



Louisiana

satralizumab-mwge (Uplizna™) (Enspryng™), inebilizumab-cdon

Policy # 00736

Original Effective Date: 03/08/2021

Current Effective Date: 03/08/2021

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.

satralizumab-mwge (Enspryng™)

Based on review of available data, the Company may consider satralizumab-mwge (Enspryng™)† 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 Authorization:

- 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

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- Patient is NOT receiving a disease modifying multiple sclerosis medication (see policy background information for examples); AND
- Patient has a history of one or more relapses that required rescue therapy during the previous 12 months OR patient has a history of two or more relapses that required rescue therapy during the previous 24 months; AND
*(Note: This specific patient 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™)‡ or eculizumab (Soliris®)‡; AND
- Patient has tried and failed (e.g., intolerance or inadequate response) at least ONE of the following treatments for NMOSD: rituximab, azathioprine, or mycophenolate mofetil 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 criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

Continuation Request:

- Patient has received initial approval for the requested medication; AND
- Patient is NOT receiving a disease modifying multiple sclerosis medication; 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 inebilizumab-cdon (Uplizna) or eculizumab (Soliris); 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 criterion is an additional company requirement 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 satralizumab-mwge (Enspryng) when the patient DOES NOT have a history of one or more relapses that required rescue therapy during the previous 12 months OR DOES NOT have a history of two or more 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 rituximab, azathioprine, or mycophenolate mofetil 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.****

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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 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™)

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) will be considered when the following criteria are met:

Initial Authorization:

- 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

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- 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 relapses that required rescue therapy during the previous 12 months OR patient has a history of two or more relapses that required rescue therapy during the previous 24 months; AND
*(Note: This specific patient 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) or eculizumab (Soliris); AND
- Patient has tried and failed (e.g., intolerance or inadequate response) at least ONE of the following treatments for NMOSD: rituximab, azathioprine, or mycophenolate mofetil 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; AND
*(Note: This specific patient criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

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- Patient has tried and failed (e.g., intolerance or inadequate response) satralizumab-mwge (Enspryng) unless there is clinical evidence or patient history that suggests the use of satralizumab-mwge (Enspryng) will be ineffective or cause an adverse reaction to the patient. *(Note: This specific patient criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

Continuation Request:

- 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
- 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) or eculizumab (Soliris); 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 criterion is an additional company requirement 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 inebilizumab-cdon (Uplizna) when the patient DOES NOT have a history of one or more relapses that required rescue therapy during the previous 12 months OR DOES NOT have a history of two or more relapses that required rescue therapy during the previous 24 months to be **not medically necessary.****

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Based on review of available data, the Company considers the use of inebilizumab-cdon (Uplizna) when the patient has NOT tried and failed rituximab, azathioprine, or mycophenolate mofetil to be **not medically necessary.****

Based on review of available data, the Company considers the use of inebilizumab-cdon (Uplizna) when the patient has NOT tried and failed satralizumab-mwge (Enspryng) to be **not medically necessary.****

Based on review of available data, the Company considers the continued use of inebilizumab-cdon (Uplizna) 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 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.***

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.

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Uplizna carries the same indication as Enspryng, however it is a CD19-directed cytolytic antibody. 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®‡. Most patients with NMOSD experience repeated attacks separated by periods of remission that may last for weeks, months, or years. 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. Clinical practice guidelines published in 2017 by the European Journal of Neurology indicate that azathioprine or rituximab are preferred first-line therapies for the prevention of NMOSD attacks. Soliris comes with an economic disadvantage given its exorbitant price tag. Between Uplizna and Enspryng, there is also an economical difference which favors Enspryng. Additionally, Enspryng carries a more user-friendly mode of administration. There are currently no head to head studies that have demonstrated superiority of any of the available NMOSD products over the other available products.

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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.

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, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal 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.

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%),

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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

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.

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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.

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.

References

1. Enspryng [package insert]. Genentech, Inc. South San Francisco, California. Updated August 2020.
2. Uplizna [package insert]. Viela Bio, Inc. Gaithersburg, Maryland. Updated June 2020.
3. Glisson, CC. Neuromyelitis optica spectrum disorders. UpToDate. August 2019.
4. Sellner J, Boggild M, Clanet M, et al. EFNS guidelines on diagnosis and management of neuromyelitis optica. European Journal of Neurology 2017;17(8):1019-1032.

Policy History

Original Effective Date: 03/08/2021

Current Effective Date: 03/08/2021

02/04/2021 Medical Policy Committee review

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

Next Scheduled Review Date: 02/2022

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 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

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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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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.

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satralizumab-mwge (Enspryng™), inebilizumab-cdon (Uplizna™)

Policy # 00736

Original Effective Date: 03/08/2021

Current Effective Date: 03/08/2021

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.

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