Dermatologic Applications of Photodynamic Therapy

Policy # 00098
Original Effective Date: 06/05/2002
Current Effective Date: 06/12/2023

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.

Note: Light Therapy for Psoriasis is addressed separately in medical policy 00131.

Note: Oncologic Applications of Photodynamic Therapy, Including Barrett's Esophagus is addressed separately in medical policy 00234.

Note: Photodynamic Therapy for Choroidal Neovascularization is addressed separately in medical policy 00097.

When Services May Be Eligible for Coverage

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

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

Based on review of available data, the Company may consider photodynamic therapy (PDT) to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility will be considered for any of the following conditions:

- Actinic keratosis; or
- Low-risk (e.g. superficial and nodular) basal cell skin cancer only when surgery and radiation are contraindicated; or
- Cutaneous squamous cell carcinoma in situ (Bowen disease) only when surgery and radiation are contraindicated.

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When Services Are Considered Investigational

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

Based on review of available data, the Company considers photodynamic therapy (PDT) for other dermatologic applications, including, but not limited to the following to be **investigational:***

- Acne vulgaris
- High-risk basal cell carcinomas
- Hidradenitis suppurativa
- Mycoses

Based on the review of available data, the Company considers the use of photodynamic therapy (PDT) when patient selection criteria are not met to be **investigational.***

When Services Are Not Covered

The use of photodynamic therapy (PDT) as a technique of skin rejuvenation, hair removal, or other cosmetic indications is **not covered. ****

Policy Guidelines

Surgery and radiation are the preferred treatments for low-risk basal cell cancer and Bowen disease (see Rationale section). If photodynamic therapy is selected for these indications because of contraindications to surgery or radiation, individuals and physicians need to be aware that it may have a lower cure rate than surgery or radiation.

Photodynamic therapy typically involves 2 office visits: 1 to apply the topical aminolevulinic acid and a second visit to expose the individual to blue light. The second physician office visit, performed solely to administer blue light, should not warrant a separate Evaluation and Management CPT code. Photodynamic protocols typically involve 2 treatments spaced a week apart; more than 1 treatment series may be required.

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Based on characteristics of individuals enrolled in randomized controlled trials, 4 or more lesions per site (face, scalp, or upper extremities) is an appropriate threshold for use of photodynamic therapy for individuals with nonhyperkeratotic actinic keratosis.

Background/Overview

Photodynamic Therapy

Photodynamic therapy refers to light activation of a photosensitizer to generate highly reactive intermediaries, which ultimately cause tissue injury and necrosis. Two common photosensitizing agents are 5-aminolevulinic acid (ALA) and its methyl ester, methyl aminolevulinate. When applied topically, these agents pass readily through abnormal keratin overlying the lesion and accumulate preferentially in dysplastic cells. The agents ALA and methyl aminolevulinate are metabolized by underlying cells to photosensitizing concentrations of porphyrins. Subsequent exposure to photoactivation (maximum absorption at 404 to 420 nm and 635 nm) generates reactive oxygen species that are cytotoxic, ultimately destroying the lesion. PDT can cause erythema, burning, and pain. Healing occurs within 10 to 14 days, with generally acceptable cosmetic results. PDT with topical ALA has been investigated primarily as a treatment of actinic keratoses (AKs).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

In 1999, Levulan®‡ Kerastick™‡, a topical preparation of ALA, in conjunction with illumination with the BLU-U™‡ Blue Light Photodynamic Therapy Illuminator, was approved by the U.S. FDA for the treatment of nonhyperkeratotic AKs of the face and scalp. In 2018, the indication was expanded to include nonhyperkeratotic AKs of the upper extremities. The product is applied in the physician's office.

FDA product code: MVF.

In 2016, the FDA approved Ameluz®‡ (aminolevulinic acid hydrochloride) gel, 10% (BF-200 ALA; Biofrontera AG) in combination with PDT using BF-RhodoLED lamp, to be used for the lesion-directed and field-directed treatment of AKs of mild-to-moderate severity on the face and scalp. The treatment is to be administered by a healthcare provider.

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ALApatch technology is available outside of the US through an agreement between Intendis (now Bayer HealthCare) and Photonamic. The ALA patch is not approved by the FDA.

Another variant of PDT for skin lesions is Metvixia®‡ used with the Aktilite CL128 lamp, each of which received the FDA approval in 2004. Metvixia®‡ (Galderma; Photocure) consists of the topical application of methyl aminolevulinate (in contrast to ALA used in the Kerastick procedure), followed by exposure with the Aktilite CL128 lamp, a red light source (in contrast to the blue light source in the Kerastick procedure). Broadband light sources (containing the appropriate wavelengths), intense pulsed light (FDA product code: ONF), pulsed dye lasers, and potassium-titanyl-phosphate lasers have also been used. Metvixia®‡ is indicated for the treatment of nonhyperkeratotic AKs of the face and scalp in immunocompetent individuals when used with lesion preparation (debridement using a sharp dermal curette) in the physician's office when other therapies are unacceptable or considered medically less appropriate.
FDA product codes: GEX and LNK.

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.

Photodynamic therapy refers to light activation of a photosensitizer to generate highly reactive intermediaries, which ultimately cause tissue injury and necrosis. Photosensitizing agents are being proposed for use with dermatologic conditions such as actinic keratoses (AKs) and nonmelanoma skin cancers.

Summary of Evidence

For individuals who have nonhyperkeratotic AKs on the face or scalp who receive PDT, the evidence includes meta-analyses and randomized controlled trials (RCTs). Relevant outcomes are symptoms, change in disease status, quality of life (QOL), and treatment-related morbidity. Evidence from multiple RCTs has found that PDT improves the net health outcome as measured by complete clinical clearance of lesions in individuals with nonhyperkeratotic AKs on the face or scalp compared

with placebo or other active interventions. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have nonhyperkeratotic AKs on the upper extremities who receive PDT, the evidence includes a systematic review and RCTs. Relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. A systematic review of interventions for nonface and non scalp AKs found PDT to be superior to placebo for complete clearance, but found a significant increase in complete clearance with cryotherapy versus PDT. In 2 placebo-controlled RCTs, significantly more individuals had a complete clearance of AKs with 5-aminolevulinic acid (ALA)/PDT with blue light compared to placebo at 12 weeks, and a third found a significantly greater reduction in mean lesion count at 4 weeks. Two small RCTs compared ALA/PDT using red light to imiquimod or 5-fluorouracil and found similar efficacy between the active treatment groups after 6 months of follow-up. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have low-risk basal cell carcinoma who receive PDT, the evidence includes RCTs and systematic reviews of RCTs. Relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. Systematic reviews of RCTs have found that PDT may not be as effective as surgery for low-risk superficial and nodular basal cell carcinoma. In the small number of trials available, PDT was more effective than a placebo. The available evidence from RCTs has suggested that PDT has better cosmetic outcomes than surgery for low-risk basal cell carcinoma. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have squamous cell carcinoma in situ who receive PDT, the evidence includes meta-analyses and RCTs. The relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. Meta-analysis and RCTs have found that PDT has similar or greater efficacy compared with cryotherapy and 5-fluorouracil. Additionally, adverse events and cosmetic outcomes appear to be better after PDT. Few RCTs have compared PDT with surgery or radiotherapy; as a result, conclusions cannot be drawn about PDT compared with these other standard treatments. Current guidance from the National Comprehensive Cancer Network notes that topical modalities, including PDT, may have lower cure rates than with surgical treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have nonmetastatic invasive squamous cell carcinoma who receive PDT, the evidence includes observational studies and a systematic review of observational studies. The relevant outcomes are overall survival, symptoms, change in disease status, QOL, and treatment-related morbidity. Conclusions cannot be drawn from small, uncontrolled studies. RCTs are needed to determine the safety and efficacy of PDT for this condition. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have acne who receive PDT, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. The available RCTs have not consistently found significantly better outcomes with PDT compared with other interventions, and meta-analyses did not find significantly better results with PDT versus placebo. Several trials have found that PDT is associated with high rates of adverse events leading to the cessation of treatment. Trials tended to have relatively small sample sizes and used a variety of comparison interventions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have noncancerous dermatologic skin conditions (eg, hidradenitis suppurativa, mycoses, port-wine stain) who receive PDT, the evidence includes case series, systematic reviews of uncontrolled series, and an RCT for port-wine stain. Relevant outcomes are symptoms, change in disease status, QOL, and treatment-related morbidity. RCTs are needed to determine the safety and efficacy of PDT for these conditions. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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American Academy of Dermatology
The American Academy of Dermatology has guidelines addressing use of PDT in actinic keratosis (AK), basal cell carcinoma, and acne:

- Actinic keratosis (2021): PDT is included in the following recommendations for individuals with AK:
  - 5-aminolevulinic acid (ALA)-red light PDT is conditionally recommended (low quality of evidence)
  - ALA-daylight PDT is conditionally recommended as less painful than but equally effective as ALA-red light PDT (moderate quality of evidence)
  - ALA-blue light PDT is conditionally recommended (moderate quality of evidence)
  - ALA-red light PDT is conditionally recommended over cryosurgery alone (low quality of evidence)
- Basal cell carcinoma (2018): Use of topical therapies, including PDT, is most appropriate for low-risk basal cell carcinoma when surgery is impractical or declined by the patient. Discussions of the relative effectiveness of topical therapies should be discussed with the patient. The guideline further notes that "Cure rates after surgical excision are 10% to 20% higher than those for topical therapies, including PDT, with excision associated with recurrence rates of less than 5%. Surgical excision may also be less painful and better tolerated."
- Acne (2016, update expected in 2023): More studies are needed on the use of PDT or other laser/light devices. PDT has the most evidence among laser/light devices for treating acne, but "additional studies are needed to determine the optimal photosensitizer, incubation time, and light source."

National Comprehensive Cancer Network
For treatment of precancers (diffuse actinic keratoses, field cancerization, and cutaneous squamous cell carcinoma prophylaxis), the National Comprehensive Cancer Network (NCCN) (squamous cell skin cancer, v. 2.2022) made the following recommendations: "Accepted treatment modalities include cryotherapy, topical 5-fluorouracil (5-FU) with or without calcipotriol (calcipotriene), topical imiquimod, topical tirbanibulin, photodynamic therapy (e.g., aminolevulinic acid, porfimer sodium), and curettage and electrodesiccation. For hyperkeratotic actinic keratoses, pretreatment with topical tazarotene, curettage, or topical keratolytics (topical urea, lactic acid, and salicylic acid) prior to above therapies may be considered."

For basal cell skin cancer, the NCCN (v. 2.2022) made the following recommendations: "In individuals with superficial basal cell skin cancer, therapies such as topical imiquimod, topical 5-fluorouracil, photodynamic therapy, or cryotherapy may be considered, even though the cure rates are approximately 10% lower than with surgical treatment modalities."

For squamous cell skin cancers, the NCCN (v. 2.2022) made the following recommendations: "In individuals with SCC [squamous cell carcinoma] in situ (Bowen's disease) alternative, therapies such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy (eg, ALA, porfimer sodium), or vigorous cryotherapy may be considered, even though the cure rates may be lower than with surgical treatment modalities."

United States and Canadian Hidradenitis Suppurativa Foundations
A joint guideline from the United States and Canadian Hidradenitis Suppurativa Foundations (2019) provides guidance on diagnosis and complementary and procedural management of hidradenitis suppurativa. The guideline recommends PDT at a level C (based on consensus, opinion, case studies, or disease-oriented evidence). The authors state that PDT has a limited role in managing hidradenitis suppurativa, mainly due to a lack of large, well-controlled studies.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
The Centers for Medicare & Medicaid Services' 2001 coverage policy on the treatment of AKs noted:

"Various options exist on treating AKs. Clinicians should select an appropriate treatment based on the patient's history, the lesion's characteristics, and the patient's preference for specific treatment…. Less commonly performed treatments for AKs include dermabrasion, excision, chemical peels, laser therapy, and photodynamic therapy...

Medicare covers the destruction of AKs without restrictions based on lesion or patient characteristics."

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05522036	Clinical Evaluation of a Short Illumination Duration (35 Minutes) When Performing Photodynamic Therapy of Actinic Keratosis Using the Dermaris®‡	25	Jun 2023
NCT05359419	Safety and Efficacy of Photodynamic Therapy with Aminolevulinic Acid 10% Topical Gel Activated by Red Light Versus Aminolevulinic Acid 20% Topical Solution Activated by Blue Light for the Treatment of Actinic Keratosis on the Upper Extremities: A Blinded Randomized Study	20	Dec 2023
NCT05245045	Efficacy and Safety of STBF Photodynamic Therapy for Moderate and Severe Acne Vulgaris	20	Feb 2023
NCT03909646	Surgical Excision Versus Photodynamic Therapy and Topical 5-fluorouracil in Treatment of Bowen's Disease: a Multicenter Randomized Controlled Trial	250	Dec 2025
NCT03642535	Aminolevulinic Acid-photodynamic Therapy for Facial Actinic Keratosis Treatment and Prevention: A Long-term (3 Years) Follow-up of Prospective, Randomized, Multicenter-clinical Trial	300	Jun 2025
NCT04167982	Efficacy and Safety of Painless 5-aminolevulinic Acid Photodynamic Therapy for the Treatment of	234	Nov 2022

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Moderate and Severe Acne Vulgaris-- A Multi-center, Randomized Controlled Clinical Trial		
NCT02367547[a]	Superficial Basal Cell Cancer's Photodynamic Therapy: Comparing Three Photosensitises: Hexylaminolevulinate and Aminolevulinic Acid Nano Emulsion Versus Methylaminolevulinate	117	Dec 2025
NCT03573401[a]	A Randomized, Double-Blind, Vehicle-controlled Multicenter Phase III Study to Evaluate the Safety and Efficacy of BF-200 ALA (Ameluz®)‡ and BF-RhodoLED®‡ in the Treatment of Superficial Basal Cell Carcinoma (sBCC) With Photodynamic Therapy (PDT)	186	Feb 2027

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

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05/16/2002	Medical Policy Committee review
06/05/2002	Managed Care Advisory Council approval
05/04/2004	Medical Director review
05/18/2004	Medical Policy Committee review. Format revision. No substance change to policy.
06/28/2004	Managed Care Advisory Council approval
06/07/2005	Medical Director review
06/21/2005	Medical Policy Committee review. Clinical criteria revision. Added coverage eligibility and investigational statement for Metvixia. Added acne, mycoses, and hidradenitis suppurativa as investigational indications for aminolevulinic acid.
07/15/2005	Managed Care Advisory Council approval
06/05/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format revisions, FDA/Governmental, No change in policy statement.
11/07/2007	Medical Director review
11/15/2007	Medical Policy Committee approval. Title changed and policy replaced.
12/03/2008	Medical Director review

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12/17/2008	Medical Policy Committee approval. No change to coverage eligibility.
12/04/2009	Medical Policy Committee approval
12/16/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility
11/04/2010	Medical Policy Committee approval
11/16/2010	Medical Policy Implementation Committee approval. Removed the restriction of face and scalp from the criteria for treatment of non-hyperkeratotic actinic keratoses.
12/08/2011	Medical Policy Committee review
12/21/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/23/2013	Updated coverage eligibility statement when patient selection criteria not met
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. No change to coverage.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. “for other dermatologic applications, including, but not limited to the following” was added to the investigational statement.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Changes to language in policy statements: Superficial or nodular changed to Low-risk and non-superficial changed to high-risk.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2018	Coding update
12/06/2018	Medical Policy Committee review

12/19/2018	Medical Policy Implementation Committee approval. Removed the word non hyperkeratotic from coverage statement. Added policy guidelines.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Deleted the specification of face and scalp from eligible for coverage requirement in the statement for actinic keratosis.
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. No change to coverage.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. No change to coverage.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. No change to coverage.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. No change to coverage.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 05/2024

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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not

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contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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	96567, 96573, 96574
HCPCS	J7308, J7309, J7345
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.

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

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

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

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

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

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