

satralizumab-mwge (EnspryngTM), inebilizumab-cdon (UpliznaTM)

Policy # 00736

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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.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

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.*

satralizumab-mwge (Enspryng)

Based on review of available data, the Company may consider satralizumab-mwge (EnspryngTM)[‡] for the treatment of neuromyelitis optica spectrum disorder (NMOSD) to be **eligible for coverage**.^{**}

Patient Selection Criteria

Coverage eligibility for satralizumab-mwge (Enspryng) will be considered when the following criteria are met:

Initial (6 months)

- Patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) as evidenced by at least ONE of the following core clinical characteristics:
 - Optic neuritis; OR
 - Acute myelitis; OR
 - Area postrema syndrome (i.e., episode of otherwise unexplained hiccups or nausea and vomiting); OR
 - Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical brain lesions; OR
 - Symptomatic cerebral syndrome with NMOSD-typical brain lesions; AND
- Patient is 18 years of age or older; AND
- Patient has a positive anti-aquaporin-4 antibody (AQP4-IgG) serologic test; AND
- Diagnosis of multiple sclerosis has been ruled out; AND
- Patient is NOT receiving a disease modifying multiple sclerosis medication (see policy background information for examples); AND

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- Patient has a history of one or more acute attacks or relapses that required rescue therapy during the previous 12 months OR patient has a history of two or more acute attacks relapses that required rescue therapy during the previous 24 months; AND
*(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met.)*
- Patient does NOT have active Hepatitis B virus (HBV) as confirmed by positive results for surface antigen [HBsAg] and anti-HBV tests; AND
- If a patient is negative for HBsAg and positive for HB core antibody [HBcAb+] OR patient is a carrier of HBV [HBsAg+]: a liver disease expert has been consulted (and agrees to therapy) prior to therapy with the requested drug; AND
- If a patient has active tuberculosis or positive tuberculosis screening without a history of appropriate treatment: an infectious disease expert has been consulted (and agrees to therapy) prior to therapy with the requested drug; AND
- Any non-live immunizations intended to be administered have been administered according to immunization guidelines at least 2 weeks prior to initiation of the requested drug; AND
- Any live or live-attenuated immunizations intended to be administered have been administered according to immunization guidelines at least 4 weeks prior to the initiation of the requested drug; AND
- Requested medication is NOT used in combination with inebilizumab-cdon (Uplizna™)‡, eculizumab (Soliris®)‡, or ravulizumab (Ultomiris™)‡; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) at least ONE other agent for the treatment of NMOSD (e.g., a rituximab product [Rituxan®, biosimilars]‡) unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient.
*(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.)*

Continuation (12 months)

- Patient has received initial approval for the requested medication; AND
- Patient is NOT receiving a disease modifying multiple sclerosis medication; AND
- Patient does NOT have active Hepatitis B virus (HBV) as confirmed by positive results for surface antigen [HBsAg] and anti-HBV tests; AND
- If a patient is negative for HBsAg and positive for HB core antibody [HBcAb+] OR patient is a carrier of HBV [HBsAg+]: a liver disease expert has been consulted (and agrees to therapy) when continuing therapy with the requested drug; AND
- If a patient has active tuberculosis or positive tuberculosis screening without a history of appropriate treatment: an infectious disease expert has been consulted (and agrees to therapy) when continuing therapy with the requested drug; AND
- Requested medication is NOT used in combination with inebilizumab-cdon (Uplizna), eculizumab (Soliris), or ravulizumab (Ultomiris); AND
- Patient has experienced a positive clinical response (e.g., reduction in the frequency of relapse) as attested to by the treating provider.
*(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.)*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of satralizumab-mwge (Enspryng) when the patient DOES NOT have a history of one or more acute attacks or relapses that required rescue therapy during the previous 12 months OR DOES NOT have a history of two or more acute attacks or relapses that required rescue therapy during the previous 24 months to be **not medically necessary.****

Based on review of available data, the Company considers the use of satralizumab-mwge (Enspryng) when the patient has NOT tried and failed at least ONE other agent for the treatment of NMOSD to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of satralizumab-mwge (Enspryng) when the patient has NOT experienced a positive clinical response (e.g., reduction in the frequency of relapse) as attested to by the treating provider to be **not medically necessary.****

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 satralizumab-mwge (Enspryng) when the patient selection criteria are not met (with the exception of those considered to be **not medically necessary****) to be **investigational.***

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.*

inebilizumab-cdon (Uplizna)

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Based on review of available data, the Company may consider inebilizumab-cdon (Uplizna) for the treatment of neuromyelitis optica spectrum disorder (NMOSD) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for inebilizumab-cdon (Uplizna) for the treatment of neuromyelitis optica spectrum disorder (NMOSD) will be considered when the following criteria are met:

Initial (6 months)

- Patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) as evidenced by at least ONE of the following core clinical characteristics:
 - Optic neuritis; OR
 - Acute myelitis; OR

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- Area postrema syndrome (i.e., episode of otherwise unexplained hiccups or nausea and vomiting); OR
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical brain lesions; OR
- Symptomatic cerebral syndrome with NMOSD-typical brain lesions; AND
- Patient is 18 years of age or older; AND
- Patient has a positive anti-aquaporin-4 antibody (AQP4-IgG) serologic test; AND
- Diagnosis of multiple sclerosis has been ruled out; AND
- Patient is NOT receiving a disease modifying multiple sclerosis medication; AND
- Patient has a history of one or more acute attacks or relapses that required rescue therapy during the previous 12 months OR patient has a history of two or more acute attacks or relapses that required rescue therapy during the previous 24 months; AND
*(Note: This specific patient selection criterion is an additional company requirement for coverage eligibility, based on clinical trials, and will be denied as not medically necessary** if not met.)*
- Requested drug is initially dosed as a 300 mg intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion AND subsequent doses are 300 mg intravenously every 6 months (starting 6 months from the first infusion); AND
- Patient does NOT have active Hepatitis B virus (HBV) as confirmed by positive results for surface antigen [HBsAg] and anti-HBV tests; AND
- If a patient is negative for HBsAg and positive for HB core antibody [HBcAb+] OR patient is a carrier of HBV [HBsAg+]: a liver disease expert has been consulted (and agrees to therapy) prior to therapy with the requested drug; AND
- If the patient has low serum immunoglobulins, an immunology expert has been consulted (and agrees to therapy) prior to therapy with the requested drug; AND
- If a patient has active tuberculosis or positive tuberculosis screening without a history of appropriate treatment: an infectious disease expert has been consulted (and agrees to therapy) prior to therapy with the requested drug; AND
- Any live or live-attenuated immunizations intended to be administered have been administered according to immunization guidelines at least 4 weeks prior to the initiation of the requested drug; AND
- Requested medication is NOT used in combination with satralizumab-mwge (Enspryng), eculizumab (Soliris), or ravulizumab (Ultomiris); AND
- Patient has tried and failed (e.g., intolerance or inadequate response) at least ONE other agent for the treatment of NMOSD (e.g., a rituximab product [Rituxan, biosimilars]) unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient.
*(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.)*

Continuation (12 months)

- Patient has received initial approval for the requested medication; AND
- Patient is NOT receiving a disease modifying multiple sclerosis medication; AND
- Requested drug is dosed as a 300 mg intravenous infusion every 6 months; AND

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- Patient does NOT have active Hepatitis B virus (HBV) as confirmed by positive results for surface antigen [HBsAg] and anti-HBV tests; AND
- If a patient is negative for HBsAg and positive for HB core antibody [HBcAb+] OR patient is a carrier of HBV [HBsAg+]: a liver disease expert has been consulted (and agrees to therapy) when continuing therapy with the requested drug; AND
- If a patient has active tuberculosis or positive tuberculosis screening without a history of appropriate treatment: an infectious disease expert has been consulted (and agrees to therapy) when continuing therapy with the requested drug; AND
- Requested medication is NOT used in combination with satralizumab-mwge (Enspryng), eculizumab (Soliris), or ravulizumab (Ultomiris); AND
- Patient has experienced a positive clinical response (e.g., reduction in the frequency of relapse) as attested to by the treating provider.

*(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.)*

Immunoglobulin G4-related disease (IgG4-RD)

Based on review of available data, the Company may consider inebilizumab-cdon (Uplizna) for the treatment of Immunoglobulin G4-related disease (IgG4-RD) to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for inebilizumab-cdon (Uplizna) for the treatment of Immunoglobulin G4-related disease (IgG4-RD) will be considered when the following criteria are met:

Initial (6 months)

- Patient has a diagnosis of Immunoglobulin G4-related disease (IgG4-RD) as evidenced by a score greater than or equal to 20 according to the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification criteria; AND
 - Other conditions that mimic IgG4-RD have been ruled out (e.g., malignancy, infection, other autoimmune disorders); AND
 - Patient is 18 years of age or older; AND
 - Patient has a history of involvement of at least 2 or more organs; 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 systemic corticosteroids for management of an IgG4-RD flare AND meets ONE of the following:
 - The patient has tried and had an inadequate response to systemic corticosteroids (e.g., greater than or equal to 1 flare, new or worsening symptoms, no improvement in organ function, inadequate reduction in organ size); OR
 - There is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction 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 does NOT have active Hepatitis B virus (HBV) as confirmed by positive results for surface antigen [HBsAg] and anti-HBV tests; AND

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- If a patient is negative for HBsAg and positive for HB core antibody [HBcAb+] OR patient is a carrier of HBV [HBsAg+]: a liver disease expert has been consulted (and agrees to therapy) prior to therapy with the requested drug; AND
- If the patient has low serum immunoglobulins, an immunology expert has been consulted (and agrees to therapy) prior to therapy with the requested drug; AND
- If a patient has active tuberculosis or positive tuberculosis screening without a history of appropriate treatment: an infectious disease expert has been consulted (and agrees to therapy) prior to therapy with the requested drug; AND
- Any live or live-attenuated immunizations intended to be administered have been administered according to immunization guidelines at least 4 weeks prior to the initiation of the requested drug; AND
- Requested medication is NOT used in combination with a rituximab product (Rituxan, biosimilars); AND
- Requested drug is initially dosed as a 300 mg intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion AND subsequent doses are 300 mg intravenously every 6 months (starting 6 months from the first infusion).

Continuation (12 months)

- Patient has received an initial approval for the requested medication; AND
- Patient has experienced a positive clinical response (e.g., reduction in the corticosteroid dose, reduction in the number of disease flares, increase in the duration of flare-free period, and absence of disease activity) as attested to by the treating provider; 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 does NOT have active Hepatitis B virus (HBV) as confirmed by positive results for surface antigen [HBsAg] and anti-HBV tests; AND
- If a patient is negative for HBsAg and positive for HB core antibody [HBcAb+] OR patient is a carrier of HBV [HBsAg+]: a liver disease expert has been consulted (and agrees to therapy) when continuing therapy with the requested drug; AND
- If a patient has active tuberculosis or positive tuberculosis screening without a history of appropriate treatment: an infectious disease expert has been consulted (and agrees to therapy) when continuing therapy with the requested drug; AND
- Requested medication is NOT used in combination with a rituximab product (Rituxan, biosimilars); AND
- Requested maintenance dosing does not exceed 300 mg every 6 months.

Generalized Myasthenia Gravis (gMG)

Based on review of available data, the Company may consider inebilizumab-cdon (Uplizna) for the treatment of generalized myasthenia gravis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for inebilizumab-cdon (Uplizna) for the treatment of generalized myasthenia gravis will be considered when the following criteria are met:

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Initial (6 months)

- 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 OR an anti-muscle-specific tyrosine kinase 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 greater than or equal to 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 or corticosteroids unless there is clinical evidence or patient history that suggests the use of pyridostigmine or corticosteroids 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 6 months 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, resulting in functional impairment (e.g., difficulty swallowing, difficulty breathing, double vision, impaired speech, or 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.)*

- Requested drug is initially dosed as a 300 mg intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion AND subsequent doses are 300 mg intravenously every 6 months (starting 6 months from the first infusion).

Continuation (12 months)

- Patient has received an initial authorization for Uplizna; 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 the Quantitative Myasthenia Gravis (QMG) total score; 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.)*

- Requested maintenance dosing does not exceed 300 mg every 6 months.

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of inebilizumab-cdon (Uplizna) for NMOSD when the patient DOES NOT have a history of one or more acute attacks or relapses that required rescue therapy during the previous 12 months OR DOES NOT have a history of two or more acute attacks or relapses that required rescue therapy during the previous 24 months to be **not medically necessary.****

Based on review of available data, the Company considers the use of inebilizumab-cdon (Uplizna) for NMOSD when the patient has NOT tried and failed at least ONE other agent for the treatment of NMOSD to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of inebilizumab-cdon (Uplizna) for NMOSD when the patient has NOT experienced a positive clinical response (e.g., reduction in the frequency of relapse) as attested to by the treating provider to be **not medically necessary.****

Based on review of available data, the Company considers the use of inebilizumab-cdon (Uplizna) for IgG4-RD when the patient does NOT have a history of involvement of at least 2 or more organs to be **not medically necessary.****

Based on review of available data, the Company considers the use of inebilizumab-cdon (Uplizna) for IgG4-RD when the patient has NOT experienced an IgG4-RD flare requiring systemic corticosteroids to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of inebilizumab-cdon (Uplizna) for IgG4-RD when the patient has NOT experienced a positive clinical response (e.g., reduction in the corticosteroid dose, reduction in the number of disease flares, increase in the duration of flare-free period, and absence of disease activity) as attested to by the treating provider to be **not medically necessary.****

Based on review of available data, the Company considers the use of inebilizumab-cdon (Uplizna) for gMG when the disease is not MGFA class II to IV, when the patient has not tried and failed pyridostigmine in addition to at least one NSIST, or does not have evidence of unresolved symptoms of gMG is considered to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of inebilizumab-cdon (Uplizna) for gMG when the patient has not experienced improvement while on therapy is considered to be **not medically necessary.****

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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 inebilizumab-cdon (Uplizna) when the patient selection criteria are not met (with the exception of those considered to be **not medically necessary****) to be **investigational**.*

Policy Guidelines

Myasthenia Gravis Foundation of America (MGFA) Clinical Classification

<i>Class</i>	<i>Description</i>
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

<i>Grade</i>	<i>0</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>Score</i>
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	

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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

<i>Test Item</i>	<i>None</i>	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>	<i>Score</i>
<i>Grade</i>	<i>0</i>	<i>1</i>	<i>2</i>	<i>3</i>	
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	

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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

Enspryng is an interleukin-6 (IL-6) receptor antagonist indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. Enspryng is available in a concentration of 120 mg/mL in a single-dose prefilled syringe for subcutaneous use. Before beginning therapy with Enspryng, screenings for hepatitis B virus and tuberculosis should be completed. Based on results of these screenings, the product may be contraindicated, or specialists may need to be consulted prior to beginning Enspryng. Consult the package insert for more details. Prior to each infusion, the provider should determine if there is an active infection so that the dose of Enspryng can be delayed. The recommended dosage of Enspryng is 120 mg given by subcutaneous injection at weeks 0, 2, and 4, followed by a maintenance dosage of 120 mg every 4 weeks.

Uplizna carries the same indication as Enspryng, however it is a CD19-directed cytolytic antibody. Uplizna has an additional indication for the treatment of Immunoglobulin G4-related disease (IgG4-RD) in adult patients making it the first FDA-approved treatment for IgG4-RD. More recently, Uplizna received FDA approval for the treatment of generalized myasthenia gravis (gMG) in adults who are anti-acetylcholine receptor (AChR) antibody positive or anti-muscle-specific tyrosine kinase (MuSK) antibody positive, further expanding its therapeutic use in antibody-mediated

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autoimmune diseases. Uplizna is available in single-dose vials containing 100 mg/10 mL of active ingredient. Before beginning therapy with Uplizna, screenings for hepatitis B virus, tuberculosis, and quantitative serum immunoglobulins should be completed. Based on results of these screenings, the product may be contraindicated, or specialists may need to be consulted prior to beginning Uplizna. Consult the package insert for more details. Prior to each infusion, the provider should determine if there is an active infection (so that treatment can be delayed) and should premedicate with a corticosteroid, an antihistamine, and an antipyretic. Uplizna is administered as an intravenous infusion given initially at a dose of 300 mg followed two weeks later by a second 300 mg dose. Six months after the first infusion, the dosage should be 300 mg given intravenously every 6 months.

Neuromyelitis Optica Spectrum Disorder (NMOSD)

Previously thought to be a subtype of multiple sclerosis, NMOSD is a rare, chronic disorder of the brain and spinal cord dominated by inflammation of the optic nerve and spinal cord. Multiple sclerosis should be ruled out prior to diagnosing NMOSD. Disease modifying multiple sclerosis drugs should not be used concurrently with Enspryng or Uplizna. Disease modifying drugs for the treatment of relapsing forms of multiple sclerosis include oral products such as Gilenya^{®‡}, Mayzent^{®‡}, Tecfidera^{®‡}, Vumerity^{®‡}, Zeposia^{®‡}, Bafiertam^{™‡}, and Aubagio^{®‡}. Other disease modifying medications include Copaxone^{®‡}, Avonex^{®‡}, Rebif^{®‡}, Extavia^{®‡}, Betaseron^{®‡}, Plegridy^{®‡}, Tysabri^{®‡}, Mavenclad^{®‡}, Kesimpta^{®‡}, and Lemtrada^{®‡}. NMOSD often causes significant, permanent damage to vision and/or spinal cord function resulting in blindness or impaired mobility.

Most patients with NMOSD experience repeated attacks separated by periods of remission that may last for weeks, months, or years. An attack of NMOSD is defined by objective neurologic worsening reflecting focal or multifocal central nervous system inflammation that develops acutely or subacutely in the absence of fever or infection, with a duration of at least 24 hours and occurring more than 30 days after the previous attack. This definition is similar to the definition of a multiple sclerosis (MS) relapse. Over 70% of patients with this disorder produce anti-AQP4 antibodies, which can be a diagnostic factor and may be prognostic of more severe disease. Treatment of acute attacks is typically high-dose intravenous corticosteroids with plasma exchange as a rescue treatment for patients who do not respond adequately to the corticosteroids. Prior to the approval of Enspryng and Uplizna, the mainstay of preventative therapy was Soliris. Prior to Soliris, the mainstay of therapy was chronic immunosuppression with azathioprine, mycophenolate mofetil, rituximab, methotrexate, mitoxantrone, or oral corticosteroids. The Neuromyelitis Optica Study Group (NEMOS) published revised recommendations for the treatment of NMOSD in 2024. Long term immunotherapy is recommended for patients with AQP4-IgG-positive NMOSD. NEMOS notes the first-choice therapies for the treatment of AQP4-IgG-positive NMOSD are satralizumab-mwge (Enspryng), eculizumab (Soliris), ravulizumab (Ultomiris), inebilizumab-cdon (Uplizna), and rituximab. The order of preference for these therapies is unclear and further comparative trials and real-world data are needed. The choice of treatment is dependent on several factors, including disease activity and severity, mode and onset of action, effect on autoimmune and other comorbidities, frequency and route of administration, side effect profile, as well as patient and physician preference. In general, if a patient fails a first-choice treatment, another first-choice treatment should be tried; other options include use of a second-choice treatment (azathioprine, mycophenolate mofetil, low-dose oral glucocorticoids) or the addition of a second-choice treatment to the regimen.

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Immunoglobulin G4-related disease (IgG4-RD)

IgG4-RD is a rare, progressive, highly destructive, autoimmune, fibroinflammatory disease. It is characterized by elevated serum levels of IgG4 and tumor-like masses. The disease can affect nearly any organ system and typically, multiple organs are affected simultaneously. The most commonly affected organs are pancreas, kidneys, orbital adnexal structures, salivary glands, and retroperitoneum. Diagnosis of IgG4-RD is challenging as there is no single definitive diagnostic test. An accurate diagnosis relies on a combination of clinical and serological features as well as radiological and histological findings. Symptoms related to specific organ involvement mimic other clinical conditions, making misdiagnosis fairly common. The exclusion of other diseases should be incorporated into the diagnostic workup. The American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR; formerly known as the European League Against Rheumatism) have developed a classification criteria scoring system for identification of the disease. The scoring system is designed to classify patients with IgG4-RD based on a combination of clinical, serologic, radiologic, and histopathologic features. A total score of ≥ 20 points is required for classification as IgG4-RD. The disease course is unpredictable with recurrent flares that cause functional and structural damage in the affected organs. If IgG4-RD is not treated, major organ dysfunction and failure can result. Corticosteroids are the mainstay of treatment for IgG4-RD. Off-label immunosuppressants (e.g., mycophenolate, azathioprine) and rituximab are also used in patients who have an inadequate response or intolerance to steroids or in patients with relapsing disease.

Generalized Myasthenia Gravis (gMG)

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 components of the neuromuscular junction, most commonly the acetylcholine receptor (AChR). However, antibodies to other proteins, such as the muscle-specific 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 lasts only a few weeks to months. Additionally, the Food and Drug Administration (FDA) recently approved eculizumab (Soliris®)†, ravulizumab

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(Ultomiris[™])[‡], and zilucoplan (Zilbrysq[®])[‡], all complement inhibitors, as well as rozanolixizumab (Rystiggo[®])[‡] and nipocalimab (Imaavy[™])[‡], IgG monoclonal antibodies that bind to the neonatal Fc receptor for the treatment of generalized myasthenia gravis. Inebilizumab (Uplizna[®])[‡], a CD19-directed cytolytic antibody, also gained FDA approval for the treatment of generalized myasthenia gravis. Although Soliris, Ultomiris, Vyvgart, Vyvgart Hytrulo, Zilbrysq, Rystiggo, Imaavy and Uplizna 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 Uplizna.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Enspryng and Uplizna are both indicated for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients who are anti-aquaporin-4 (AQP4) antibody positive. Uplizna gained approval for a second indication, the treatment of Immunoglobulin G4-related disease (IgG4-RD) in adults, in April 2025. Additionally, Uplizna received FDA approval in December 2025 for the treatment of generalized myasthenia gravis (gMG) in adults who are anti-acetylcholine receptor (AChR) antibody positive or anti-muscle-specific tyrosine kinase (MuSK) 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 regulations, other plan medical policies, and accredited national guidelines.

Enspryng

The efficacy of Enspryng for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in adult patients was established in two studies. Study 1 was a randomized (2:1), placebo-controlled trial in 95 patients without concurrent immunosuppressive therapy in which 64 patients were anti-AQP4 antibody positive and 31 patients were anti-AQP4 antibody negative. Study 2 was a randomized (1:1), placebo-controlled trial in 76 adult patients with concurrent immunosuppressive therapy. Of these, 52 adult patients were anti-AQP4 antibody positive and 24 adult patients were anti-AQP4 antibody negative. Patients met the following eligibility criteria: 1) Study 1: Clinical evidence of 1 relapse in the previous 12 months; 2) Study 2: Clinical evidence of at least 2 relapses in the previous 2 years, at least one of which must have occurred in the previous year; 3) Both studies: EDSS (expanded disability status scale) score of 0 to 6.5; 4) Study 1: Patients were excluded if previously treated with immunosuppressive therapy within an interval specified for each such therapy; 5) Study 2: One of the following baseline treatments at a stable dose as a monotherapy for 8 weeks prior to baseline: azathioprine, mycophenolate mofetil, oral corticosteroids.

In Study 1, 41 anti-AQP4 antibody positive adult patients were randomized to and received Enspryng and 23 received placebo. The mean EDSS score was 3.8.

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In Study 2, 26 anti-AQP4 antibody positive adult patients were randomized to and received Enspryng and 26 received placebo. All patients were receiving either concurrent azathioprine (42%), oral corticosteroids (52%), or mycophenolate mofetil (6%) during the trial. The mean EDSS score was 4.0.

All potential relapses were adjudicated by a blinded Clinical Endpoint Committee (CEC). The primary efficacy endpoint for both studies was the time to the first CEC-confirmed relapse.

In Study 1, the time to the first CEC-confirmed relapse was significantly longer in Enspryng treated patients compared to patients who received placebo (risk reduction 55%; hazard ratio 0.45; $p = 0.0184$). In the anti-AQP4 antibody positive population, there was a 74% risk reduction; hazard ratio 0.26; $p = 0.0014$. There was no evidence of a benefit in the anti-AQP4 antibody negative patients.

In Study 2, the time to the first CEC-confirmed relapse was significantly longer in patients treated with Enspryng compared to patients who received placebo (risk reduction 62%; hazard ratio 0.38; $p = 0.0184$). In the anti-AQP4 antibody positive population, there was a 78% risk reduction; hazard ratio 0.22; $p = 0.0143$. There was no evidence of a benefit in the anti-AQP4 antibody negative patients.

Uplizna

Neuromyelitis Optica Spectrum Disorder (NMOSD)

The efficacy of Uplizna for the treatment of NMOSD was established in Study 1, a randomized (3:1), double-blind, placebo-controlled trial that enrolled 213 patients with NMOSD who were anti-AQP4 antibody positive and 17 who were anti-AQP4 antibody negative. Patients met the following eligibility criteria: 1) A history of one or more relapses that required rescue therapy within the year prior to screening, or 2 or more relapses that required rescue therapy in 2 years prior to screening; 2) EDSS score of 7.5 or less. Patients with an EDSS score of 8.0 were eligible if they were deemed capable of participating; 3) Patients were excluded if previously treated with immunosuppressant therapies within an interval specified for each such therapy.

The use of immunosuppressants during the blinded phase of the trial was prohibited.

The use of oral or intravenous corticosteroids during the blinded phase of the trial was prohibited, with the exception of premedication for investigational treatment and treatment for a relapse.

Of the 213 enrolled anti-AQP4 antibody positive patients, a total of 161 were randomized to receive treatment with Uplizna, and 52 were randomized to receive placebo. The mean EDSS score was 4.0. The number of relapses in the two years prior to randomization was 2 or more in 83% of the patients.

Uplizna was administered according to the recommended dosage regimen.

All potential relapses were evaluated by a blinded, independent, adjudication committee, who determined whether the relapse met protocol-defined criteria. Patients who experienced an adjudicated relapse in the randomized-controlled period (RCP), or who completed the Day 197 visit without a relapse, exited the RCP.

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The primary efficacy endpoint was the time to the onset of the first adjudicated relapse on or before Day 197.

The time to the first adjudicated relapse was significantly longer in patients treated with Uplizna compared to patients who received placebo (relative risk reduction 73%; hazard ratio: 0.272; $p < 0.0001$). In the anti-AQP4 antibody positive population there was a 77.3% relative reduction (hazard ratio: 0.227, $p < 0.0001$). There was no evidence of a benefit in patients who were anti-AQP4 antibody negative.

Immunoglobulin G4-related disease (IgG4-RD)

The efficacy of Uplizna for the treatment of IgG4-RD was established in Study 2, a randomized, double-blind, multicenter, 52-week placebo-controlled trial that enrolled 135 adult patients who met the following eligibility criteria: 1) Newly diagnosed or recurrent IgG4-RD that required glucocorticoid (GC) treatment at screening; 2) Confirmed history of organ involvement at any time in the course of disease.

The concomitant use of biologic and non-biologic immunosuppressive agents was prohibited during the blinded phase of the trial.

Of the 135 enrolled IgG4-RD patients, 68 patients were randomized to receive Uplizna and 67 were randomized to receive placebo.

Patients were at a uniform 20 mg per day dose of glucocorticoids at the time of randomization and then began a prespecified taper of 5 mg dose every two weeks until discontinuation at the end of 8 weeks. The use of glucocorticoids during the trial was permitted for premedication for investigational treatment, treatment for a relapse and in certain situations other than an IgG4-RD flare.

Uplizna was administered according to the recommended dosage regimen.

Disease flare was defined as new/worsening signs or symptoms that were positively adjudicated and warranted treatment by the investigator. All potential flares were assessed by the investigator and subsequently reviewed by a blinded, independent, adjudication committee, who determined whether the flare met one or more of the protocol-defined, organ-specific flare diagnostic criteria.

The primary efficacy endpoint was the time to First Treated and Adjudication Committee (AC)-determined IgG4-RD flare within the 52-week RCP. The time to the First Treated and AC determined IgG4-RD flare was significantly longer in the Uplizna group, compared with the placebo group. Uplizna reduced the risk of treated and AC-determined IgG4-RD flare by 87%, compared with placebo (hazard ratio: 0.13; $p < 0.0001$).

Generalized Myasthenia Gravis (gMG)

The efficacy of Uplizna for the treatment of gMG in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle specific tyrosine kinase (MuSK) antibody positive was established in Study 3, a randomized, double-blind, multicenter, placebo controlled trial. The randomized, controlled treatment period was 52 weeks for the anti-AChR antibody positive population and 26 weeks for the anti-MuSK antibody positive population. The primary analysis was conducted after

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week 26 in both populations. Uplizna was administered according to the recommended dosage regimen. Included patients had the presence of autoantibodies against AChR or MuSK, a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV, a Myasthenia Gravis-Activities of Daily Living (MG-ADL) score between 6 and 10 with > 50% of this score attributed to non-ocular items or an MG-ADL score ≥ 11 , a Quantitative Myasthenia Gravis (QMG) score of ≥ 11 , and were on a stable dose of a corticosteroid or a specified non-steroidal immunosuppressive therapy, or a combination of both prior to randomization.

In Study 3, a total of 238 patients with gMG were randomized in a 1:1 ratio to receive Uplizna or placebo. The majority of patients, 80% (n = 190) were anti-AChR antibody positive and 20% (n = 48) were anti-MuSK antibody positive.

The efficacy of Uplizna was measured using MG-ADL scale, which 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. The total MG-ADL score ranges from 0 to 24, with higher scores indicating more impairment.

The primary efficacy endpoint was the change from baseline in the MG-ADL score at week 26, in the overall population. A statistically significant difference favoring Uplizna was observed in the mean change from baseline in MG-ADL total score (-4.2 points in the UPLIZNA-treated group compared to -2.2 points for placebo, difference of -1.9, 95% CI: -2.9, -1.0; p-value < 0.0001).

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Policy History

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02/04/2021 Medical Policy Committee review

02/10/2021 Medical Policy Implementation Committee approval. New policy.

02/03/2022 Medical Policy Committee review

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02/09/2022	Medical Policy Implementation Committee approval. No change to coverage.
02/02/2023	Medical Policy Committee review
02/08/2023	Medical Policy Implementation Committee approval. No change to coverage.
02/01/2024	Medical Policy Committee review
02/14/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2025	Medical Policy Committee review.
02/12/2025	Medical Policy Implementation Committee approval. Updated criteria for both Enspryng and Uplizna to not be used in combination with Ultomiris. Also, clarified trial/failure criterion to allow coverage of requested medication after trial and failure of at least ONE other treatment for NMOSD. Requirement to try and fail Enspryng was removed from Uplizna's criteria. Background information and references were also updated with most recent clinical guidelines.
09/04/2025	Medical Policy Committee review
09/10/2025	Medical Policy Implementation Committee approval. Added new FDA approved indication for Uplizna, Immunoglobulin G4-related disease (IgG4-RD), with relevant criteria and background information.
07/21/2026	Pre Pharmacy & Therapeutics Committee review
07/22/2026	Pharmacy & Therapeutics Committee review approval. Updated NMOSD criteria to include acute attack language in addition to relapse wording and added a definition of NMOSD attack to the background section. Added new generalized myasthenia gravis indication for Uplizna with relevant criteria and background information. A policy guidelines section relating to the gMG criteria was also added. In addition, authorization approval lengths were added to each indication reflecting a 6 month approval for initial requests and a 12 month approval for continuation requests.

Next Scheduled Review Date: 07/2027

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1823
ICD-10 Diagnosis	All related diagnoses

*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.

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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.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.