through the placenta, especially in the third trimester of pregnancy. As a result, consideration should be given to the risks versus benefits before administration of live or live-attenuated vaccines to infants with exposure to satralizumab-mwge in utero.

Pediatrics

Safety and efficacy of satralizumab-mwge has not been established in pediatric patients (< 18 years).

Geriatrics

Clinical trials did not include an adequate number of patients ≥ 65 years of age to inform of differences in response of satralizumab-mwge compared to younger patients. Based on population pharmacokinetic analysis, age does not appear to impact the pharmacokinetics.

Hepatic Impairment and Renal Impairment

Data for satralizumab-mwge use in hepatic or renal impairment are not sufficient to address pharmacokinetic differences in these populations, as no formal studies were performed in these patient populations.

DOSAGES

Satralizumab-mwge is administered as a subcutaneous (SC) injection in the abdomen or thigh. It requires three 120 mg loading doses, administered at weeks 0, 2, and 4, with subsequent maintenance doses of 120 mg given every 4 weeks. Satralizumab-mwge may be self-administered by the patient or administered by the patient's caregiver after receiving proper injection technique training.

CLINICAL TRIALS[2,3,4,5]

A literature search was performed using "satralizumab" and "neuromyelitis optica spectrum disorder "

The efficacy and safety of satralizumab-mwge was established in 2 double-blind, parallel-group, multicenter, phase 3, randomized controlled trials, SAkuraSky and SAkuraStar. SAkuraSky included 83 patients between the ages of 12 to 74 years with either AQP4-IgG seropositive (66% of participants) or AQP4-IgG seronegative (33% of participants) NMOSD. All study participants were required to have had ≥ 2 NMOSD relapses in the 2 years prior to screening with ≥ 1 relapse within the preceding year. Study inclusion criteria also required that patients have an Expanded Disability Status Scale (EDSS) score ≤ 6.5 (scale from 0 to 10, 0 = no disability; 10 = death). Participants were randomized 1:1 to receive either subcutaneous satralizumab 120 mg (n=41) at weeks 0, 2, and 4, with subsequent doses every 4 weeks thereafter, or matching placebo (n=42). SAkuraSky allowed satralizumab and placebo to be added on to stable immunosuppressant therapy (IST) with either azathioprine, mycophenolate mofetil, or oral glucocorticoids. Therapy with an anti-CD20 agent was not allowed in the 6 months prior to study inclusion or during the study. The primary outcome was the time to first NMOSD relapse.

In total, 8 patients (20%) in the satralizumab group and 18 patients (43%) in the placebo group experienced a primary event of relapse (hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.16 to 0.88; p=0.02), demonstrating a significantly longer time to first relapse for those treated with satralizumab. Within the AQP4-IgG seropositive patient population, 3 patients (11%) experienced a relapse in the satralizumab group compared to 12 patients (43%) in the placebo group (HR, 0.21; 95% CI, 0.06 to 0.75). Differences between the satralizumab and placebo groups were not significant within the AQP4-IgG seronegative population, with 5 and 6 patients (36% and 43%) experiencing relapses, respectively (HR, 0.66; 95% CI, 0.2 to 2.24).

SAkuraStar included 95 participants with either AQP4-IgG seropositive (67% of patients) or seronegative (33% of patients) NMOSD. Included participants were 18 to 74 years of age with ≥ 1 attack or relapse of NMOSD in the previous year. Participants were also required to have an EDSS score of ≤ 6.5. In total, 77 (81%) of the study participants were female. Study participants were randomized 2:1 to receive monotherapy with either subcutaneous satralizumab 120 mg (n=63) at weeks 0, 2, and 4 with subsequent doses every 4 weeks thereafter, or matching placebo (n=32). Notably, concurrent IST was not allowed during the study. The primary outcome was defined as the time to first NMOSD relapse.

At study conclusion, 19 (30%) relapses were reported for satralizumab-treated patients compared to 16 (50%) of placebo patients (HR, 0.45; 95% CI, 0.23 to 0.89; p = 0.018). Satralizumab-treated patients demonstrated a significantly longer time to first relapse than those receiving placebo. At 96 weeks, 72% of satralizumab patients were relapse free compared to 51% of those taking placebo. Within the AQP4-IgG seropositive population, 9 patients (22%) in the satralizumab group experienced relapse compared to 13 patients (57%) receiving placebo (HR, 0.26; 95% CI, 0.11 to 0.63). There was no statistically significant difference in relapses seen between groups in AQP4-IgG seronegative patients.

Overall adverse effects in both studies were reported as events/100 patient-years, with similar adverse event rates observed between satralizumab-treated patients and placebo-treated patients. In SAkuraSky, 3 patients (7%) discontinued satralizumab therapy due to adverse effects compared to 5 patients (12%) in the placebo group. In SAkuraStar, 1 patient in each study group withdrew due to adverse effects.

OTHER DRUGS USED FOR CONDITION[6,7]

There are 2 other FDA-approved medications for the treatment of adults with AQP4-IgG positive NMOSD, eculizumab (Soliris®) and inebilizumab-cdon (Uplizna™). Eculizumab is a humanized antibody that targets complement protein C5 and inhibits the formation of the terminal complement complex, C5b-9, that is proposed to be involved in NMOSD. Inebilizumab-cdon is a humanized monoclonal antibody that depletes B cells by binding to CD19 surface antigens.

PLACE IN THERAPY[8,9,10,11,12,13,14,15,16,17]

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune, inflammatory, central nervous system (CNS) syndrome involving the optic nerve, spinal cord, and brain stem, with an estimated prevalence of 0.5 to 10 cases per 100,000 persons. NMOSD is proposed to primarily be mediated by B cells and aquaporin-4 immunoglobulin G antibodies (AQP4-IgG). AQP4-IgG antibodies are likely involved in the pathogenesis of NMOSD as they bind to astrocytes in the CNS. This binding can trigger attacks, such as loss of vision, paralysis, nerve pain, and respiratory failure. Approximately 60 to 80% of patients with NMOSD test positive for anti-AQP4 antibodies. Similar to multiple sclerosis, NMOSD is more common in women than in men.

There are currently no clinical practice guidelines for the treatment of NMOSD. In practice, the standard treatment for acute attacks involves steroids, such as high-dose IV methylprednisolone, or plasma exchange for patients with severe symptoms. The chances of relapse and permanent disability are approximately 90%. For relapse prevention, retrospective studies and case studies have evaluated immunotherapies such as rituximab, mycophenolate mofetil, and azathioprine; however, none of these therapies are FDA-approved for NMOSD.

For adult patients with NMOSD who are seropositive for AQP4-IgG antibodies, eculizumab (Soliris) provides an FDA-approved treatment option. Eculizumab carries a boxed warning due to the potential for serious meningococcal infections and is notably only available in the United States (US) through a Risk Evaluation and Mitigation Strategy (REMS) program. Limited high-quality data from the phase 3, randomized, double-blind, placebo-controlled, multicenter PREVENT trial supports the IV administration of 900 mg of eculizumab every week for the first 4 doses, followed by the fifth dose 1 week later of 1,200 mg, then maintenance dosing of 1,200 mg every 2 weeks thereafter to reduce the risk of relapse in NMOSD. Inebilizumab-cdon (Uplizna) provides an additional FDA-approved treatment option for adult patients with AQP4-IgG seropositive NMOSD. Similar to eculizumab, inebilizumab-cdon is administered via IV infusion. Inebilizumab-cdon 300 mg by IV infusion is administered on day 1 and administered again 2 weeks later as a second 300 mg IV infusion. Subsequent 300 mg doses are then administered every 6 months thereafter, starting 6 months following the initial IV infusion.

As an IL-6 receptor antagonist, satralizumab-mwge provides a unique mechanism of action and offers an additional FDA-approved treatment option for AQP4-IgG positive NMOSD. Satralizumab-mwge requires three 120 mg loading doses given every 2 weeks, followed by maintenance doses every 4 weeks. Satralizumab-mwge differs from other available therapies in that it is given via SC injection rather than IV infusion. Notably, after receiving proper injection technique training, patients may self-administer or the patient's caregiver may administer satralizumab-mwge. Additional studies are needed to assess the efficacy and safety of satralizumab-mwge compared to other NMOSD therapies, such as eculizumab and inebilizumab-cdon.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Cytokine and CAM Antagonists
Clinical Edit	**Initial Approval Criteria** ▪ Patient is ≥ 18 years; **AND** ▪ Patient has a confirmed diagnosis based on the following: – Patient was found to be seropositive for aquaporin-4 (AQP4) IgG antibodies; **AND** – Patient has ≥ 1 core clinical characteristic (e.g., optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions, symptomatic cerebral syndrome with NMOSD-typical brain lesions); **AND** – Alternative diagnoses have been excluded (e.g., multiple sclerosis, sarcoidosis, cancer, chronic infection); **AND** ▪ Patient has a history of ≥ 1 relapses that required rescue therapy within the prior year or ≥ 2 relapses that required rescue therapy within the prior 2 years; **AND** ▪ Patient has an Expanded Disability Status Score (EDSS) of ≤ 6.5 (e.g., requires 2 walking aids [pair of canes, crutches, etc.] to walk about 20 m without resting); **AND** ▪ Patient is at risk of having a disabling relapse of NMOSD for which oral agents (e.g., corticosteroids and immunosuppressants such as azathioprine and mycophenolate) alone are inadequate and biologic therapy is necessary; **AND** ▪ Patient has been evaluated and screened for the presence of hepatitis B virus (HBV) prior to initiating treatment and confirmed negative for active HBV; **AND** ▪ Patient has NOT received any live or live-attenuated vaccinations in the 4-weeks prior to or non-live vaccinations in the 2-weeks prior to, the start of therapy; **AND** ▪ Patient has been evaluated and screened for the presence of latent tuberculosis (TB) infection prior to initiating treatment and will receive ongoing monitoring for the presence of TB during treatment; **AND** ▪ Patient does NOT have an active infection, including clinically important localized infections; **AND** ▪ Satralizumab will NOT be administered concurrently with live vaccines; **AND** ▪ Patient is NOT on concomitant therapy with, and does NOT have hypersensitivity to, other interleukin-6 (IL-6) receptor antagonists (e.g., tocilizimab, sarilumab); **AND** ▪ Patient has NOT previously received, and will NOT concomitantly receive therapy with, other drugs which can result in prolonged additive immunosuppression (e.g., alemtuzumab, cladribine,

	cyclophosphamide, or mitoxantrone) [Note: concomitant therapy with corticosteroids and/or immunosuppressants such as azathioprine or mycophenolate are allowed] **OR** other immunosuppressant procedures (e.g., total lymphoid irradiation, bone marrow transplant); **AND** ▪ Patient has NOT received therapy within the prior 6 months with any of the following: – Anti-BLyS monoclonal antibody (e.g., belimumab); **OR** – Therapies for prevention of multiple sclerosis (MS) relapse (e.g., interferon, natalizumab, glatiramer acetate, fingolimod, teriflunomide, or dimethyl fumarate); **AND** ▪ Patient will NOT concomitantly receive therapy with any of the following: – Complement-inhibitors (e.g., eculizumab, ravulizumab); **OR** – Anti-CD20-directed antibody (e.g., rituximab); **OR** – Anti-CD19-directed antibody (e.g., inebilizumab). **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Disease response as indicated by stabilization/improvement in any of the following: neurologic symptoms as evidenced by a decrease in acute relapses, stability, or improvement in EDSS, reduced hospitalizations, reduction/discontinuation in plasma exchange treatments, and/or reduction/discontinuation of corticosteroids without relapse; **AND** ▪ Absence of unacceptable toxicity from the drug (e.g., severe hypersensitivity reactions, serious infections, severe hepatotoxicity, severe neutropenia).
Quantity Limit	Loading Doses: 1 mL prefilled syringe (120 mg) on days 1, 15, and 29 (total of 3 syringes) Maintenance Doses: 1 mL prefilled syringe (120 mg) every 28 days
Duration of Approval	Initial: 6 months Renewal: 12 months
Drug to Disease Hard Edit	Active hepatitis B infection, active or untreated latent tuberculosis

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