etanercept (Enbrel®)

Policy # 00219
Original Effective Date: 01/17/2007
Current Effective Date: 10/17/2018

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.*

Rheumatoid Arthritis
Based on review of available data, the Company may consider the use of etanercept (Enbrel®)‡ for the treatment of rheumatoid arthritis (RA) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of etanercept (Enbrel) for the treatment of rheumatoid arthritis (RA) will be considered when all of the following criteria are met:

- Patient has moderately to severely active RA; AND
- Patient has failed treatment with one or more disease-modifying anti-rheumatic drugs (DMARDs); 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).*
- Enbrel is NOT used in combination with other biologic DMARDs, such as adalimumab (Humira®)‡ OR other drugs such as apremilast (Otezla®)‡ or tofacitinib (Xeljanz/XR®)‡; AND
- Patient has a negative TB (tuberculosis) test (e.g. purified protein derivative [PPD], blood test) prior to treatment.

Psoriatic Arthritis
Based on review of available data, the Company may consider the use of etanercept (Enbrel) † for the treatment of psoriatic arthritis (PsA) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of etanercept (Enbrel) for the treatment of PsA will be considered when all of the following criteria are met:

- Patient has a diagnosis of PsA; AND
- Patient has failed treatment with one or more DMARDs; 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).*
- Enbrel is NOT used in combination with other biologic DMARDs, such as adalimumab (Humira) OR other drugs such as apremilast (Otezla) or tofacitinib (Xeljanz/XR); AND
- Patient has a negative TB test (e.g. PPD, blood test) prior to treatment.

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Polyarticular Juvenile Idiopathic Arthritis
Based on review of available data, the Company may consider the use of etanercept (Enbrel)† for the treatment of polyarticular juvenile idiopathic arthritis (PJIA) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of etanercept (Enbrel) for the treatment of polyarticular juvenile idiopathic arthritis (PJIA) will be considered when all of the following criteria are met:

- Patient is 2 years of age or older with moderately to severely active PJIA; AND
- Patient has failed treatment with one or more DMARDs; 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).*
- Enbrel is NOT used in combination with other biologic DMARDs, such as adalimumab (Humira) OR other drugs such as apremilast (Otezla) or tofacitinib (Xeljanz/XR); AND
- Patient has a negative TB test (e.g. PPD, blood test) prior to treatment.

Ankylosing Spondylitis
Based on review of available data, the Company may consider the use of etanercept (Enbrel) for the treatment of active ankylosing spondylitis (AS) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of etanercept (Enbrel) for the treatment of active AS will be considered when all of the following criteria are met:

- Patient has a diagnosis of active AS; AND
- Patient has failed treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or has documented contraindications to NSAIDs usage; 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).*
- Enbrel is NOT used in combination with other biologic DMARDs, such as adalimumab (Humira) OR other drugs such as apremilast (Otezla) or tofacitinib (Xeljanz/XR); AND
- Patient has a negative TB test (e.g. PPD, blood test) prior to treatment.

Plaque Psoriasis
Based on review of available data, the Company may consider the use of etanercept (Enbrel) for the treatment of plaque psoriasis (PsO) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility for the use of etanercept (Enbrel) for the treatment of PsO will be considered when all of the following criteria are met:

- Patient is 4 years of age or older with chronic moderate to severe PsO; AND
- Enbrel is NOT used in combination with other biologic DMARDs, such as adalimumab (Humira) OR other drugs such as apremilast (Otezla) or tofacitinib (Xeljanz/XR); AND

- Patient has a negative TB test (e.g. PPD, blood test) prior to treatment; AND
- Patient has failed treatment with adalimumab (Humira) after at least TWO months of therapy unless there is clinical evidence or patient history that suggests the use of adalimumab (Humira) 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).*
- Patient has greater than 10% of body surface area or less than or equal to 10% body surface area with PsO involving sensitive areas or areas that would significantly impact daily function (such as palms, soles of feet, head/neck or genitalia) ; 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).*
- Patient is a candidate for phototherapy or systemic therapy; AND
- Patient has failed to respond to an adequate trial of one of the following treatment modalities:
  - Ultraviolet B; or
  - Psoralen positive Ultraviolet A; or
  - Systemic therapy (i.e. methotrexate [MTX], cyclosporine, acitretin).

  *(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 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 etanercept (Enbrel) when patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****), OR for use in any other indication than those listed above to be **investigational.***

When Services Are Considered Not Medically Necessary:
Based on review of available data, the Company considers the use of etanercept (Enbrel) when any of the following criteria for their respective disease listed below (and denoted in the patient selection criteria above) are not met to be **not medically necessary**:**

- For RA, PsA, and PJIA:
  - Patient has failed treatment to one or more DMARDs
- For AS:
  - Patient has failed treatment with NSAIDs or has documented contraindications to NSAIDs usage
- For PsO:
  - Patient has failed treatment with adalimumab (Humira) after at least TWO months of therapy

- Patient has greater than 10% of body surface area or less than or equal to 10% body surface area with PsO involving sensitive areas or areas that would significantly impact daily function (such as palms, soles of feet, head/neck or genitalia)
- Patient has failed to respond to an adequate trial of one of the following treatment modalities:
  - Ultraviolet B
  - Psoralen positive Ultraviolet A
  - Systemic therapy (i.e. MTX, cyclosporine, acitretin)

Background/Overview

Tumor necrosis factor (TNF) is a naturally occurring cytokine that is involved with the inflammatory and immune responses. Excessive activation of immune effector cells and overproduction of TNF can cause severe inflammation and tissue damage. Inhibition of TNF activity in certain inflammatory diseases may alleviate symptoms and prevent disease progression.

Enbrel is a type of protein TNF blocker that blocks the action of a TNF that is produced by the body's immune system. People with an immune disease such as RA, AS, PsA or PsO have too much TNF. Enbrel can reduce the amount of TNF.

Rheumatoid Arthritis
RA is a chronic (long-term) disease that causes inflammation of the joints and surrounding tissues. It can also affect other organs. It is considered an autoimmune disease. In an autoimmune disease, the immune system confuses healthy tissue for foreign substances. Typically first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include MTX.

Psoriatic Arthritis
PsA is an arthritis that is often associated with psoriasis of the skin. Typically first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include MTX.

Polyarticular Juvenile Idiopathic Arthritis
PJIA includes the inflammation of joints and presence of arthritis in children. PJIA typically occurs in a symmetrical manner with knees, wrists, and ankles most frequently affected. However certain subgroups of children do have predominantly asymmetrical involvement. Typically first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include MTX.

Ankylosing Spondylitis
AS is a chronic inflammatory disease that affects the joints between the vertebrae of the spine, and the joints between the spine and the pelvis. It eventually causes the affected vertebrae to fuse or grow together. NSAIDs such as aspirin are used to reduce inflammation and pain associated with the condition. Corticosteroid therapy or medications to suppress the immune system may be prescribed to control various symptoms.

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Plaque Psoriasis
Psoriasis is a common skin condition that is caused by an increase in production of skin cells. It is characterized by frequent episodes of redness, itching and thick, dry silvery scales on the skin. It is most commonly seen on the trunk, elbows, knees, scalp, skin folds and fingernails. This condition can appear suddenly or gradually and may affect people of any age; it most commonly begins between the ages of 15 and 35. Psoriasis is not contagious. It is an inherited disorder related to an inflammatory response in which the immune system produces too much TNF-alpha. It may be severe in immunosuppressed people or those who have other autoimmune disorders such as RA. Treatment is focused on control of the symptoms and prevention of secondary infections. Lesions that cover all or most of the body may be acutely painful and require hospitalization. The body loses vast quantities of fluid and becomes susceptible to severe secondary infections that can involve internal organs and even progress to septic shock. Typical treatments for severe cases of PsO include ultraviolet therapy or systemic therapies such as MTX or cyclosporine.

Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
DMARDS drugs are typically used for the treatment of RA, AS, PJIA, and PsO. These drugs slow the disease process by modifying the immune system.

- MTX
- Cyclosporine
- Sulfasalazine
- Mercaptopurine
- Gold Compounds

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Enbrel (etanercept) is currently approved for the treatment of RA, PsA, PJIA, AS, and PsO.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA 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.

Rheumatoid Arthritis
The safety and efficacy of Enbrel were assessed in four randomized, double-blind, controlled studies. The results of all four trials were expressed in percentage of patients with improvement in RA using American College of Rheumatology (ACR) response criteria. Study I evaluated 234 patients with active RA. Doses of 10 mg or 25 mg Enbrel or placebo were administered subcutaneous (SC) twice a week for 6 consecutive months. Study II evaluated 89 patients and had similar inclusion criteria to Study I except that patients in Study II had additionally received MTX for at least 6 months with a stable dose for at least 4 weeks. Patients in Study II received a dose of 25 mg Enbrel or placebo SC twice a week for 6 months in addition to

their stable MTX dose. Study III compared the efficacy of Enbrel to MTX in patients with active RA. This study evaluated 632 patients. Doses of 10 mg or 25 mg Enbrel were administered SC twice a week for 12 consecutive months. The study was unblinded after all patients had completed at least 12 months (and a median of 17.3 months) of therapy. The majority of patients remained in the study on the treatment to which they were randomized through 2 years, after which they entered an extension study and received open-label 25 mg Enbrel. MTX tablets (escalated from 7.5 mg/week to a maximum of 20 mg/week over the first 8 weeks of the trial) or placebo tablets were given once a week on the same day as the injection of placebo or Enbrel doses, respectively. Study IV evaluated 682 adult patients with active RA who had an inadequate response to at least one DMARD other than MTX. Patients were randomized to MTX alone (7.5 to 20 mg weekly, dose escalated as described for Study III; median dose 20 mg), Enbrel alone (25 mg twice weekly), or the combination of Enbrel and MTX initiated concurrently (at the same doses as above). The study evaluated ACR response, Sharp radiographic score, and safety. A higher percentage of patients treated with Enbrel and Enbrel in combination with MTX achieved ACR 20, ACR 50, and ACR 70 responses and Major Clinical Responses than in the comparison groups.

Polyarticular Juvenile Idiopathic Arthritis (JIA)
The safety and efficacy of Enbrel were assessed in a 2-part study in 69 children with PJIA who had a variety of JIA onset types. In part 1, all patients received 0.4 mg/kg (maximum 25 mg per dose) Enbrel SC twice weekly. In part 2, patients with a clinical response at day 90 were randomized to remain on Enbrel or receive placebo for 4 months and assessed for disease flare. Responses were measured using the JIA Definition of Improvement (DOI), defined as ≥ 30% improvement in at least three of six and ≥ 30% worsening in no more than one of the six JIA core set criteria, including active joint count, limitation of motion, physician and patient/parent global assessments, functional assessment, and erythrocyte sedimentation rate (ESR). Disease flare was defined as a ≥ 30% worsening in three of the six JIA core set criteria and ≥30% improvement in not more than one of the six JIA core set criteria and a minimum of two active joints. In part 1 of the study, 51 of 69 (74%) patients demonstrated a clinical response and entered part 2. In part 2, 6 of 25 (24%) patients remaining on Enbrel experienced a disease flare compared to 20 of 26 (77%) patients receiving placebo ($p = 0.007$). From the start of part 2, the median time to flare was ≥ 116 days for patients who received Enbrel and 28 days for patients who received placebo. Each component of the JIA core set criteria worsened in the arm that received placebo and remained stable or improved in the arm that continued on Enbrel. The data suggested the possibility of a higher flare rate among those patients with a higher baseline ESR. Of patients who demonstrated a clinical response at 90 days and entered part 2 of the study, some of the patients remaining on Enbrel continued to improve from month 3 through month 7, while those who received placebo did not improve. The majority of JIA patients who developed a disease flare in part 2 and reintroduced Enbrel treatment up to 4 months after discontinuation re-responded to Enbrel therapy in open-label studies. Most of the responding patients who continued Enbrel therapy without interruption have maintained responses for up to 48 months.

Psoriatic Arthritis
The safety and efficacy of Enbrel were assessed in a randomized, double-blind, placebo-controlled study in 205 patients with PsA. Doses of 25 mg Enbrel or placebo were administered SC twice a week during the initial 6-month double-blind period of the study. Patients continued to receive blinded therapy in an up to 6-

month maintenance period until all patients had completed the controlled period. Following this, patients received open-label 25 mg Enbrel twice a week in a 12-month extension period. Compared to placebo, treatment with Enbrel resulted in significant improvements in measures of disease activity. Among patients with PsA who received Enbrel, the clinical responses were apparent at the time of the first visit (4 weeks) and were maintained through 6 months of therapy. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline. At 6 months, the ACR 20/50/70 responses were achieved by 50%, 37%, and 9%, respectively, of patients receiving Enbrel, compared to 13%, 4%, and 1%, respectively, of patients receiving placebo. The results of this study were similar to those seen in an earlier single-center, randomized, placebo-controlled study of 60 patients with PsA. The skin lesions of psoriasis were also improved with Enbrel, relative to placebo, as measured by percentages of patients achieving improvements in the Psoriasis Area and Severity Index (PASI). Responses increased over time, and at 6 months, the proportions of patients achieving a 50% or 75% improvement in the PASI were 47% and 23%, respectively, in the Enbrel group (N = 66), compared to 18% and 3%, respectively, in the placebo group (N = 62). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Ankylosing Spondylitis
The safety and efficacy of Enbrel were assessed in a randomized, double-blind, placebo-controlled study in 277 patients with active AS. Patients were between 18 and 70 years of age and had AS as defined by the modified New York Criteria for Ankylosing Spondylitis. Doses of 25 mg Enbrel or placebo were administered SC twice a week for 6 months. The primary measure of efficacy was a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS) response criteria. Compared to placebo, treatment with Enbrel resulted in improvements in the ASAS and other measures of disease activity. At 12 weeks, the ASAS 20/50/70 responses were achieved by 60%, 45%, and 29%, respectively, of patients receiving Enbrel, compared to 27%, 13%, and 7%, respectively, of patients receiving placebo ($p \leq 0.0001$, Enbrel vs placebo). Similar responses were seen at week 24. Responses were similar between those patients receiving concomitant therapies at baseline and those who were not.

Plaque Psoriasis
The safety and efficacy of Enbrel were assessed in two randomized, double-blind, placebo-controlled studies in adults with chronic stable PsO involving ≥ 10% of the body surface area, a minimum PASI score of 10 and who had received or were candidates for systemic antipsoriatic therapy or phototherapy. Study I evaluated 672 patients who received placebo or Enbrel SC at doses of 25 mg once a week, 25 mg twice a week, or 50 mg twice a week for 3 months. After 3 months, patients continued on blinded treatments for an additional 3 months during which time patients originally randomized to placebo began treatment with blinded Enbrel at 25 mg twice weekly; patients originally randomized to Enbrel continued on the originally randomized. Study II evaluated 611 patients who received placebo or Enbrel SC at doses of 25 mg or 50 mg twice a week for 3 months. After 3 months of randomized, blinded treatment, patients in all three arms began receiving open-label Enbrel at 25 mg twice weekly for 9 additional months. Response to treatment in both studies was assessed after 3 months of therapy and was defined as the proportion of patients who achieved a reduction in PASI score of at least 75% from baseline. The PASI is a composite score that takes into consideration both the fraction of body surface area affected and the nature and severity of psoriatic

changes within the affected regions (induration, erythema and scaling). More patients randomized to Enbrel than placebo achieved at least a 75% reduction from baseline PASI score (PASI 75) with a dose response relationship across doses of 25 mg once a week, 25 mg twice a week and 50 mg twice a week.

Enbrel was also evaluated in a 48 week, randomized, double-blind, placebo-controlled study which enrolled 211 pediatric subjects aged 4 to 17 years of age with moderate to severe PsO. Subjects received 0.8 mg/kg (up to a max of 50 mg per dose) of Enbrel or placebo once weekly for the first 12 weeks. After 12 weeks, subjects entered a 24 week open label treatment period, in which all subjects received Enbrel at the same dose. This was followed by a 12 week withdrawal-retreatment period. Response to treatment was assessed after 12 weeks of therapy and was defined as the proportion of subjects who achieved a reduction in PASI score of at least 75% from baseline. In the Enbrel treatment group, 57% of the subjects achieved a PASI 75 vs. 11% of subjects in the placebo arm.

References

1. Food and Drug Administration. Labeling of the Drug Enbrel. www.fda.gov
2. Enbrel. [package insert]. Amgen. Thousand Oaks, California. Updated November 2016.

Policy History

Original Effective Date: 01/17/2007
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01/10/2007	Medical Director review
01/17/2007	Medical Policy Committee approval
01/09/2008	Medical Director review
01/23/2008	Medical Policy Committee approval. Format revision; Coverage eligibility unchanged. Restrictions to prescribing specialist removed from patient selection criteria. Patient selection criteria for plaque psoriasis expanded to include hand, feet head /neck and genitalia.
01/07/2009	Medical Director review
01/14/2009	Medical Policy Committee approval. No change to coverage eligibility. Black box warning added.
01/07/2010	Medical Policy Committee approval
01/20/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/06/2011	Medical Policy Committee review
01/19/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Changed the Juvenile Rheumatoid Arthritis language to Polyarticular Juvenile Idiopathic Arthritis. Split the Rheumatoid arthritis, psoriatic arthritis and Juvenile Idiopathic Arthritis into separate sections. Added age of 2 or older to Juvenile Idiopathic Arthritis. Clarified that PPD is required for each indication. Denoted which criteria are not medically necessary. Cleaned up the When Services are Considered Investigational and When Services are Considered Not Medically Necessary sections.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015	Medical Policy Committee review
06/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Changed age to 4 years old for plaque psoriasis due to updated FDA approved indication.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. Updated the tuberculosis test criteria. Clarified that these drugs are not to be used in combination with certain drugs. Added a requirement that Humira be used first prior to Enbrel for plaque psoriasis.
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2019

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 2017 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	J1438			
ICD-10 Diagnosis	L40.0-L40.9	M05.40-M05.59	M05.70-M05.9	M06.00-M06.09
	M06.20-M06.39	M06.80-M06.9	M08.00-M08.3	M08.80-M08.99
	M45.0-M45.9	M48.8X1-M48.8X9		

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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 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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