Zilbrysq (zilucoplan) Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, FocusRx, KeyRx and Health Insurance Marketplace formularies.

This is a FlexRx standard and GenRx standard prior authorization.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
04-01-2024	04-01-2024

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Zilbrysq® (zilucoplan) Injection for subcutaneous use	Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Myastenia Gravis	Myasthenia gravis (MG) is a neuromuscular disorder primarily characterized by muscle weakness and muscle fatigue. Although the disorder usually becomes apparent during adulthood, symptom onset may occur at any age. The condition may be restricted to certain muscle groups, particularly those of the eyes (ocular myasthenia), or may become more generalized (generalized myasthenia gravis [gMG]), involving multiple muscle groups. Most individuals with myasthenia gravis develop weakness and drooping of the eyelids (ptosis); weakness of eye muscles, resulting in double vision (diplopia); and excessive muscle fatigue following activity. Additional features commonly include weakness of facial muscles; impaired speech (dysarthria); difficulties chewing and swallowing (dysphagia); and weakness of the upper arms and legs (proximal limb weakness). In addition, in about 10% of patients, affected individuals may develop potentially life-threatening complications due to severe involvement of muscles used during breathing (myasthenic crisis). Myasthenia gravis results from an abnormal immune reaction in which antibodies inappropriately attack and gradually injure certain receptors in muscles that receive nerve impulses (antibody-mediated autoimmune response).(2) The course of myasthenia gravis is highly variable. For example, the degree of muscle weakness may vary over hours, from day to day, or over weeks and months, tending to increase with repeated muscle use and to improve with rest. In addition, particularly during the first years after disease onset, some affected individuals may experience alternating periods in which symptoms temporarily subside or worsen. A short-term aggravation of symptoms may be triggered by a variety of factors, including infection, excessive physical activity, menstruation, and after delivery of a child.(2)

	Corticosteroids are a standard treatment for MG but may cause transient worsening within the first 2 weeks and patients should be monitored closely for this possibility. Because of this a MG consensus panel lists corticosteroids as one of many agents to avoid or use with caution in MG. A nonsteroidal immunosuppressive agent should be used initially in treating MG. Nonsteroidal immunosuppressive agents that can be used in MG include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. For nonsteroidal immunosuppressive agents, once treatment goals have been achieved and maintained for 6 months to 2 years, the immunosuppressive dose should be tapered slowly to the minimal effective amount. Patients must be monitored for potential adverse effects and complications from immunosuppressive drugs. Changing to an alternative immunosuppressive agent should be considered if adverse effects and complications are medically significant or create undue hardship for the patient.(3) Plasma exchange and IVIg are appropriately used as short-term treatments in patients with MG with life-threatening signs such as respiratory insufficiency or dysphagia; in preparation for surgery in patients with significant bulbar dysfunction; when a rapid response to treatment is needed; when other treatments are insufficiently effective; and prior to beginning corticosteroids if deemed necessary to prevent or minimize exacerbations. The use of IVIg as maintenance therapy can be considered for patients with refractory MG or for those in whom immunosuppressive agents are contraindicated. Refractory MG is defined as post-intervention status is unchanged or worse after corticosteroids and at least 2 other immunosuppressive agents, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by the patient and physician.(3) Time to onset of effect and time to maximal effect varies between products. Azathioprine, mycophenolate mofetil, cyclosporine, and tacrolimus all take between 6 to 12 months to onset of effect and take 1 to 2 years to see maximal effect in MG. Rapid therapies such as plasmapheresis or IVIg therapy take approximately 1 week to time of onset of effect and 1 to 3 weeks for time to maximal effect.(7) Certain medications have established pharmacologic adverse effects on neuromuscular transmission. Use of these medications in a patient with MG can further reduce the effectiveness of neuromuscular transmission and cause increased clinical weakness. However, reported associations do not necessarily mean these medications should never be prescribed in MG. Clinical judgment and the risk-to-benefit ratio of the drug should be considered when it is deemed important for a patient's treatment. Medications that can cause a significant increase in weakness in patients with MG include fluoroquinolones, botulinum toxin, ketolides (particularly telithromycin) and aminoglycoside antibiotics, beta blockers, macrolide antibiotics, procainamide, quinidine, quinine, and magnesium. A number of other medications may unmask or exacerbate MG, particularly the neuromuscular blocking agents used during anesthesia, which can lead to prolonged postoperative weakness and ventilator dependence.(3)
Efficacy	The efficacy of Zilbrysq for the treatment of gMG in adult patients who are anti-AChR antibody positive was established in a 12-week, multicenter, randomized, double-blind placebo-controlled study (NCT04115293). Patients who met the following criteria at screening were enrolled in this study:(1) • Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV • Positive serology for AChR binding autoantibodies • AG-Activities of Daily Living (MG-ADL) total score of greater than or equal to 6 • Those on MG therapy prior to screening (including acetylcholinesterase [AChE] inhibitors, steroids, or non-steroidal immunosuppressive therapies wither in combination or alone), needed to maintain a stable dose The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the MG-ADL total score after 12 weeks of treatment. The efficacy of Zilbrysq was also measured using the Quantitative MG (QMG) total score. Other

secondary endpoints included the proportion of patients with improvements of at least 3 in the MG-ADL total score and at least 5 points in the QMG total score 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.(1)

Efficacy Endpoints: Least Square (LS) Mean (95% CI)	**Zilbrysq**	**Placebo**	**Zilbrysq change LS mean difference vs placebo (95% CI)**	**p-value**
MG-ADL Total Score	-4.39 (-5.25, -3.50)	-2.30 (-3.17, -1.43)	-2.09 (-3.24, -0.95)	< 0.001
QMG Total Score	-6.19 (-7.29, -5.08)	-3.25 (-4.32,-2.17)	-2.94 (-4.39, -1.49)	< 0.001

MG-ADL

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, 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	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				Total Score _____	

The Myasthenia Gravis Foundation of America (MGFA) clinical classification divides MG into 5 main classes and several subclasses. It is designed to identify subgroups of patients with MG who share distinct clinical features or severity of disease that may indicate different prognoses or responses to therapy.(6)

Class	Features

I	Any ocular muscle weakness: may have weakness of eye closure; All other muscles are normal
II	Mild weakness affecting muscles other than the ocular muscles: may also have ocular muscle weakness of any severity
IIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal, respiratory muscles or both. May also have lesser or equal involvement of limb, axial muscles, or both.
III	Moderate weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity
IIIa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIIb	Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
IV	Severe weakness affecting muscles other than the ocular muscles; may also have ocular muscle weakness of any severity.
IVa	Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal, respiratory muscles or both. May also have lesser or equal involvement of limb, axial muscles, or both.
V	Intubation with or without mechanical ventilation (exception: intubation for routine perioperative management). The use of a feeding tube without intubation places a patient in class IVb.

The QMG is a 13-item scale used to quantify disease severity in myasthenia gravis (MG). The scale measures ocular, bulbar, respiratory, and limb function, grading each finding and ranges from 0 (no myasthenic findings) to 39 (maximal myasthenic deficits). Drawbacks to the QMG are that it requires special instrumentation (dynamometer for grip strength and spirometer for vital capacity) and is time consuming, requiring 25-30 minutes to perform. The QMG has also been criticized as not being fully representative of MG disease activity due to the lack of weighting of different domains.(8)

Safety	Zilbrysq is contraindicated in patients with unresolved *Neisseria meningitidis* infection.(1)

REFERENCES

Number	Reference
1	Zilbrysq prescribing information. UCB, Inc. October 2023.
2	National Institute of Neurological Disorders and Stroke. Myasthenia Gravis Fact Sheet. NIH Publication No. 17-768. July 2018.

Number	Reference
3	Narayanaswami P, Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. 2020 Update. Neurology Volume 96 Number 3. January 19, 2021.
4	Ulrichts P, Guglietta A, Dreier T, et al. J Clin Invest. 2018;128(10):4372-4386. 8. Huijbers MG, Plomp JJ, van Es IE, et al. Exp Neurol. 2019;317:133-143.
5	Dhavalkumar DP, Bussel JB. Neonatal Fc receptor in human immunity Function and role in therapeutic intervention. J Allergy Clin Immunol 2020;146:467-78.
6	Jayam Trouth A, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: a review. Autoimmune Dis. 2012;2012:874680. doi:10.1155/2012/874680.
7	Bird SJ. UpToDate. Overview of the treatment of myasthenia gravis. Literature review current through April 2023.
8	Barnett, C, Katzberg H, Nabavi M, Bril V. The Quantitatyve Myasthenia Gravia Score Comparison with Clinical, Electrophysiological, and Laboratory Markers. Journal of Clinical Neuromuscular Disease 13(4):p 201-205, June 2012.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Zilbrysq	zilucoplan sodium subcutaneous soln pref syr	16.6 MG/0.416ML ; 23 MG/0.574ML ; 32.4 MG/0.81ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Zilbrysq 16.6 mg/0.416 mL	zilucoplan	16.6 MG/0.416ML	28	Syringes	28	DAYS			
Zilbrysq 23 mg/0.574 mL	zilucoplan	23 MG/0.574ML	28	Syringes	28	DAYS			
Zilbrysq 32.4 mg/0.81 mL	zilucoplan	32.4 MG/0.81ML	28	Syringes	28	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Zilbrysq	zilucoplan sodium subcutaneous soln pref syr	16.6 MG/0.416ML ; 23 MG/0.574ML ; 32.4 MG/0.81ML	

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Zilbrysq 16.6 mg/0.416 mL	zilucoplan	16.6 MG/0.416ML	
Zilbrysq 23 mg/0.574 mL	zilucoplan	23 MG/0.574ML	
Zilbrysq 32.4 mg/0.81 mL	zilucoplan	32.4 MG/0.81ML	

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The patient has a diagnosis of generalized Myasthenia Gravis (gMG) AND ALL of the following:
      1. The patient has a positive serological test for anti-AChR antibodies (lab test must be submitted) **AND**
      2. The patient has a Myasthenia Gravis Foundation of America (MGFA) clinical classification class of II-IVb **AND**
      3. The patient has a MG-Activities of Daily Living total score of greater than or equal to 6 **AND**
      4. ONE of the following:
         A. The prescriber has assessed the patient's current medications and discontinued any medications known to exacerbate myasthenia gravis (e.g., beta blockers, procainamide, quinidine, magnesium, anti-programmed death receptor-1 monoclonal antibodies, hydroxychloroquine, aminoglycosides) **OR**
         B. The prescriber has provided clinical rationale indicating that discontinuation of the offending agent is not clinically appropriate **AND**
      5. ONE of the following:
         A. The patient has tried and had an inadequate response to at least ONE conventional agent used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) **OR**
         B. The patient has an intolerance or hypersensitivity to ONE conventional agent used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) **OR**
         C. The patient has an FDA labeled contraindication to ALL conventional agents used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) **OR**
         D. The patient is currently being treated with the requested agent as indicated by ALL of the following:
            1. A statement by the prescriber that the patient is currently taking the requested agent **AND**
            2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND**
            3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR**
         E. The prescriber has provided documentation that conventional agents used for the treatment of myasthenia gravis (i.e., corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil, tacrolimus, methotrexate, cyclophosphamide) cannot be used due to a documented medical condition or comorbid

Module	Clinical Criteria for Approval
	condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **OR** F. The patient required chronic intravenous immunoglobulin (IVIG) **OR** G. The patient required chronic plasmapheresis/plasma exchange **OR** B. The patient has another FDA approved indication for the requested agent **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with any of the following for the requested indication: A. Rystiggo (rozanolixizumab-noli) B. Soliris (eculizumab) C. Ultomiris (ravulizumab-cwvz) D. Vyvgart (efgartigimod) E. Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The prescriber has provided information that the patient has had clinical benefit with the requested agent (e.g., improved MG-Activities of Daily Living total score, improved quantitative myasthenia gravis total score) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with any of the following for the requested indication: A. Rystiggo (rozanolixizumab-noli) B. Soliris (eculizumab) C. Ultomiris (ravulizumab-cwvz) D. Vyvgart (efgartigimod) E. Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval:** Initial 3 months, Renewal 12 months