LOUISIANA BLUE

zilucoplan (Zilbrysq®)

Policy # 00874
Original Effective Date: 05/13/2024
Current Effective Date: 05/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider zilucoplan (Zilbrysq®)‡ for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor antibody positive to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for zilucoplan (Zilbrysq) will be considered when the following criteria are met:

- **Initial**
  - Patient is greater than or equal to 18 years of age; AND
  - Patient has a diagnosis of generalized myasthenia gravis; AND
  - Patient has an anti-acetylcholine receptor autoantibody positive serologic test; AND
  - Patient has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient has a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of ≥6; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient has received or is currently receiving pyridostigmine unless there is clinical evidence or patient history that suggests the use of pyridostigmine will cause an adverse effect or inadequate response to the patient; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

  - Patient has received or is currently receiving at least one nonsteroidal immunosuppressive therapy (NSIST) for at least 1 year unless there is clinical evidence or patient history that suggests NSISTs will be ineffective or cause an adverse reaction to the patient. Examples of NSISTs include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient has evidence of unresolved symptoms of myasthenia gravis, such as difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility); AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient has received vaccination against meningococcal infections at least 2 weeks prior to administering the first dose; OR if the drug is initiated <2 weeks after meningococcal vaccination, patient will receive prophylactic antibiotics
- **Continuation**
  - Patient has received an initial authorization for Zilbrysq; AND
  - Patient has experienced improvement on therapy as evidenced by at least ONE of the following:
    - Improvement in the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score; OR
    - Improvement in Quantitative Myasthenia Gravis (QMG) total score

    *(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of zilucoplan (Zilbrysq) when any of the following criteria are not met to be **not medically necessary.****

- For **initial** requests:
  - Patient has a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV
  - Patient has a Myasthenia Gravis Activities of Daily Living (MG-ADL) total score of ≥6
  - Patient has received or is currently receiving pyridostigmine

  - Patient has received or is currently receiving at least one nonsteroidal immunosuppressive therapy (NSIST) for at least 1 year. Examples of NSISTs include azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide
  - Patient has evidence of unresolved symptoms of myasthenia gravis, such as difficulty swallowing, difficulty breathing, or a functional disability resulting in the discontinuation of physical activity (e.g., double vision, talking, impairment of mobility)
- For **continuation** requests:
  - Patient has experienced improvement on therapy as evidenced by at least ONE of the following:
    - Improvement in the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score; OR
    - Improvement in Quantitative Myasthenia Gravis (QMG) total score

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of zilucoplan (Zilbrysq) when the patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) to be **investigational.***

Policy Guidelines

Myasthenia Gravis Foundation of America (MGFA) Clinical Classification

Class	***Description***
I	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal
IIa	Mild weakness affecting muscles other than ocular muscles. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles
IIb	Mild weakness affecting muscles other than ocular muscles. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
IIIa	Moderate weakness affecting muscles other than ocular muscles. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIIb	Moderate weakness affecting muscles other than ocular muscles. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

IVa	Severe weakness affecting muscles other than ocular muscles. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IVb	Severe weakness affecting muscles other than ocular muscles. 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 except when employed during routine postoperative management.

Myasthenia Gravis Activities of Daily Living (MG-ADL) profile

Grade	***0***	***1***	***2***	***3***	***Score***
1. Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. 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	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				MG-ADL score total (items 1-8)=	

Quantitative Myasthenia Gravis (QMG) Score

Test Item	***None***	***Mild***	***Moderate***	***Severe***	***Score***
Grade	***0***	***1***	***2***	***3***	
Double vision on lateral gaze (secs)	61	11-60	1-10	Spontaneous	
Ptosis (upward gaze)	61	11-60	1-10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete without resistance	Incomplete	
Swallowing 4 oz water	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal congestion	Cannot swallow (test not attempted)	
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9	
Right arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9	
Left arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9	
Forced Vital Capacity	≥80	65-79	50-64	≤50	
Rt-hand grip, kg Men Women	 ≥45 ≥30	 15-44 10-29	 5-14 5-9	 0-4 0-4	
Lt-hand grip, kg Men Women	 ≥35 ≥25	 15-34 10-24	 5-14 5-9	 0-4 0-4	
Head lifted (45 degrees supine), seconds	120	30-119	1-29	0	

Right leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0	
Left leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0	
				Total QMG Score:	

Background/Overview

Zilbrysq is a complement C5 inhibitor indicated for the treatment of generalized myasthenia gravis (gMG) in adults who are anti-acetylcholine receptor (AChR) antibody-positive. Zilbrysq 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 precise mechanism by which Zilbrysq exerts its therapeutic effect in gMG is unknown but is presumed to involve reduction of C5b-9 deposition at the neuromuscular junction.

Zilbrysq is supplied as prefilled syringes in the following strengths: 16.6 mg, 23 mg, and 32.4 mg. Zilbrysq is given as a subcutaneous (SC) injection once daily. Zilbrysq can be self-administered or given by a caregiver. The recommended dose of Zilbrysq is weight-based: patients < 56 kg, the dose is 16.6 mg once daily; patients 56 kg to < 77 kg, the dose is 23 mg once daily; and patients ≥ 77 kg, the dose is 32.4 mg once daily. Zilbrysq has a Boxed Warning regarding serious meningococcal infections. Life-threatening and fatal meningococcal infections have occurred in patients treated with complement inhibitors. Meningococcal vaccination should occur at least 2 weeks prior to the first dose of Zilbrysq. Zilbrysq is only available through a restricted access program called the Zilbrysq Risk Evaluation and Mitigation Strategy (REMS).

Myasthenia gravis is a chronic autoimmune neuromuscular disease that causes weakness in the skeletal muscles. The hallmark of the condition is muscle weakness that worsens after periods of activity and improves after periods of rest. Certain muscles such as those that control eye and eyelid movement, facial expression, chewing, talking, and swallowing are often involved in the disorder, however, the muscles that control breathing and neck and limb movements may also be affected. Acquired myasthenia gravis results from the binding of autoantibodies to the components of the neuromuscular junction, most commonly the acetylcholine receptor (AChR). However, antibodies to other proteins, such as the muscle-specific tyrosine kinase (MuSK) protein, can also lead to impaired transmission at the neuromuscular junction. Myasthenia gravis most commonly occurs in young adult women (<40 years of age) and older men (>60 years of age), but it can occur at any age,

including childhood. The incidence ranges from 0.3 to 2.8 per 100,000 and it is estimated to affect more than 700,000 people worldwide. Various clinical scoring systems are available to assess the severity of disease and include the Myasthenia Gravis Foundation of America (MGFA) clinical classification system, Myasthenia Gravis Activities of Daily Living (MG-ADL), and Quantitative Myasthenia Gravis (QMG) test.

Medications to treat myasthenia gravis include anticholinesterase agents (e.g., pyridostigmine), which slow the breakdown of acetylcholine at the neuromuscular junction and thereby improve neuromuscular transmission and increase muscle strength. Immunosuppressive drugs improve muscle strength by suppressing the production of abnormal antibodies and may include prednisone, azathioprine, mycophenolate mofetil, tacrolimus, and rituximab. Plasmapheresis and intravenous immunoglobulin (IVIG) may be options in severe cases to remove the destructive antibodies; however, their effectiveness frequently only lasts a few weeks to months. Additionally, the Food and Drug Administration (FDA) has approved eculizumab (Soliris®)‡ and ravulizumab (Ultomiris™)‡, both complement inhibitors, as well as rozanolixizumab (Rystiggo®)‡ and efgartigimod alfa products (Vyvgart®, Vyvgart® Hytrulo)‡ which contain an IgG monoclonal antibody that binds to the neonatal Fc receptor for the treatment of generalized myasthenia gravis. Although Soliris, Ultomiris, Vyvgart, Vyvgart Hytrulo, Rystiggo, and Zilbrysq are the only agents with FDA approval for the condition, the other agents have been used off-label and are still recommended as first-line therapy in clinical practice guidelines. Available guidelines have not been updated to address these newer treatments.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Zilbrysq was approved in 2023 for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Zilbrysq was evaluated in one 12-week Phase III, multicenter, randomized, double-blind, placebo-controlled pivotal trial. The study enrolled 174 adult patients with anti-acetylcholine receptor antibody-positive generalized myasthenia gravis. In addition, patients had a Myasthenia Gravis Foundation of America (MGFA) clinical classification class II to IV and a Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score of ≥ 6. MG-ADL assesses the impact of generalized myasthenia gravis on daily functions of eight signs or symptoms that are typically

impacted by this disease. Each sign or symptom is assessed on a 4-point scale; a higher score indicates greater impairment. Patients were randomized to receive either Zilbrysq 0.3 mg/kg or placebo. The primary efficacy endpoint was a comparison of the change from baseline between treatment groups in the MG-ADL total score at Week 12. Key secondary efficacy endpoints compared the mean change from baseline to Week 12 in the following: quantitative myasthenia gravis (QMG) score, myasthenia gravis composite (MGC) score, and myasthenia gravis quality of life 15-item revised (MG-QoL 15r) score. Statistically significantly greater improvement in the MG-ADL total score was observed in the Zilbrysq group compared with placebo: -4.39 points vs. -2.30 points, respectively ($P < 0.001$). Statistically significant improvement in the secondary efficacy endpoints were also observed in the Zilbrysq group vs. placebo.

References

1. Zilbrysq [package insert]. UCB, Inc. Smyrna, Georgia. October 2023.
2. Zilbrysq (zilucoplan) New Drug Review. IPD Analytics. November 2023.
3. Zilbrysq Drug Evaluation. Express Scripts. November 2023.

Policy History

Original Effective Date: 05/13/2024
Current Effective Date: 05/01/2025

04/04/2024	Medical Policy Committee review
04/10/2024	Medical Policy Implementation Committee approval. New policy.
04/03/2025	Medical Policy Committee review
04/09/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 04/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.