APPENDIX to Photodynamic Therapy for Cancer Policy

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

In photodynamic therapy (PDT) the photosensitizing agent, (Photofrin®), is injected and absorbed by all cells, but stays in cancer cells longer than it does in normal cells. Approximately 24 to 72 hours after injection, when most of the agent has left normal cells but remains in cancer cells, the tumor is exposed to light. The photosensitizer in the tumor absorbs the light and produces an active form of oxygen that destroys nearby cancer cells.

In addition to directly killing cancer cells, PDT appears to shrink or destroy tumors in two other ways. The photosensitizer can damage blood vessels in the tumor, thereby preventing the cancer from receiving necessary nutrients. In addition, PDT may activate the immune system to attack the tumor cells.

The light used for PDT can come from a laser or other sources of light. Laser light can be directed through fiber optic cables (thin fibers that transmit light) to deliver light to areas inside the body. A fiber optic cable can be inserted through an endoscope into the lungs or esophagus to treat cancer in these organs.

Photodynamic therapy is usually performed as an outpatient procedure and may be repeated and may be used with other therapies, such as surgery, radiation, or chemotherapy (National Cancer Institute, 2004).

Photodynamic therapy with Photofrin® (QLT Photo Therapeutics, Inc., Seattle, WA) was approved by the United States Food and Drug Administration (FDA) for the following indications:

- 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 Nd:YAG laser therapy
- Reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small cell lung cancer (NSCLC)
- Treatment of microinvasive endobronchial NSCLC in patients for whom surgery and radiotherapy are not indicated
- Treatment of high-grade dysplasia in Barrett's esophagus

An oral photosensitizing agent, 5-aminolevulinic acid (5-ALA), has not yet received FDA approval for any indication. Topical 5-ALA is used for treatment of actinic keratoses which is addressed in a separate policy.

Obstructing Esophageal Tumors

When used for palliative treatment, relevant outcomes include short-term resolution of symptoms, such as dysphagia or improvement in swallowing. Long-term outcomes, such as disease-free survival, may not be relevant in the palliative setting. The product insert for porfimer sodium (Photofrin®) describes a multicenter, single-arm study of the use of PDT in 17 patients with obstructing esophageal cancer (Photofrin®, 2008). Patients received one to three monthly treatments of PDT. Of the 17 treated patients, 11 (65%) received clinically important benefit from PDT, defined as complete tumor response, normal swallowing, or improvement in dysphagia. Endoscopic debridement of the esophagus may be required after the PDT. At that time, the residual tumor can also be retreated.

Obstructing Endobronchial Tumors

Similar to obstructing esophageal tumors, short-term outcomes are also relevant for PDT as a treatment of endobronchial tumors. Laser ablation is commonly used to treat endobronchial lesions, and, thus, the relative efficacy of PDT and laser ablation is also relevant. The product insert cites two studies totaling 211 patients with obstructing endobronchial tumors who were randomized to receive PDT or Nd:YAG laser therapy (Photofrin®, 2008). The response rates for the two treatments were similar at one week (59% PDT, 58% laser therapy) with a slight increase in response rates for PDT at six weeks (60% PDT, 41% laser therapy). Clinical improvement, as evidenced by improvements in dyspnea, cough, and hemoptysis, were similar in the two groups at one week (25% to 29%). However, at one month or later, 40% of patients treated with PDT reported clinical improvement compared to 27% treated with laser therapy.

In another small, published randomized study comparing PDT and Nd:YAG laser therapy in patients with airway obstruction, Diaz-Jimenez and colleagues (1999) reported the two techniques had similar effectiveness over a 24-month period. The authors noted a better

immediate response rate associated with laser therapy, and suggested that laser therapy may be particularly appropriate for those requiring rapid relief of symptoms. Results of a larger case series of 100 patients with unresectable lesions also report that PDT is associated with successful palliation (Moghissi et al., 1999).

Similar to treatment of obstructing esophageal lesions, repeat endoscopy may be required for tumor debridement, at which time repeat PDT may be performed to treat residual tumor.

Early Stage Lung Cancer

It is anticipated that only a minimal number of patients with non-obstructing lung cancer would be appropriate candidates for PDT. Of the 178,000 new cases of lung cancer annually, only 15% are detected with early stage lung cancer. Of these, approximately 60% are treated with surgery and another 25% are treated with radiation therapy. Candidates for PDT are limited to those patients who cannot tolerate surgery or radiation therapy, most commonly due to underlying emphysema, other respiratory disease, or prior radiation therapy. In this primary treatment setting, long-term outcomes such as response rates and disease-free survival are important. The product insert for porfimer sodium (Photofrin®, 2008) also refers to three case series totaling 62 patients with microinvasive lung cancer. The complete tumor response rate, biopsy-proved, at least three months after treatment was 50%, median time to tumor recurrence was more than 2.7 years, median survival was 2.9 years, and disease-specific survival was 4.1 years. The labeled indication suggests that PDT for early stage lung cancer should be limited to those who are not candidates for either surgery or radiation therapy.

The NCCN (2010) guideline on NSCLC states that PDT is a treatment option in patients in whom recurrence of NSCLC is suspected only on the basis of positive sputum cytology and, upon further evaluation, detection of tumor in situ. Photodynamic therapy is also an alternative to conventional techniques for palliative debridement of endobronchial obstructions in NSCLC patients and a treatment option for severe hemoptysis.

Barrett's Esophagus with High-Grade Dysplasia

Five-year follow-up of subjects in the randomized controlled trial (RCT) of PDT with Photofrin® in Barrett's high-grade dysplasia conducted for the FDA approval process was reported by Overholt et al., (2007). Patients with Barrett's esophagus and high-grade dysplasia were randomized to PDT plus omeprazole or omeprazole only. At five years, PDT plus omeprazole was significantly more effective than omeprazole alone in eliminating high-grade dysplasia (77% versus 39%, $p < 0.0001$). Patients in the PDT group were about half as likely to progress to cancer as those in the omeprazole alone group (15% versus 29%, $p = 0.027$), with a significantly longer time to progression to cancer favoring PDT. The small number of subjects available for long-term follow-up is a limitation of this study.

Pech and colleagues (2008), in a study from Germany, reported long-term (i.e., five-year) outcomes of endoscopic treatment of high-grade intraepithelial neoplasia and mucosal adenocarcinoma in patients with Barrett's esophagus. Patients were excluded if staging examinations did not confirm the suspected diagnosis of Barrett's carcinoma or high-grade intraepithelial neoplasia or if they showed more advanced tumor stage (greater than T1), lymph-node involvement or metastasis. Patients with localized neoplasia were offered endoscopic

resection. Patients with lesions that were not clearly localized, those with superficial subtle multifocal neoplasia, and those with no neoplasia found in esophageal biopsies were treated with 5-aminolevulinic acid (ALA) PDT. Fifty-five patients received only PDT, and 13 had endoscopic resection and PDT. A complete response was achieved in 98.5% of the patients, and complete response was achieved in 17% during median follow-up of 37 months.

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

Badreddine and colleagues (2010) performed a retrospective analysis of a cohort of Barrett's esophagus patients seen at a specialized Barrett's esophagus clinic in the United States to identify risk factors for recurrence of dysplasia after ablative treatment including PDT. Three-hundred sixty-three patients underwent PDT with or without endoscopic mucosal resection. Indications for ablation were low-grade dysplasia in 53 patients, high-grade dysplasia in 152 patients, and intramucosal cancer in 56 patients. Median follow-up was 36 months. Recurrence occurred in 45 patients, and median time to recurrence was 17 months. Significant predictors of recurrence on the multivariate model were older age, presence of residual non-dysplastic Barrett's, and a history of smoking.

The National Comprehensive Cancer Network (NCCN) (2010) guideline on esophageal cancer lists PDT as an ablative method for patients with Barrett's esophagus with high-grade dysplasia, and for palliation of dysphagia in patients with esophageal cancer.

Cholangiocarcinoma

There have been ongoing research interests in PDT as ad adjunct to endoscopic management of cholangiocarcinoma, primarily as a palliative strategy. In an editorial, Baron (2008) reviewed the pros and cons of PDT for palliation of cholangiocarcinoma and the questions remaining concerning its role, given the available options of chemoradiation, brachytherapy, and plastic and metal stents. On the negative side, he noted PDT is not available at all centers and requires expertise in endoscopy and PDT. In addition, the procedure is time consuming and post-treatment photosensitivity lasts for four to six weeks and may limit quality of life. In favor of PDT, it is reasonably well tolerated, seems to be effective, and can be repeated without a ceiling dosage effect. It is the only treatment to date where data suggests improved survival over plastic stent placement alone for advanced cholangiocarcinoma. Baron concluded that the answer to whether PDT should be used for palliation of cholangiocarcinoma is yes, but further comparative trials are needed to determine the optimal regimen of palliation of obstructive jaundice in these patients.

In a retrospective study by Kahaleh et al., (2008), 19 patients were treated with endoscopic retrograde cholangiopancreatography (ERCP) with PDT and stents, and 29 patients treated with ERCP and stents alone at a U.S. center. Most of the patients had Bismuth III and IV lesions, however some had Bismuth I and II lesions. Some patients in each group received chemoradiation therapy. Mortality in the PDT/stent group at three, six, and 12 months was 0%,

16%, and 56% respectively, and 28%, 52%, and 82% in the stent-alone group. The difference was statistically significant at three and six months. The authors noted that it remains to be proved whether this effect is attributable to PDT or the number of ERCP sessions and a randomized multicenter study is required to confirm this data.

Gao and colleagues (2009) performed a systematic review of the literature on PDT for unresectable cholangiocarcinoma. The authors reviewed two RCTs, two comparative trials with concurrent controls, one comparative trial with historical controls, and 15 case series. The two randomized trials were rated of moderate quality and the other available studies were of low to moderate quality. After PDT, it was reported bilirubin serum levels declined, quality of life improved and survival time increased in most of the patients. At the same time, there were few complications. The authors concluded, based on current available evidence, PDT was safe and effective for patients with inoperable cholangiocarcinoma.

The NCCN (2010) lists ablation (PDT is an ablative technique) as a treatment option in patients with microscopic margins (R1) or residual local disease (R2) post-resection of intrahepatic cholangiocarcinoma. The NCCN described PDT as a relatively new therapy for the local treatment of unresectable cholangiocarcinoma indicating that the combination of PDT and biliary stenting has been shown to significantly improve the overall survival of patients with unresectable cholangiocarcinoma based on two small RCTs.

Other

There is research interest in a variety of other applications of PDT, including cervical neoplasia, bladder cancer, and soft tissue sarcoma, using a variety of sensitizers. However, the published data consisted of case series and phase I studies (Yamaguchi et al., 2005; Kusuzaki et al., 2005).

A phase II European trial with 20 patients using imiquimod and PDT for vulval intraepithelial neoplasia reported by Winters et al., (2008) demonstrated an overall response rate of 55% by intention-to-treat analysis. Symptom response at 52 weeks was 65% asymptomatic versus 5% at baseline. The potential benefit of this treatment is its ability to treat multifocal disease. Results from this small trial need to be replicated in additional larger studies. Other reports of phase I and II trials of PDT of prostate cancer are also small, involving fewer than 20 patients.

In a 2008 review, Biel (2007) reported his own experience with 276 patients treated with Photofrin® PDT for early oral and laryngeal cancers over a period of nearly 16 years. Of 115 patients in the author's series with recurrent or primary carcinoma-in-situ, T1N0 and T2N0, there were 10 recurrences (five-year cure rate 100%) at mean follow-up of 91 months. Five-year cure rate for 113 patients with recurrent or primary carcinoma in situ and T1N0 squamous cell carcinomas of the oral cavity was 100% with six recurrences within eight months of initial treatment salvaged with either repeat PDT or surgical resection. Two patients with T1 tongue tumors developed positive regional lymph nodes within three months of PDT, had conventional neck dissection, and had been free of disease for at least five years. In the 48 patients treated for superficial T2N0 and T3N0 squamous cell carcinomas of the oral cavity, there were five recurrences, all salvaged with repeat PDT or surgical resection. Three-year cure rate was 100% (mean follow-up 56 months). Again, these data need to be replicated in larger, multicenter studies that include a comparison group.

Some studies report experience with photosensitizers that have not been approved by the FDA. Wildeman and colleagues (2009) reviewed all of the available literature to determine the efficacy of PDT therapy for patients with recurrent nasopharyngeal carcinoma. Of five studies, one was a series of 135 patients reported complete response in 76 cases and marked response in 47 cases after hematoporphyrin-derivative-mediated PDT. However it was not clear if the patients had recurrent nasopharyngeal carcinoma or PDT was primary treatment. The other four studies had 12 or fewer subjects.

The National Institute for Health and Clinical Excellence guidance on PDT for brain tumors states that current evidence is limited in quality and quantity. The procedure should only be used in context of RCTs with well-defined inclusion criteria and treatment protocols, and collection of both survival and quality of life outcomes (2009).

The National Institute for Health and Clinical Excellence has published guidance on a number of other applications for PDT stating that current evidence on safety and efficacy is sufficient to support the use of PDT for these indications:

- Palliative treatment of advanced esophageal cancer (2007)
- Treatment of localized inoperable endobronchial cancer (2005)
- Treatment of advanced bronchial carcinoma (2004)

The National Institute for Health and Clinical Excellence also states PDT should be used only with special arrangements for clinical governance, consent and audit for the following four indications:

- Interstitial PDT for malignant parotid tumors (2008)
- Early stage esophageal cancer (2006)
- Bile duct cancer (2005)
- High-grade dysplasia in Barrett's esophagus (2004)

In summary, radiofrequency ablation and endoscopic mucosal resection appear to be replacing PDT as the preferred methods of ablation for high-grade dysplasia in Barrett's esophagus. Evidence for efficacy of PDT for palliative treatment of unresectable cholangiocarcinoma is accumulating; however, RCTs are needed to confirm its utility compared to alternative treatments such as chemoradiation.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In

these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	31641	Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy)
	43228	Esophagoscopy, rigid or flexible; with ablation of tumor(s), polyp(s), or other lesion(s), not amenable to removal by hot biopsy forceps, bipolar cautery or snare technique
	96570	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); first 30 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestinal tract)
	96571	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue via activation of photosensitive drug(s); each additional 15 minutes (List separately in addition to code for endoscopy or bronchoscopy procedures of lung and gastrointestin
HCPC	J9600	Injection, porfimer sodium, 75 mg
ICD9 Procedure	None	
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

N/A

Definitions

N/A

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- Photodynamic Therapy for the Treatment of Actinic Keratoses and Other Skin Lesions
- Photodynamic Therapy for Subfoveal Choroidal Neovascularization

Key / Related Searchable Words

N/A

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/1/2010	New policy Combined the following BSC policies: • Photodynamic Therapy (PDT) for Esophageal and Lung Cancers • Photodynamic Therapy (PDT) for High Grade Esophageal Dysplasia	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

Click here to view the policy statement for this policy

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