Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Zilbrysq®
Common Name: zilucoplan
PDL Category: Complement Inhibitors

Comparable Products	Preferred Drug List Status
Rystiggo	Medical
Vyvgart	Medical

Pharmacology/Usage: Zilucoplan, the active ingredient of Zilbrysq®, is a complement inhibitor. It binds to the complement protein C5 and inhibits its cleavage to C5a and C5b, preventing the generation of the terminal complement complex, C5b-9. The exact mechanism of action of zilucoplan for its approved indication is not known but it is presumed to involve reduction of C5b-9 deposition at the neuromuscular junction.

Indication: For the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data with use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Solution in single-dose prefilled syringes for injection:

- 16.6mg/0.416ml.
- 23mg/0.574ml.
- 32.4mg/0.81ml.

Store in the refrigerator in the original carton; can also be stored at room temperature in the original carton for up to 3 months or until the expiration date, which occurs first. If stored in the refrigerator, allow to reach room temperature out of direct sunlight (30 to 45 minutes) before injection.

Recommended Dosage: Vaccinate patients for meningococcal infection per current Advisory Committee on Immunization Practices (ACIP) recommendations at least 2 weeks prior to administering the first dose of Zilbrysq®. If urgent Zilbrysq® therapy is indicated in a patient who is not up to date with vaccines for both MenACWY and MenB per ACIP recommendations, administer meningococcal vaccine(s) as soon as possible and provide the patient with antibacterial drug prophylaxis.

Healthcare providers who prescribe Zilbrysq® must enroll in the Zilbrysq® REMS.

Before starting treatment, obtain baseline lipase and amylase levels.

The recommended dosage is given once daily as a SC injection and is dependent on actual body weight. The table below, adapted from the prescribing information, presents the totally daily dosage by body weight range.

Body Weight	Once daily dosage	Plunger Rod color of prefilled syringe
Less than 56kg	16.6mg	Rubine Red
56kg to less than 77kg	23mg	Orange
77kg and above	32.4mg	Dark Blue

Zilbrysq® is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject after training in subcutaneous injection technique. Administer subcutaneously into areas of the abdomen, thighs, or back of the upper arms that are not tender, bruised, red, or hard. Administration in the upper, outer arm should be performed by a caregiver. Rotate injection sites for each administration.

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time. Do not administer more than 1 dose per day.

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

Box Warning: There is a box warning regarding serious meningococcal infections. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors; Zilbrysq® is a complement inhibitor. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early.

- Complete or update meningococcal vaccination (for serogroups A, C, W, and Y, and serogroup B) at least 2 weeks prior to administering the first dose of Zilbrysq®, unless the risk of delaying therapy outweighs the risk of developing a meningococcal infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccinations in patients receiving a complement inhibitor.
- Persons receiving Zilbrysq® are at increased risk for invasive disease caused by *N. meningitidis*, even if they develop antibodies following vaccination. Monitor patients for signs of meningococcal infections and assess immediately if infection is suspected.

Because of the risk of serious meningococcal infections, Zilbrysq® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called Zilbrysq® REMS.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Zilbrysq®) minus reported % incidence for placebo. 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 injection site reactions (13%), upper respiratory tract infections (7%), diarrhea (9%), urinary tract infection (3%), nausea or vomiting (1%), lipase increased (7%), amylase increased (4%).

Because of the risk of meningococcal infections, Zilbrysq® is available only through a restricted program under a REMS called the Zilbrysq® REMS. Notable requirements of the REMs include:

- Prescribers must enroll in the REMS.
- Prescribers must counsel patients about the risk of meningococcal infection.
- Prescribers must provide the patients with the REMS educational materials.
- Prescribers must assess patient vaccination status for both meningococcal vaccines (MenACWY and MenB) and vaccinate if needed per current ACIP recommendations for meningococcal vaccinations in patients receiving a complement inhibitor 2 weeks prior to the first dose of Zilbrysq®.
- Prescribers must provide a prescription for antibacterial drug prophylaxis if treatment must be started urgently, and the patient is not up to date with both MenACWY and MenB vaccines per current ACIP recommendations at least 2 weeks prior to the first dose of Zilbrysq®.
- Pharmacies that dispense Zilbrysq® must be certified in the REMS and must verify prescribers are certified.

- Patients must receive counseling from the prescriber about the need to receive both meningococcal vaccines per ACIP recommendations, the need to take antibiotic as directed by the prescriber, and the signs and symptoms of meningococcal infection.
- Patients must be instructed to carry the Patient Safety Card with them at all times during and for 2 months following treatment discontinuation with Zilbrysq®.
- Further information is available at www.ZILBRYSQREMS.com or by calling 1-877-414-8353.

Zilbrysq® blocks terminal complement activation; thus, patients may have increased susceptibility to infections, especially with encapsulated bacteria. Administer vaccinations for the prevention of *Streptococcus pneumoniae* and *Haemophilus influenza type b* (Hib) infections per ACIP guidelines. Persons receiving Zilbrysq® are at increased risk for infections due to these bacteria, even after vaccination.

Pancreatitis and pancreatic cysts have been reported in patients treated with Zilbrysq®. In the 3 month study (Study 1), adverse reactions of increased lipase were reported in 6.9% of the Zilbrysq® group compared to no patients in the placebo group, and adverse reactions of increased amylase were reported in 4.7% of the Zilbrysq® group compared to 1.1% of the placebo group. Patients should be informed of this risk before starting Zilbrysq®. Obtain lipase and amylase levels at baseline before starting treatment with Zilbrysq®. Discontinue Zilbrysq® in patients with suspected pancreatitis and start appropriate management until pancreatitis is ruled out or has resolved.

Contraindications: In patients with unresolved *Neisseria meningitidis* infection.

Manufacturer: UCB, Inc.

Analysis: The efficacy of Zilbrysq® for the treatment of gMG in adults who are anti-AChR antibody positive was established in a 12-week, multicenter, randomized, double-blind, placebo-controlled study. Study 1 enrolled patients who met the following criteria at screening:

- Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV.
- Positive serology for AChR binding autoantibodies.
- MG-Activities of Daily Living (MG-ADL) total score of ≥6.
- Those on MG therapy prior to screening (including acetylcholinesterase inhibitors, steroids, or non-steroidal immunosuppressive therapies [NSISTs], either in combination or alone), needed to maintain a stable dose.

Patients (N=174) were randomized to receive either Zilbrysq® or placebo once daily by SC injection. Patients had a mean age of 53 years and a mean time since diagnosis of 9 years. In addition, 57% of patients were females, 74% were white, and the mean baseline MG-ADL total score was 10.6. At baseline, about 85% of patients in each group received cholinesterase inhibitors, 63% received steroids, and 51% received NSISTs, at stable doses.

The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in MG-ADL total score after 12 weeks of treatment. The MG-ADL assesses the impact of gMG on daily functions of 8 signs or symptoms that are typically affected in gMG. Each item is assessed on a 4-point scale where a score of 0 represents normal function and a score of 3 represents loss of ability to perform that function. A total score ranges from 0 to 24, with the higher scores indicating more impairment.

The efficacy of Zilbrysq® was also measured using the Quantitative MG (QMG) total score, which is a 13-item categorical grading system that assesses muscle weakness. Each item is assessed on a 4-point scale where a score of 0 represents no weakness and a score of 3 represents severe weakness. A total possible score ranges from 0 to 39, where higher scores indicate more severe impairment.

Other secondary endpoints included the proportion of patients with improvements of at least 3 and 5 points in the MG-ADL total score and QMG total score, respectively, at week 12 without rescue therapy.

At week 12, treatment with Zilbrysq® demonstrated a statistically significant improvement from baseline compared to placebo for MG-ADL total score and QMG total score. Results are presented in the table below, which was adapted from the prescribing information.

Efficacy Endpoints: LS mean	Zilbrysq® (N=86)	Placebo (N=88)	Zilbrysq® change LS mean difference vs placebo	p-value
MG-ADL Total Score	-4.39	-2.30	-2.09	<0.001
QMG Total Score	-6.19	-3.25	-2.94	<0.001

The proportion of MG-ADL responders with at least a 3-point improvement at week 12 was greater for Zilbrysq® (73.1%) compared to placebo (46.1%, p<0.001; NNT 4). The proportion of QMG responders with at least a 5-point improvement was also greater for Zilbrysq® (58%) compared to placebo (33%, p=0.0012; NNT 4). The proportion of clinical responders at higher response thresholds was consistently greater for Zilbrysq® compared to placebo.

Place in Therapy: Zilbrysq® is a complement inhibitor indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. Patients may self-inject Zilbrysq® after training in subcutaneous injection technique. Prior to treatment, obtain baseline lipase and amylase levels, and vaccinate patients for meningococcal infection per current ACIP recommendations at least 2 weeks prior to administration of the first Zilbrysq® dose. Note that if urgent Zilbrysq® therapy is indicated in a patient who is not up to date with vaccines for both MenACWY and MenB per ACIP recommendations, administer the meningococcal vaccine(s) as soon as possible and provide the patient with antibacterial drug prophylaxis. In addition, Zilbrysq® has a box warning regarding serious meningococcal infections. Because of the risks of serious meningococcal infections, Zilbrysq® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called Zilbrysq® REMS.

The safety and efficacy of Zilbrysq® were assessed in a randomized, double-blind, placebo-controlled study that included adults with gMG who were anti-AChR antibody positive. At week 12, treatment with Zilbrysq® demonstrated a statistically significant improvement from baseline compared to placebo for MG-ADL total score (primary endpoint) and QMG total score. Zilbrysq® is the first FDA-approved treatment for adults with anti-AChR antibody-positive gMG that may be self-administered.

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

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

References

[1] Zilbrysq® [package insert]. Smyrna, GA: UCB, Inc,; 2023.