Oncologic Applications of Photodynamic Therapy, Including Barrett's Esophagus

Policy # 00234
Original Effective Date: 03/18/2009
Current Effective Date: 11/09/2020

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: Photodynamic Therapy for Subfoveal Choroidal Neovascularization, Dermatologic Applications of Photodynamic Therapy and Endoscopic Radiofrequency Ablation or Cryoablation for Barrett's Esophagus are addressed separately in medical policies 00097, 00098 and 00261, respectively.

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 one or more courses of photodynamic therapy (PDT) for oncologic applications to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for photodynamic therapy (PDT) for oncologic applications will be considered when any of the following criteria are met:

- Palliative treatment of obstructing esophageal cancer; or
- Palliative treatment of obstructing endobronchial lesions; or
- Treatment of early-stage non-small cell lung cancer in patients who are ineligible for surgery and radiation therapy; or
- Treatment of high-grade dysplasia in Barrett's esophagus; or
- Palliative treatment of unresectable cholangiocarcinoma when used with stenting

When Services Are Considered Investigational

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

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

Based on review of available data, the Company considers other oncologic applications of photodynamic therapy (PDT) including, but not limited to, other malignancies and Barrett's esophagus without associated high-grade dysplasia to be **investigational.***

Background/Overview

Photodynamic Therapy

PDT has been investigated for use in a wide variety of tumors, including esophageal, lung, cholangiocarcinoma, prostate, bladder, breast, brain (administered intraoperatively), skin, and head and neck cancers. Barrett esophagus also has been treated with PDT.

Several photosensitizing agents have been used in PDT: porfimer sodium (Photofrin), administered intravenously 48 hours before light exposure, and 5-aminolevulinic acid, administered orally 4 to 6 hours before the procedure. Aminolevulinic acid is metabolized to protoporphyrin IX, which is preferentially taken up by the mucosa. Clearance of porfimer occurs in a variety of normal tissues over 40 to 72 hours, but tumor cells retain porfimer for a longer period. Laser treatment of Barrett esophagus may be enhanced by the use of balloons containing a cylindrical diffusing fiber. The balloon compresses the mucosal folds of the esophagus, thus increasing the likelihood that the entire Barrett mucosa is exposed to light. All patients who receive porfimer become photosensitive and must avoid exposure of skin and eyes to direct sunlight or bright indoor light for 30 days.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Labeled indications for porfimer sodium (Photofrin®; Pinnacle Biologics)‡, as approved by the U.S. FDA through a new drug application in 2011, are as follows. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020451s020lbl.pdf

Esophageal Cancer

- Palliation of patients with completely obstructing esophageal cancer, or of patients with partially obstructing esophageal cancer who, in the opinion of their physician, cannot be satisfactorily treated with neodymium-doped yttrium aluminum garnet laser therapy.

Endobronchial Cancer

- Reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small-cell lung cancer.
- Treatment of microinvasive endobronchial non-small-cell lung cancer in patients for whom surgery and radiotherapy are not indicated.

High-Grade Dysplasia in Barrett Esophagus

- Treatment of high-grade dysplasia in Barrett esophagus patients who do not undergo esophagectomy.

As of June 2018, oral 5-aminolevulinic acid has not received FDA approval as a photosensitizing agent for PDT. Topical 5-aminolevulinic acid, used for the treatment of actinic keratoses, is addressed separately.

This evidence review addresses only the nondermatologic oncology applications of PDT and does not address its use in dermatologic applications, such as actinic keratosis and superficial basal cell cancer, or age-related macular degeneration. In addition, PDT should not be confused with extracorporeal photopheresis, which involves withdrawing blood from the patient, irradiating it with ultraviolet light, and then returning the blood to the patient. Extracorporeal photopheresis is addressed separately.

Rationale/Source

Description

Photodynamic therapy (PDT; also called phototherapy, photoradiotherapy, photosensitizing therapy, or photochemotherapy) is an ablative treatment that uses a photosensitizing agent to expose tumor cells to a light source of a specific wavelength for the purpose of damaging the cells. After administration of the photosensitizing agent, the target tissue is exposed to light using a variety of laser techniques. For example, a laser fiber may be placed through the channel of the endoscope, or a specialized modified diffuser may be placed via fluoroscopic guidance. Treatment for tumor cells occurs through selective retention of the photosensitizing agent and the selective delivery of light.

Summary of Evidence
For individuals who have obstructing esophageal cancer who receive PDT as palliation, the evidence includes systematic reviews, randomized controlled trials (RCTs), and uncontrolled single-arm studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. A meta-analysis comparing PDT with neodymium-doped yttrium aluminum garnet laser suggested that improvements in dysphagia are similar, although estimates are imprecise. Compared with the neodymium-doped yttrium aluminum garnet laser, PDT is associated with a lower risk of perforation and a higher risk of adverse reactions to the light (e.g. photosensitivity). PDT plus argon plasma coagulation appears to prolong the time to recurrence of dysphagia as opposed to argon plasma coagulation alone. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have obstructing endobronchial lesions who receive PDT as palliation, the evidence includes RCTs and uncontrolled single-arm studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. Evidence from RCTs comparing PDT with neodymium-doped yttrium aluminum garnet laser has generally supported reductions in symptoms using PDT similar to those using a laser. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy who receive PDT, the evidence includes uncontrolled single-arm studies. Relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. There are few patients with early-stage non-small-cell lung cancer who are not candidates for surgery or radiotherapy. While several treatment methods (eg, laser, electrocautery, cryotherapy, brachytherapy) are available for this population, studies comparing the treatment methods are not available. Case series of PDT include between 21 and 95 patients and have reported complete response rates ranging from 72% to 100%. Given the small size of this potential population and the ineligibility for standard surgical treatment or radiotherapy, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with Barrett esophagus with high-grade dysplasia who receive PDT, the evidence includes 2 systematic reviews and 2 RCTs. Relevant outcomes are OS, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. One RCT compared PDT

plus a proton pump inhibitor with a proton pump inhibitor alone and demonstrated higher response rates and lower risk of progression with cancer persisting during 5 years of follow-up for patients in the PDT plus proton inhibitor group. The results of the RCT also revealed that patients treated with PDT had significantly more complications, including a high rate of strictures. Another RCT compared PDT performed with different photosensitizers; results revealed that neither were valuable long-term treatments for dysplastic Barrett esophagus. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have unresectable cholangiocarcinoma who receive PDT plus stenting as palliation, the evidence includes systematic reviews, RCTs, and observational studies. Relevant outcomes are change in disease status, symptoms, quality of life, and treatment-related morbidity. Two small RCTs and several observational studies have found that PDT plus stenting is associated with the greater elimination of bile duct stenosis and improved survival benefit compared with stenting alone. One RCT comparing stenting plus chemotherapy and PDT with stenting plus chemotherapy without PDT reported longer progression-free survival, but not OS, with similar adverse event rates. Case series have suggested an improvement in the quality of life with PDT. The main complication of PDT in cholangiocarcinoma is cholangitis. Given the small size of this potential population, it is unlikely that stronger evidence will become available. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have other malignancies (eg, gynecologic, bladder, head and neck, brain, soft tissue) who receive PDT, the evidence includes controlled observational studies and uncontrolled single-arm studies. Relevant outcomes are OS, disease-specific survival, change in disease status, quality of life, and treatment-related morbidity. The published literature on PDT for these malignancies is generally comprised of small case series without comparator groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

American College of Chest Physicians

In 2013, the American College of Chest Physicians updated its evidence-based guidelines on the diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of the central airways. The College recommended photodynamic therapy (PDT) and other endobronchial treatments (brachytherapy, cryotherapy, electrocautery) "for patients with superficial limited mucosal lung cancer in the central airway who are not candidates for surgical resection" (grade 1C: strong recommendation based on low-quality evidence). The guidelines summarized the evidence for PDT in early lung cancer as follows:

- "PDT appears to be an effective therapeutic modality for small early-stage centrally located lung cancers, the majority of which are SqCCs [squamous cell carcinomas]. CR [complete response] rates have been achieved in 32% to 100% of cancers, with the longitudinal length of the cancer being an important predictor of response. However, some patients experience local recurrences, and long-term outcomes remain suboptimal. NPe6 [talaporfin sodium], a newer-generation photosensitizer, appears to be as effective but better tolerated than older agents. However, these data have only been reported by 1 group and need to be validated in larger numbers of patients."

American Gastroenterological Association
In 2011, the American Gastroenterological Association's position statement on Barrett esophagus management recommended PDT as an option for treatment of confirmed high-grade dysplasia (HGD) with Barrett esophagus.

American College of Gastroenterology
In 2015, the American College of Gastroenterology guidelines on diagnosis and management of Barrett esophagus stated that there is level I evidence for prevention of cancer for PDT and radiofrequency ablation in Barrett esophagus with HGD. The guidelines also stated: "Given the costs and side-effect profile of photodynamic therapy, as well as the large body of data supporting the safety and efficacy of radiofrequency ablation, this modality appears to be the preferred therapy for most patients."

National Comprehensive Cancer Network
Esophageal Cancer and Barrett Esophagus
The NCCN guidelines (v.7.2020) for esophageal cancer state that radiofrequency ablation has become the preferred treatment while PDT is an alternative strategy for patients who have Barrett esophagus with HGD. The guidelines also state that PDT can effectively treat esophageal obstruction

but "is less commonly performed due to photosensitivity and costs" compared with radiotherapy and brachytherapy.

Cholangiocarcinoma
The NCCN (v.4.2020) guidelines on hepatobiliary cancers describe PDT as a relatively new therapy for local treatment of unresectable cholangiocarcinoma, stating that the combination of PDT and biliary stenting "was reported to be associated with prolonged overall survival in patients with unresectable cholangiocarcinoma based on 2 small randomized clinical trials [Ortner et al (2003) and Zoepf et al (2005)]."

Non-Small-Cell Lung Cancer
The NCCN guidelines (v.6.2020) on non-small-cell lung cancer state that PDT is a treatment option for patients with locoregional recurrence of non-small-cell lung cancer with an endobronchial obstruction or severe hemoptysis.

National Institute for Health and Care Excellence
The NICE has published guidance on a number of applications of PDT.

- Guidance for palliative treatment of advanced esophageal cancer, treatment of localized inoperable endobronchial cancer, and treatment of advanced bronchial carcinoma has indicated that current evidence on safety and efficacy is sufficient to support the use of PDT for these indications.
- NICE guidance has indicated that PDT should not be used for the following 3 indications due to poor quality evidence: interstitial photodynamic therapy for malignant parotid tumors, early-stage esophageal cancer, and bile duct cancer.
- NICE guidance has indicated that PDT may be considered for Barrett esophagus with flat HGD, taking into account the evidence of their long-term efficacy, cost, and complication rates. The guidance notes that current evidence on the use of PDT for Barrett esophagus with either low-grade dysplasia or no dysplasia is inadequate so that the balance of risk and benefit is unclear.
- NICE guidance on PDT for brain tumors has indicated that current evidence is limited in quality and quantity, and the procedure should only be used in the context of randomized controlled trials with well-defined inclusion criteria and treatment protocols, and collection of both survival and quality of life outcomes.

Society of Thoracic Surgeons
The Society of Thoracic Surgeons (2009) published practice guidelines on the management of Barrett esophagus with HGD. The guidelines stated that, based on grade B evidence, "PDT should be considered for eradication of HGD in patients at high risk for undergoing esophagectomy and for those refusing esophagectomy" and that "it is reasonable to use PDT to ablate residual intestinal metaplasia after endoscopic mucosal resection (EMR) of a small intramucosal carcinoma in high-risk patients."

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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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			
NCT02153229	A Randomized Phase 2 Trial of Radical Pleurectomy and Post-Operative Chemotherapy With or Without Intraoperative Porfimer Sodium - Mediated Photodynamic Therapy for Patients With Epitheliod Malignant Pleural Mesothelioma	102	April 2020 (suspended due to COVID-19)
NCT03090412	A Randomized Multicenter Phase II Study Using (2-1[Heyloxyethyl]-2-Devinylpyropheophorbide-a) (HPPH) With PDT Versus Standard of Care	114	Nov 2021

	Surgery for Patients With T1/T2 N0 Squamous Cell Carcinoma of the Oral Cavity		
Unpublished			
NCT00587600	Biomarkers in Phototherapy of Barrett's Esophagus	208	Sep 2017
Unknown			
NCT01755013	Open-label Observational Study of Plastic Cylindrical Fiber Optic Diffuser (Pioneer Optics) in Photodynamic Therapy for the Management of Cholangiocarcinoma	55	Last update: February 2017; current status unknown
NCT02628665	Two-Arm Phase III Trial Comparing Different Time of Endoscopic Photodynamic Therapy on Esophageal and/or Gastric Cardiac Cancer	40	Last update: December 2015; current status unknown

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

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Policy History

Original Effective Date: 03/18/2009
Current Effective Date: 11/09/2020

03/04/2009	Medical Director review
03/18/2009	Medical Policy Committee approval. New policy.
03/05/2010	Medical Policy Committee approval
03/19/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/03/2011	Medical Policy Committee review
03/16/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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
05/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Updated rationale and references.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. No change to coverage.
10/01/2016	Coding update
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. No change to coverage.
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. Policy statements changed to include treatment for unresectable cholangiocarcinoma as eligible for coverage.
01/01/2018	Coding update
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. No change to coverage.
10/03/2019	Medical Policy Committee review
10/09/2019	Medical Policy Implementation Committee approval. No change to coverage.
10/01/2020	Medical Policy Committee review
10/07/2020	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 10/2021

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 2019 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 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	31641, 43229, 96570, 96571
HCPCS	J7345, J9600
ICD-10 Diagnosis	C15.3-C15.9, C22.1, C34.00-C34.02, C34.10-C34.12, C34.2, C34.30-C34.32, C34.80-C34.82, C34.90-C34.92, C49.A0-C49.A2, C78.00-C78.02, C78.7-C78.89, D00.1-D00.2, D02.20-D02.22

*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.

‡ 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.

Oncologic Applications of Photodynamic Therapy, Including Barrett's Esophagus

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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.