



Louisiana

Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754

Original Effective Date: 09/13/2021

Current Effective Date: 07/10/2023

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 Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of aducanumab-avwa (Aduhelm[™])[†] or lecanemab-irmb (Leqembi[™])[‡] in patients with Alzheimer's disease in the mild cognitive impairment or mild dementia stage of disease 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 aducanumab-avwa (Aduhelm) or lecanemab-irmb (Leqembi) for non-FDA approved indications to be **investigational**.*

Background/Overview

Aduhelm and Leqembi are monoclonal antibodies directed against soluble and insoluble forms of beta-amyloid, a proposed cause of Alzheimer's disease. According to the prescribing information for both products, the presence of amyloid beta pathology should be confirmed prior to initiating treatment. Aduhelm is dosed at 10 mg/kg intravenously every 4 weeks after an initial 6 month titration. Leqembi is dosed at 10 mg/kg intravenously every two weeks. Additionally, the product labels recommend that a baseline brain magnetic resonance imaging (MRI) must be done within 1 year prior to initiating treatment due to the risk of amyloid-related imaging abnormalities (ARIA). Subsequently, MRI should be repeated prior to the 5th, 7th, 9th, and 12th infusions of Aduhelm and the 5th, 7th, and 14th infusions of Leqembi. If radiographic severe ARIA-hemorrhage (ARIA-H) is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H).

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Additional recommendations are provided in the package inserts for the management of patients with ARIA-edema (ARIA-E) if it is detected on MRI.

Alzheimer's Disease

Alzheimer's disease is a fatal neurodegenerative disease that causes progressive loss in memory, language, and thinking, with the eventual loss of ability to perform social and functional activities in daily life. Survival after a diagnosis of dementia due to Alzheimer's disease generally ranges between 4 and 8 years; however, life expectancy can be influenced by other factors, such as comorbid medical conditions. It is estimated that 6.2 million Americans aged 65 and older are currently living with Alzheimer's disease dementia, and the number is projected to reach over 12 million by 2050.

The pathologic hallmarks of Alzheimer's disease are extracellular deposits of beta-amyloid (A- β), referred to as amyloid plaques, and intracellular aggregates of hyperphosphorylated tau in the form of neurofibrillary tangles. There are different forms of amyloid such as plaques, oligomers, and monomers, and the roles of these different forms and how specifically they are pathophysiologically associated with Alzheimer's disease is not well understood. Generally referred to as "amyloid hypothesis", it is believed that aggregation of A- β oligomers in the brain leads to amyloid plaques and thought to be the primary driver of the disease process. Amyloid aggregation is thought to precede accumulation of tau pathology and neurodegeneration. These changes in the brain result in widespread neurodegeneration and cell death, and ultimately cause the clinical signs and symptoms of dementia.

Salient known risk factors for Alzheimer's disease are older age, genetics, and family history. Of these, increasing age has the largest known impact on risk of developing Alzheimer's disease. While several genes have been found to increase the risk of Alzheimer's disease, the $\epsilon 4$ allele of the apolipoprotein E (*ApoE*) gene is the strongest known genetic risk factor. Having 1 copy of the gene is associated with a 2- to 3-fold increase in developing Alzheimer's disease while 2 copies of the gene may increase risk of Alzheimer's disease by as much as 15 times. Approximately two-thirds of pathology-confirmed Alzheimer disease cases are $\epsilon 4$ positive (homozygous or heterozygous), compared with about 15% to 20% of the general population. Autosomal dominant genetic mutations are estimated to account for less than 1% of Alzheimer's disease cases.

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The pathophysiological changes and clinical manifestations of Alzheimer's disease are progressive and occur along a continuum, and accumulation of A- β may begin 20 years or more before symptoms arise. National Institute on Aging-Alzheimer's Association (NIA-AA) have created a "numeric clinical staging scheme" (Table 1) that avoids traditional syndromal labels and is applicable for only those in the Alzheimer continuum. This staging scheme reflects the sequential evolution of Alzheimer's disease from an initial stage characterized by the appearance of abnormal Alzheimer's disease biomarkers in asymptomatic individuals. As biomarker abnormalities progress, the earliest subtle symptoms become detectable. Further progression of biomarker abnormalities is accompanied by progressive worsening of cognitive symptoms, culminating in dementia. This numeric cognitive staging scheme is not designed to be used in a clinical setting but to be used for interventional trials such as those of aducanumab. The phase 3 randomized controlled trials for aducanumab were stratified to include 80% of stage 3 patients and 20% of stage 4 patients. This numeric staging scheme is very similar to the categorical system for staging Alzheimer's disease outlined in the Food and Drug Administration (FDA) guidance for industry pertaining to developing drugs for treatment of early Alzheimer's disease.

Table 1. National Institute on Aging-Alzheimer's Association Numerical Clinical Staging for Individuals in the Alzheimer Continuum

Stage	Severity	Clinical Features
Stage 1	Pre-clinical	<ul style="list-style-type: none">• Performance within expected range on objective cognitive tests.• No evidence of recent cognitive decline or new neurobehavioral symptoms
Stage 2	Pre-clinical	<ul style="list-style-type: none">• Normal performance within expected range on objective cognitive tests.• Transitional cognitive decline (change from individual baseline within past 1 to 3 years, and persistent for at least 6 months).• Mild neurobehavioral changes may coexist or may be the primary complaint rather than cognitive.• No functional impact on daily life activities.
Stage 3	Mild Cognitive Impairment	<ul style="list-style-type: none">• Performance in the impaired/abnormal range on objective cognitive tests.• Evidence of decline from baseline.

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	(MCI) due to Alzheimer disease	<ul style="list-style-type: none"> Performs daily life activities independently, but cognitive difficulty may result in detectable but mild functional impact on the more complex activities of daily life.
Stage 4	Mild Dementia	<ul style="list-style-type: none"> Substantial progressive cognitive impairment affecting several domains, and/or neurobehavioral disturbance. Clearly evident functional impact on daily life, affecting mainly instrumental activities. No longer fully independent/requires occasional assistance with daily life activities.
Stage 5	Moderate Dementia	<ul style="list-style-type: none"> Progressive cognitive impairment or neurobehavioral changes. Extensive functional impact on daily life with impairment in basic activities. No longer independent and requires frequent assistance with daily life activities.
Stage 6	Severe Dementia	<ul style="list-style-type: none"> Progressive cognitive impairment or neurobehavioral changes. Clinical interview may not be possible. Complete dependency due to severe functional impact on daily life with impairment in basic activities, including basic self-care.

Adapted from Table 6, Jack et al (2018)

Many tests are available in the market to detect the underlying core pathology using certain biomarkers in the cerebrospinal fluid (CSF) (e.g., decreased A- β and increased CSF tau protein levels) or on imaging (e.g., amyloid on positron emission tomography [PET] scans). Approved amyloid PET tracers in the US include [^{18}F]-florbetapir, [^{18}F]-flutemetamol and [^{18}F]-florbetaben. In addition, there are several CSF tests for A- β confirmation that are currently in development. CSF tests and amyloid PET tracers are routinely used in the enrollment of participants in contemporary Alzheimer's disease studies.

Current treatment goals for patients with Alzheimer's disease are often directed to maintain quality of life, treat cognitive symptoms, and manage behavioral and psychological symptoms of dementia. Treatment remains largely supportive, including creation and implementation of individualized dementia care plans, caregiver education and support, care navigation, care coordination, and referral

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Policy # 00754

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to community-based organizations for services (e.g., adult day care, caregiver training, etc). Non-pharmacologic treatments include physical activity as well as behavioral strategies to ameliorate neuropsychiatric symptoms (e.g., agitation, delusions, disinhibition), and problem behaviors (e.g., resistance to care, hoarding, obsessive-compulsive behaviors). Currently FDA-approved drugs for Alzheimer's disease include the cholinesterase inhibitors donepezil, rivastigmine, and galantamine, and the N-methyl-D-aspartate antagonist memantine. Cholinesterase inhibitors are indicated in mild, moderate, and severe Alzheimer's disease, while memantine is approved for moderate-to-severe disease. These drugs, either alone or in combination, focus on managing cognitive and functional symptoms of the disease and have not been shown to alter disease trajectory. The evidence for efficacy is limited and associated with significant side effects.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In June 2021, Aduhelm was approved for the treatment of Alzheimer's disease. This indication was approved under accelerated approval based on reduction in A- β plaques observed in patients treated with Aduhelm. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

In July 2021, the FDA amended the approved label to emphasize the disease stages studied in the clinical trials. The amended label states, "Treatment with aducanumab should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied."

The FDA, under the accelerated approval regulations, requires that Biogen conduct a randomized, controlled trial to evaluate the efficacy of aducanumab-avwa compared to an appropriate control for the treatment of Alzheimer's disease. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial. The expected date of trial completion is August 2029 and the final report submission to the FDA by February 2030.

In January 2023, the FDA granted accelerated approval to Leqembi for the treatment of Alzheimer's disease. The label notes that treatment should be initiated in patients with mild cognitive impairment

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Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754

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or mild dementia stage of disease. Continued approval for the indication may be contingent upon verification of clinical benefit in a confirmatory trial.

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.

Aduhelm-Efficacy

The evidence for aducanumab includes a dose-finding and proof of concept phase 1 trial (PRIME) and 2 phase 3 pivotal trials (ENGAGE [study 301] and EMERGE [study 302]). PRIME was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging, staggered study conducted in the United States with the primary objectives of safety and tolerability. The phase 3 studies were multicenter, global, randomized, double-blind, placebo-controlled studies of identical design with the primary objective of efficacy and safety. In all 3 studies, the diagnosis of Alzheimer's disease was confirmed by presence of amyloid pathology measured by [¹⁸F]-florbetapir PET imaging. The pivotal trials ensured enrollment of patients at an earlier stage of their disease; Mild Cognitive Impairment (MCI) due to Alzheimer disease or mild Alzheimer disease dementia based on an entry criteria of baseline Mini-Mental State Examination (MMSE) score of 24 to 30, baseline Clinical Dementia Rating (CDR) global score of 0.5 and Repeatable Battery for the Assessment of Neurological Status (RBANS) delayed memory index score ≤ 85. Per the protocol design, most participants had a diagnosis of MCI due to Alzheimer disease (81.6%), while 18.4% of participants had mild Alzheimer disease dementia. Approximately two-thirds of the study population in the phase 3 trials are *apolipoprotein E (ApoE) ε4* carriers. The trial had approximately 90% power to detect a true mean difference of 0.5 in change from baseline CDR Sum of Boxes (CDR-SB) at week 78. The range for CDR-SB is 0 to 18, with higher scores indicating greater disease severity.

The phase 3 studies randomized patients to aducanumab low dose (3 or 6 mg/kg for *ApoE ε4* carriers and noncarriers, respectively), aducanumab high dose (10 mg/kg), or placebo every 4 weeks for 18 months, followed by an optional, dose-blind, long-term extension period. Although aducanumab 10 mg/kg was hypothesized to be the most efficacious dose, due to safety concerns and limited

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Policy # 00754

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understanding of amyloid-related imaging abnormalities (ARIA), both studies included an initial titration period of up to 6 months to the maximum target dose. At the beginning of the study, *ApoE* $\epsilon 4$ carriers were initially titrated up to a maximum of 6 mg/kg in the high-dose group, which was later adjusted to 10 mg/kg. Both pivotal trials were terminated prior to their planned completion. Study endpoints were analyzed based on a prespecified statistical analysis plan. Due to the early termination and consequent administrative censoring, data was missing for up to 45% of patients randomized in the 2 trials. Approximately 60 percent of patients had the opportunity to complete week 78 of the trial before the trials were terminated for futility.

Study 302 (N=1638 randomized patients) met the primary endpoint in patients treated with high-dose aducanumab with an absolute difference of -0.39 in favor of aducanumab on the 18-point CDR-SB scale (a relative 22% less decline in high dose aducanumab group compared to placebo, $p=0.0120$). The reported minimum clinically important difference is generally considered to be 1 to 2 points on a scale from 0 to 18. Results of responder analysis describing proportion of individuals who achieved a predefined level of improvement was not reported. Results in the low-dose aducanumab group were not statistically significant compared with placebo (absolute difference -0.26, relative difference -15%, $p=0.0901$) and therefore no statistically valid conclusions can be made for any of the secondary endpoints for either of treatment arms.

Study 301 (N=1647 randomized patients) did not meet its primary end point of a reduction relative to placebo in the CDR-SB score. For the high-dose arm, an absolute difference of 0.03 and a relative difference of 2% favored placebo ($p=0.8330$). For the low-dose arm, an absolute difference of -0.18 and a relative difference of 12% favored aducanumab ($p=0.8330$). Because of the pre-specified plans to control for type I error for multiple comparisons, no statistically valid conclusions can therefore be made for any of the secondary endpoints.

Change in brain amyloid signal was measured by [^{18}F]-florbetapir PET and quantified by a composite standard uptake value ratio (SUVR) in a subset of sites and patients ($n=488$) at week 78. In study 302, adjusted mean change from baseline to week 78 relative to placebo showed a dose-dependent reduction in A- β by -0.179 and -0.278 in the low- and high-dose arms respectively. In study 301, adjusted mean change from baseline to week 78 relative to placebo showed a dose-dependent reduction in A- β by -0.167 and -0.232 in the low- and high-dose arms respectively. While aducanumab showed statistically significant dose dependent changes from baseline in A- β plaques, there are no satisfactory data clearly establishing individual changes in amyloid correlate with or

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predict long term cognitive and functional changes as measured by CDR-SB. The FDA statistical review reported no correlation in study 302 between reduction in amyloid plaque and long-term clinical change among the high-dose cohort or full 10 mg/kg dosed subgroup. In the absence of clinical data convincingly demonstrating a clinical effect, it cannot be concluded that observed reduction in amyloid will translate into a clinical benefit to patients.

Change from baseline in markers of downstream Alzheimer's disease tau pathophysiology and neurodegeneration were reported for a small subset of patients collected from a voluntary non-directly randomized sample (n=45 in study 302 and n=33 in study 301). While the prescribing label reports a statistically significant lowering of both phosphorylated tau and total tau in the treatment arms, aducanumab is not known to directly target tau pathways. Therefore, it is difficult to clinically interpret the observed findings on an off-target exploratory biomarker from a small voluntary non-directly randomized sample.

Aduhelm-Safety

Data with limited follow-up are available to analyze safety because the phase 3 trials were stopped prematurely due to futility. Pooled safety data from the phase 3 clinical trials showed that about 35% (compared to 3% in the placebo arm) of patients on aducanumab experienced ARIA, with clinical effects ranging from asymptomatic to severe. Although the majority of patients were asymptomatic or had symptoms such as headache, confusion, or dizziness that resolved with temporary stoppage of the drug, 6.2% of participants receiving the high dose of aducanumab discontinued the drug due to ARIA. The incidence of ARIA-edema was higher in *ApoE* ϵ 4 carriers than non-carriers (42% and 20%, respectively). The majority of ARIA-edema radiographic events occurred early in treatment (within the first 8 doses), although ARIA can occur at any time. Among patients treated with a planned dose of aducanumab 10 mg/kg who had ARIA-edema, the maximum radiographic severity was mild in 30%, moderate in 58%, and severe in 13% of patients. Resolution occurred in 68% of ARIA-edema patients by 12 weeks, 91% by 20 weeks, and 98% overall after detection. Ten percent of all patients who received aducanumab 10 mg/kg had more than 1 episode of ARIA-edema.

An increase in falling adverse events was observed in the high-dose as compared to placebo across the 2 phase 3 studies (15% vs. 12%, respectively). FDA statistical review reported a hazard ratio of 1.33 (p=.016) suggesting a 33% relative increase in hazard of falling for 10 mg/kg compared to placebo. A quantitative integration of benefit and risk was not done, but if the high dose increases falls, it could be a significant risk for the Alzheimer's disease population.

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A confirmatory, prospective and adequately powered trial is necessary to assess the net health benefit of Aduhelm in patients with early Alzheimer's disease. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Leqembi

The efficacy of Leqembi was evaluated in a double-blind, placebo-controlled, parallel-group, dose finding study in patients with Alzheimer's disease (patients with confirmed presence of amyloid pathology and mild cognitive impairment [64% of patients] or mild dementia stage of disease [36% of patients], consistent with Stage 3 and Stage 4 Alzheimer's disease). The study had a 79-week double-blind, placebo-controlled period, followed by an open-label extension period for up to 260 weeks, which was initiated after a gap period (range 9 to 59 months; mean 24 months) off treatment.

In Study 1, 856 patients were randomized to receive one of 5 doses (161 of which were randomized to the recommended dosing regimen of 10 mg/kg every two weeks) of Leqembi or placebo (n=247). Of the total number of patients randomized, 71.4% were ApoE ϵ 4 carriers. During the study, the protocol was amended to no longer randomize ApoE ϵ 4 carriers to the 10 mg/kg every two weeks dose arm. ApoE ϵ 4 carriers who had been receiving Leqembi 10 mg/kg every two weeks for 6 months or less were discontinued from study drug. As a result, in the Leqembi 10 mg/kg every two weeks arm, 30.3% of patients were ApoE ϵ 4 carriers. At baseline, the mean age of randomized patients was 71 years, with a range of 50 to 90 years. Patients were enrolled with a Clinical Dementia Rating (CDR) global score of 0.5 or 1.0 and a Memory Box score of 0.5 or greater. All patients had a MMSE score of ≥ 22 , had objective impairment in episodic memory as indicated by at least 1 standard deviation below age-adjusted mean in the Wechsler-Memory Scale-IV Logical Memory II (subscale). Patients were enrolled with or without concomitant approved therapies for Alzheimer's disease.

In Study 1, a subgroup of 315 patients were enrolled in the amyloid PET substudy; of these, 277 were evaluated at week 79. Results from this substudy demonstrated a reduction in brain amyloid beta plaque with Leqembi 10 mg/kg every 2 weeks compared to placebo.

The primary endpoint of Study 1 was change from baseline on a weighted composite score consisting of selected items from the CDR-SB, MMSE, and ADAS-Cog 14 at Week 53. Leqembi had a 64% likelihood of 25% or greater slowing of progression on the primary endpoint relative to placebo at Week 53, which did not meet the prespecified success criterion of 80%.

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Monoclonal Antibodies for the Treatment of Alzheimer's Disease

Policy # 00754

Original Effective Date: 09/13/2021

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Policy History

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08/05/2021	Medical Policy Committee review
08/11/2021	Medical Policy Implementation Committee approval. New policy.
12/20/2021	Coding update
08/04/2022	Medical Policy Committee review
08/10/2022	Medical Policy Implementation Committee approval. No change to coverage.
06/01/2023	Medical Policy Committee review
06/14/2023	Medical Policy Implementation Committee approval. Added new drug, Leqembi, to policy. Changed title to "Monoclonal Antibodies for the Treatment of Alzheimer's Disease"
08/10/2023	Coding update

Next Scheduled Review Date: 06/2024

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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 2022 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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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	C9399, J3490, J3590, J0172 Add code effective 09/01/2023: J0174
ICD-10 Diagnosis	All related diagnoses

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***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.

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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.

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