09-J4000-78

Original Effective Date: 04/01/24

Reviewed: 05/14/25

Revised: 06/15/25

Subject: Zilucoplan (Zilbrysq) Subcutaneous Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Generalized myasthenia gravis is an autoimmune neuromuscular disorder characterized by muscle weakness and fatigue. IgG antibodies occur in up to 85% of patients which are most frequently directed at the acetylcholine receptor (85% of patients) or the anti-muscle-specific tyrosine kinase (MuSK) antibody (6% of patients). Treatment includes the use of cholinesterase inhibitors to prevent the breakdown of acetylcholine at the neuromuscular junction, immunosuppressive therapies, and thymectomy. Myasthenic crisis may occur which is a medical emergency due to respiratory failure and treatment includes plasmapheresis, IVIG, and corticosteroids.

Zilucoplan (Zilbrysq) is FDA-approved for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive. It is a complement inhibitor that binds to C5 and subsequently prevents generation of the terminal complement complex, C5b-9. It is the first targeted C5 complement inhibitor for gMG that is administered subcutaneously once daily and that can be self-administered.

The approval of zilucoplan was based on safety and efficacy data from the Phase 3, randomized, double-blind, placebo-controlled trial in adults with anti-AChR antibody–positive gMG. The study included subjects with MG 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 greater than or equal to 6, and use of MG therapy either alone or in combination prior to screening needed to maintain a stable dose. Subjects were receiving MG therapy which included acetylcholinesterase inhibitors (85%), steroids (63%), or non-steroidal immunosuppressive therapies (51%). The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the MG-ADL total score (range 0 to 24 with higher score indicating more impairment) at week 12. The secondary endpoint was Quantitative Myasthenia Gravis (QMG) total score which assess muscle weakness (range 0 to 39 where higher scores indicate more severe impairment). The study met its primary endpoint by demonstrating a

clinically meaningful and statistically significant improvement from baseline compared to placebo in the Myasthenia Gravis–Activities of Daily Living (MG-ADL) score at Week 12 [least squares mean difference compared to placebo (95% CI), – 2.09 (-3.24, -0.95), p <0.001]. The QMG total score was also improved as compared to placebo at week 12 [least squares mean difference compared to placebo (95% CI), – 2.94 (-4.39, -1.49), p <0.001]. The most common adverse events were injection-site bruising, upper respiratory tract infection, or diarrhea. Zilucoplan has a Risk Evaluation and Mitigation Strategy (REMS) and includes a boxed warning for the risk of serious or fatal meningococcal infection.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of zilucoplan (Zilbrysq) **meets the definition of medical necessity** when used to treat the following indications and the indication-specific criteria are met:

1. **Generalized Myasthenia Gravis (MG)**
    a. Member meets **ALL** of the following - documentation must be provided:
        i. Anti-acetylcholine receptor (AchR) antibody positive disease – lab documentation must be provided
        ii. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II – IV
        iii. Myasthenia Gravis Activities of Daily Living (MG-ADL) total score greater than or equal to 6
        iv. **ONE** of the following – documentation must be provided[a]:
            1. Member had an inadequate response to at least **ONE** of the following immunosuppressants:
                a. azathioprine
                b. cyclosporine
                c. mycophenolate mofetil
                d. tacrolimus
                e. methotrexate
                f. cyclophosphamide
                g. rituximab
            2. Member required chronic immune globulin therapy or chronic plasmapheresis/plasma exchange

b. The member has an inadequate response to **ONE** of the following OR the member has a contraindication to **ALL** of the following– documentation must be provided:
    i. eculizumab-aagh (Epysqli)
    ii. efgartigimod (Vyvgart) OR efgartigimod-hyaluronidase (Vyvgart Hytrulo)
    iii. ravulizumab (Ultomiris)
    iv. rozanolixizumab (Rystiggo)
c. The member will not receive zilucoplan concurrently with eculizumab or biosimilars, efgartigimod, efgartigimod-hyaluronidase, nipocalimab, ravulizumab, rituximab, rozanolixizumab, or chronic immune globulin therapy
d. Treatment is prescribed by or in consultation with a neurologist
e. **ONE** of the following:
    i. Member has been vaccinated against meningococcal infection at least 2 weeks prior to therapy initiation
    ii. Member has been vaccinated against meningococcal infection less than 2 weeks prior to therapy initiation and will receive prophylactic antibiotics for at least 2 weeks following vaccination
f. There is no evidence of an active meningococcal infection
g. The dose does not exceed the following based on actual body weight:
    i. Less than 56 kg: 16.6 mg daily
    ii. 56 kg to less than 77 kg: 23 mg daily
    iii. 77 kg and above: 32.4 mg daily

Approval duration: 6 months

Continuation of zilucoplan **meets the definition of medical necessity** when **ALL** of the following are met

1. The member has been previously approved for zilucoplan in the treatment of generalized myasthenia gravis by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage
2. For continuation of therapy for Generalized Myasthenia Gravis, member's diagnosis has been confirmed by the following –lab documentation must be provided:
    a. Anti-acetylcholine receptor (AchR) antibody positive disease
3. Member has a history of beneficial response to zilucoplan therapy for the treatment of generalized Myasthenia Gravis – examples of beneficial response include improved MG-ADL total score, Quantitative myasthenia gravis total score – documentation must be provided
4. Member has been revaccinated against meningococcal infection according to current medical guidelines for vaccination while on zilucoplan therapy
5. There is no evidence of an active meningococcal infection

6. The member will not receive zilucoplan concurrently with eculizumab and biosimilars, efgartigimod, efgartigimod-hyaluronidase, nipocalimab, ravulizumab, rituximab, rozanolixizumab, or chronic immune globulin therapy
7. The dose does not exceed indication specific limitations:
    i. Less than 56 kg: 16.6 mg daily
    ii. 56 kg to less than 77 kg: 23 mg daily
    iii. 77 kg and above: 32.4 mg daily

Approval duration: 1 year

[a] Step not required if the member previously received treatment with eculizumab (Soliris, Bkemv, Epysqli), efgartigimod (Vyvgart), efgartigimod-hyaluronidase (Vyvgart Hytrulo), nipocalimab (Imaavy), ravulizumab (Ultomiris), or rozanolixizumab (Rystiggo)

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Zilucoplan is indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are antiacetylcholine receptor (AChR) antibody positive. See prescribing information for preparation instructions. Before initiating, obtain baseline lipase and amylase levels. It is administered as a subcutaneous injection once daily according to actual body weight.

Body Weight	Once Daily Dosage	Plunger rod color of prefilled syringe
Less than 56 kg	16.6 mg	Rubine red
56 kg to less than 77 kg	23 mg	Orange
77 kg and above	32.4 mg	Dark blue

PRECAUTIONS:

Boxed Warning

Life-threatening and fatal meningococcal infections have occurred in persons treated with complement inhibitors and may become rapidly life-threatening or fatal if not recognized and treated early.

- Immunize members with a meningococcal vaccine at least 2 weeks prior to administering the first dose of zilucoplan, unless the risks of delaying therapy outweigh the risks of developing a meningococcal infection.
- Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for meningococcal vaccination in persons receiving complement inhibitors.

- Monitor members for early signs of meningococcal infections and evaluate immediately if infection is suspected.
- Prescribers and pharmacies must enroll in the Zilbrysq REMS.

Contraindications

- Unresolved serious Neisseria meningitidis infection

Precautions/Warnings

- Use caution when administered to members with any other systemic infection.
- Pancreatitis and pancreatic cysts have been reported. Discontinue in patients with suspected pancreatitis and initiate appropriate management until pancreatitis is ruled out or has resolved.

Drug Availability

16.6 mg/0.416 mL, 23 mg/0.574 mL, or 32.4 mg/0.81 mL in a single-dose prefilled syringe

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J3490	Unclassified drugs

ICD-10 Diagnosis Codes That Support Medical Necessity

G70.00 – G70.01	Myasthenia gravis

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

DEFINITIONS:

None

RELATED GUIDELINES:

Eculizumab (Soliris), 09-J1000-17

Efgartigimod (Vyvgart, Vyvgart Hytrulo), 09-J4000-18

Immune Globulin Therapy, 09-J0000-06

Ravulizumab (Ultomiris), 09-J3000-26

Rituximab Products, 09-J0000-59

Rozanolixizumab-noli (Rystiggo), 09-J4000-55

OTHER:

Table 1: Myasthenia Gravis Foundation of America (MGFA) Clinical Classification System

Class I	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
Class II	Mild weakness affecting muscles other than 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.
Class III	Moderate weakness affecting muscles other than 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.
Class IV	Severe weakness affecting muscles other than 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.
Class V	Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

Table 2: Myasthenia Gravis Activities of Daily Living (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 needed	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					

Table 3: Quantitative Myasthenia Gravis Score for Disease Severity

Test item	None	Mild	Moderate	Severe	Score
Grade	**0**	**1**	**2**	**3**	
(1) Double vision on lateral gaze, seconds	61	11-60	1-10	Spontaneous	
(2) Ptosis on upward gaze, seconds	61	11-60	1-10	Spontaneous	
(3) Weakness of facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	

(4) Swallowing water	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)	
(5) Speech after counting aloud from 1-50	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9	
(6) Ability to keep right arm outstretched, seconds	240	90-239	10-89	0-9	
(7) Ability to keep left arm outstretched, seconds	240	90-239	10-89	0-9	
(8) Vital capacity as percent of predicted	Greater or equal to 80	65-79	50-64	Less than 50	
(9) Right hand grip strength, kgW	Men – 45 or greater Women – 30 or greater	Men – 15-44 Women – 10-29	Men – 5-14 Women – 5-9	Men –0-4 Women – 0-4	
(10) Left hand grip strength, kgW	Men – 45 or greater Women – 30 or greater	Men – 15-44 Women – 10-29	Men – 5-14 Women – 5-9	Men –0-4 Women – 0-4	
(11) Ability to keep head lifted when lying supine, seconds	120	30-119	1-29	0	
(12) Ability to keep the right leg outstretched, seconds	100	31-99	1-30	0	
(13) Ability to keep the left leg	100	31-99	1-30	0	

outstretched, seconds					
Total QMG Score:					

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc. Accessed May 1, 2025
2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Accessed May 1, 2025
3. National Organization of Rare Diseases. https://rarediseases.org/rare-diseases.
4. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited May 1, 2025]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
5. Zilbrysq (zilucoplan) injection. UCB, Inc. Smyrna, GA. February 2025.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/14/25.

GUIDELINE UPDATE INFORMATION:

04/01/24	New Medical Coverage Guideline.
05/15/24	Revision to guideline consisting of updating the lab documentation requirements in the position statement.
06/15/25	Revision to guideline consisting of updating the step requirements in the position statement.