zilucoplan (Zilbrysq®)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO293

Description

Zilucoplan (Zilbrysq) a targeted C5 complement inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zilucoplan (Zilbrysq)	Myasthenia Gravis	16.6 mg/0.416 mL	11.648 mL/28 days
		23 mg/ 0.574 mL	16.072 mL/28 days
		32.4 mg/ 0.81 mL	22.68 mL/28 days

Initial Evaluation

I. **Zilucoplan (Zilbrysq)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a specialist (e.g., neurologist or rheumatologist); **AND**
   C. Medication will not be used in combination with maintenance immunoglobulin therapy (IVIG), rituximab, or another biologic for gMG [i.e., eculizumab (Soliris), ravulizumab (Ultomiris), efgartigimod alfa (Vyvgart), rozanolixizumab (Rystiggo)]
   D. A diagnosis of **generalized myasthenia gravis (gMG)** when the following are met:
      1. Provider attestation that the member is acetylcholine receptor antibody positive (AChR-AB+); **AND**
      2. Provider attestation that the member has Myasthenia Gravis Foundation of America (MGFA) Clinical Classification class II to IV disease (i.e., not defined as ocular myasthenia gravis and not intubated); **AND**
      3. Member has a baseline MG-activities of daily living (MG-ADL) score ≥6; **AND**
   E. Member has had an inadequate response (e.g., unable to maintain baseline MG-ADL score) after a minimum of one-year trial of each of the following therapies, unless both were not tolerated or contraindicated:
      1. Acetylcholinesterase inhibitor (e.g., pyridostigmine); **AND**
      2. An oral immunosuppressant (e.g., azathioprine, cyclosporine, mycophenolate, low dose daily glucocorticoids); **OR**
   F. Member required chronic treatment with plasmapheresis or plasma exchange or intravenous immunoglobulin (IVIG) in addition to immunosuppressant therapy; **AND**

G. Member will be continuing on standard of care therapies (e.g., pyridostigmine, azathioprine, low dose daily glucocorticoids) unless all are contraindicated or not tolerated

II. Zilucoplan (Zilbrysq) is considered investigational when used for all other conditions, including but not limited to:
   A. Ocular Myasthenia Gravis
   B. Myasthenia Gravis MUSK antibody positive or other antibodies that are not AChR
   C. Pediatric Myasthenia Gravis
   D. Postural Orthostatic Tachycardia Syndrome
   E. Primary Immune Thrombocytopenia
   F. Paroxysmal Nocturnal Hemoglobinuria

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attests that the member continues to have a clinical response to zilucoplan (Zilbrysq) (i.e., an improvement in the MG-ADL score, a reduction/elimination of oral steroids/immunosuppressants required, etc.); **AND**
IV. Medication will not be used in combination with maintenance immunoglobulin therapy (IVIG), rixtuximab, or another biologic for gMG [i.e., eculizumab (Soliris), ravulizumab (Ultomiris), efgartigimod alfa (Vyvgart), rozanolixizumab (Rystiggo)]

Supporting Evidence

I. Zilucoplan (Zilbrysq) is FDA approved to treat adult patients with generalized myasthenia gravis (gMG) that are anti-acetylcholine receptor antibody positive (AChR-AB+). Use in individuals under the age of 18 years as well as use in other antibody positive patients has not been determined to be safe and effective at this time.
II. Due to the complexity of diagnosing and treating gMG, zilucoplan (Zilbrysq) must be prescribed by, or consultation with, a specialist in neurology or rheumatology.
III. Myasthenia gravis is a chronic, autoimmune, neuromuscular disease characterized by fluctuating motor weakness involving the ocular, spinal column, limb and/or respiratory muscles. The weakness is due to an antibody-mediated, immunologic attack directed at the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors [AChR] or receptor associated proteins, such as MUSK) led by an IgG immune response. This causes common

symptoms such as drooping eyelids (ptosis) and double vision (diplopia), muscle weakness and fatigue, trouble swallowing or pronouncing words, and facial muscle involvement causing a mask-like appearance or sneer.

IV. AChR are the most common receptor affected; about 85% of patients will test positive for AchR antibodies, which is considered a positive indicator of a MG diagnosis. Those who do not test positive for AchR, may then test positive for a different receptor protein, such as muscle-specific tyrosine kinase (MuSK) or LR4 antibody. AchR antibody (AchR-AB) negative patients do not tend to respond as well to regular standards of care as the AB positive patients do and tend to respond better to rituximab (Inflectra) instead.

V. Additionally, there are two clinical forms of MG: ocular and generalized. Although the majority of patients present with a vision symptom as the first indicator of MG, roughly 15% of patients remain as ocular MG, while the rest become generalized MG. Those with ocular MG are less likely to be AchR-AB positive and have mixed response to traditional therapies usually favoring eye patches or eye "crutches" to assist with drooping eyelids, and in severe cases, surgery.

VI. Clinical presentation of MG is staged by ocular versus generalized and the severity of their symptoms. Stage I is ocular only and Stage V is those patients who require intubation; Stages II-IV encompass those patients in between as mild to moderate and the systems involved. MG are further assessed by two common scoring systems: the Quantitative Myasthenia Gravis (QMG) and the MG activity of daily living (MG-ADL). Both are quality of life scales assessing muscle strength and weakness, higher scores on each scale indicate more severe disease. QMG is a 13-item scale with a possible worst score of 39 and MG-ADL is an 8-item scale with a possible worst score of 24. Based on clinical data and physician input, a three-point change is clinically meaningful in QMG for moderate-severe presentation and a two-point change for milder presentation; a two-point change is clinically meaningful in MG-ADL for mild-moderate, there is not an agreement on severe patients in the MG-ADL scale.

VII. Currently there is no cure for MG, patients tend to reach their peak in symptoms and severity within the first three years of diagnosis and then stabilize or move into remission. Available treatments control symptoms and prevent relapses allowing patients to live a relatively high quality of life with a normal life expectancy. Treatment options include symptomatic treatment (e.g., acetylcholinesterase inhibitors [e.g., pyridostigmine]), corticosteroids, long-term immunosuppressive therapy (e.g., azathioprine, cyclosporine, methotrexate), plasma exchange, and rapid immunomodulating treatments (e.g., immune globulin IV). Thymectomy is also an option and according to the Internal Consensus Guidelines on MG 2020, thymectomy should be considered early in the disease for those under 50 years of age with generalized MG or those who fail to respond to an adequate trial of immunotherapy and have stable MG amenable to surgery (i.e., no current flares, on stable dose of medications without changes being made). The only biologic treatment currently included in these same guidelines is eculizumab (Soliris), also a C5 inhibitor, which is recommended in the treatment of severe, refractory, AchR-AB+ gMG. Internal Consensus Guidelines define refractory disease as an unchanged or worse MG-ADL/QMG after corticosteroids and at least two other immunosuppressant agents. The presence

of persistent symptoms or side effects that limit functioning after treatment used at the maximum dose the patient is able to tolerate for an adequate duration (typically 12 weeks).

VIII. Pyridostigmine is recommended as initial therapy and unless not tolerated. Patients should remain on this therapy lifelong as a standard of care. The ability to discontinue pyridostigmine can be indicative of meeting therapy goals and may guide tapering of other drugs. For patients that continue to experience bothersome symptoms, next line agents include nonsteroidal immunosuppressants (NISTs) such as azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. NIST can be used in combination with a corticosteroid (prednisone) for flares or more rapid deceleration of exacerbation/crisis. Myasthenia crisis can occur from concurrent infection, surgery, pregnancy, and certain medication classes. Mild flares may simply respond to changes in standard of care doses or frequency, such as increasing pyridostigmine, or beginning a course of prednisone. More severe cases where patients are experiencing increased dysphagia or dyspnea, initiation of intravenous immune globulin (IVIG) or plasmapheresis, are used to return to clinical baseline.

IX. The safety and efficacy of zilucoplan (Zilbrysq) was evaluated in RAISE, a Phase 3 multicenter, randomized, double-blind, placebo-controlled study. The trial evaluated 174 AChR-Ab+ adult patients with gMG between Stage II-IV. All patients had a MG-ADL score ≥6 and were randomized 1:1 to receive either placebo (n=88) or 0.3mg/kg zilucoplan (Zilbrysq, n=86) SC daily over 12 weeks. Patients were required to remain on standard-of-care therapies during the study that they were on preceding the trial start (i.e., pyridostigmine, NISTs) so long as there was not a change in dose or frequency or an anticipated need to change during the 12-week study. Approximately 85% of patients were on pyridostigmine, 63% steroids, and 51% NISTs. Data was considered missing if rescue therapy for a crisis or relapse was required. MG-ADL response was the primary endpoint at the end of week 12.

X. A statistically significant difference favoring zilucoplan (Zilbrysq) over placebo was seen at the end of the 12-week trial. Patients taking zilucoplan (Zilbrysq) had a change of 4.39 points versus 2.30 in placebo of the MG-ADL score [-2.09 (-3.24, -0.95); *p <0.001*]. Secondary endpoints looked at additional standard improvement/severity scales such as response in QMG, MGC, and MG-QoL 15r scores. These also met a statistically different response in zilucoplan (Zilbrysq) versus placebo. A total of 200 patients enrolled into the ongoing extension trial (RAISE-XT). RAISE-XT was primarily a safety extension trial, but secondary endpoints continued to monitor the endpoints of RAISE. These endpoints were maintained or improved at the interim data analysis at week 90. There were no new safety signals at week 90.

XI. There are currently four other biologics approved in the treatment of MG; two complement factors: eculizumab (Soliris) and raculizumab (Ultomiris) and two neonatal Fc receptor (FcRn) inhibitors: efgartigimod (Vyvgart) and rozanolixizumab (Rystiggo). The Internal Consensus Guidelines on Myasthenia Gravis 2020 recommend eculizumab (Soliris) in refractory MG after failure of IVIG, plasmapheresis, and immunosuppressive agents. The exclusion criteria of all four of these trials did not allow concurrent use of each other or IVIG, plasmapheresis, or rituximab

within at least four weeks of the trial onset. The combination use of any of these therapies would be considered experimental.

Investigational or Not Medically Necessary Uses

I. Zilucoplan (Zilbrysq) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Ocular Myasthenia Gravis
   B. Myasthenia Gravis MUSK antibody positive or other antibodies that are not AChR
   C. Pediatric Myasthenia Gravis
   D. Postural Orthostatic Tachycardia Syndrome
   E. Primary Immune Thrombocytopenia
   F. Paroxysmal Nocturnal Hemoglobinuria

Appendix

I. **MGFA Clinical Classification:**

Class	Distribution and Severity	
1	Any ocular muscle weakness, all other muscle strength is normal	
2	Mild, generalized	• 2a: Mainly limp, axial muscles
		• 2b: mainly oropharyngeal/respiratory muscles
3	Moderate, generalized	• 3a: Mainly limp, axial muscles
		• 3B: Mainly oropharyngeal/respiratory muscles
4	Severe, generalized	• 4a: Mainly limp, axial muscles
		• 4B: Mainly oropharyngeal/respiratory muscles
5	Intubation	

II. **MG-ADL Score:**

	Score=0	Score=1	Score=2	Score=3	Your Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal speech, but can be understood	Difficult to understand speech	

Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilatory dependence	
Brushing teeth or hair	Normal	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Arising from chair	Normal	Mild, sometimes uses arms	Moderate, always uses arms,	Severe, requires assistance	
Double vision	Normal	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	Normal	Occurs, but not daily	Daily, but not constant	Constant	
				Total Score=	

References

1. Zilbrysq [Prescribing Information]. UCB, Inc. Smyrna, GA. October 2023.
2. Narayanaswami P, Sanders DB, Wolfe G, et al. International Consensus Guidance for Management of Myasthenia Gravis: 2020 Update. *Neurology*. 2021 Jan 19;96(3):114-122.
3. Howard JF Jr, Bresch S, Genge A, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Neurol*. 2023;22(5):395-406. doi:10.1016/S1474-4422(23)00080-7
4. Zilucoplan – Long-term data in adult patients with generalized myasthenia gravis (RAISE-XT) MED-GL--2202942

Related Policies

Currently there are no related pharmacy policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2024