CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject **Photodynamic Therapy for Cancer**

Effective Date 2/15/2011
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Coverage Policy Number 0023

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INSTRUCTIONS FOR USE

*Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines.*

Coverage Policy

CIGNA covers photodynamic therapy (PDT) with light-activated porfimer sodium (Photofrin®) as medically necessary for the treatment of EITHER of the following specific types of cancer meeting the criteria indicated:

- esophageal cancer for EITHER of the following:
  - completely or partially obstructing esophageal cancer that cannot be treated satisfactorily with neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy
  - Barrett's esophagus carcinoma in situ and high-grade disease in individuals who are not esophagectomy candidates (e.g., obstructive disease with limited pulmonary function and/or cardiovascular disease with poor cardiac function that precludes surgical resection)
- lung cancer for EITHER of the following:
  - early-stage non-small cell lung cancer (NSCLC) in individuals who are not candidates for surgery or radiotherapy (e.g., obstructive disease with limited pulmonary function and/or cardiovascular disease with poor cardiac function that precludes surgical resection)
  - the reduction of obstruction and palliation of symptoms in individuals with advanced-stage, completely or partially obstructing endobronchial NSCLC

CIGNA does not cover PDT with light-activated porfimer sodium (Photofrin) for the treatment of any other cancers because it is considered experimental, investigational or unproven.

General Background

Photodynamic therapy (PDT), also referred to as photoradiation or photosensitizing therapy, is a two-step drug and device procedure that causes selective damage to defined cancerous tissue. The patient is given an intravenous injection of a photosensitizing agent, porfimer sodium (Photofrin®, QLT Photo Therapeutics, Inc., Seattle, WA), which is activated in the cells by a nonthermal laser light inducing a photochemical effect. The drug is absorbed by all body cells but tends to stay in cancerous cells longer. Because the normal cells excrete porfimer faster than cancerous cells, the laser treatment is administered 40–72 hours following the administration of the drug, creating a reactive oxygen species that destroys cancerous tissue. A second effect of PDT involves damage to blood vessels in the tumor, which may result in tumor death by ischemic necrosis from vascular occlusion. Thirdly, PDT may aid in the destruction of cancerous tissue by activating the immune system. The use of PDT, a local treatment with shallow penetration (i.e., one to three centimeters [cm]), is limited to tumors on the lining of organs and cavities and to smaller-sized tumors.

U.S. Food and Drug Administration (FDA)
PDT with photofrin systems are approved by the FDA premarket approval (PMA) process to be used for the treatment of patients with completely- or partially-obstructing esophageal cancer who cannot be treated satisfactorily with Nd:YAG laser therapy and for the ablation of high-grade dysplasia in Barrett's esophagus in patients who do not undergo esophagectomy. PDT is also approved for the treatment of microinvasive endobronchial nonsmall cell lung cancer (NSCLC) in patients who are not candidates for surgery and radiotherapy. The therapy may be used for the reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial NSCLC. Originally approved devices included the Coherent PDL1 and PDL2 Lambda Plus™ Photodynamic Lasers (Coherent, Inc., Palo Alto, CA) and the Diomed 630 PDT Laser (Angiodynamics, UK LTD, Cambridge, UK) (FDA, 2009; FDA, 2003; FDA 2000; FDA, 1998).

Esophageal Cancer and Barrett's Esophagus
The most common types of esophageal cancer are squamous cell and adenocarcinoma. Barrett's esophagus is a precancerous condition in which part of the normal lining of the esophagus is replaced by the type of tissue normally found in the intestine (i.e., intestinal metaplasia) due to chronic gastroesophageal reflux disease (GERD). The columnar mucosa progresses through low- and high-grade dysplasia until adenocarcinoma supervenes.

Primary treatment modalities for esophageal cancer are surgical intervention or chemotherapy with radiation therapy. Effective palliation treatment typically involves combination therapies such as surgery, chemotherapy, radiation therapy, stents, and neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy. PDT is a recognized treatment option for patients with obstructing esophageal cancer who cannot be satisfactorily treated with Nd:YAG. For patients with adenocarcinoma arising in Barrett's esophagus, surgical excision is a standard treatment approach. However, the surgical procedure is controversial. One alternative approach is transhiatal esophagectomy with anastomosis of the stomach to the cervical esophagus (National Cancer Institute [NCI], 2010; Sabel, 2000). Because of the high mortality and morbidity rate of esophagectomy, and the concern for unnecessary resection, PDT is an established treatment alternative for esophageal cancer for patients who are not candidates for esophagectomy (e.g., obstructive disease with limited pulmonary function and/or cardiovascular disease with poor cardiac function that precludes surgical resection).

Literature Review: Evidence in the published peer-reviewed literature in the form of systematic reviews and meta-analyses (Fayter, et al., 2010; Rees, et al., 2010; Li, et al., 2008), randomized controlled trials (Overholt, et al., 2007; Overholt, et al., 2005; Ackroyd, et al., 2000), case series (Yano, et al., 2005; Maunoury, et al., 2005; Overholt, et al., 2003; Ackroyd, et al., 2003) and retrospective reviews (Wolfsen, et al., 2004) support the safety and efficacy of PDT for the treatment of Barrett's esophagus and esophageal cancer.

Professional Societies/Organizations: In their discussion of alternative treatments (e.g., argon beam coagulation, thermal laser ablation, endoscopic mucosal resection, PDT) for the treatment of Barrette's esophagus with HGD, the ©National Comprehensive Cancer Network® (NCCN®) (2010a) stated that PDT is

"superior for achieving ablation of metaplastic and dysplastic epithelium as well as obviating the need for further interventions". They also stated that PDT may be used alone as a palliative treatment to overcome dysphagia in esophageal cancer, or may be used in combination with self-expanding stents for patients with obstructive esophageal adenocarcinoma.

In a guidance document on PDT for the treatment of Barrett's esophagus, National Institute for Clinical Excellence (NICE) (2010) (United Kingdom) stated that the evidence supports PDT for the treatment of high-grade dysplasia (HGD). There are no major safety concerns but there is a risk of esophageal stricture and photosensitivity reactions. The evidence does not support the safety and efficacy of PDT for low-grade dysplasia (LGD) or no dysplasia. A 2007 NICE interventional procedure guidance on palliative PDT of advanced esophageal cancer stated that although the evidence on safety and efficacy is of "poor quality, it appears adequate to support" the use of PDT to relieve symptoms in poor prognosis patients and stated that PDT should only be used in experienced specialty centers for this population. NICE (2006) also stated that PDT "appears efficacious in reducing tumor bulk in carefully selected patients with small early-stage" esophageal cancer but the evidence is of poor quality and involves only short-term outcomes.

The Society of Thoracic Surgeons' (2009) recommendations on the treatment of Barrett's HGD stated that PDT should be considered in patients at high risk for undergoing esophagectomy and for those refusing esophagectomy. STS also stated that "it is reasonable to use photodynamic therapy (PDT) to ablate residual intestinal metaplasia after endoscopic mucosal resection (EMR) of a small intramucosal carcinoma in high-risk patients".

The Cancer Care Ontario (CCO) (Malthaner, et al., Jan 2006) guideline on the use of PDT as palliative treatment for esophageal cancer stated that flexible metal stents offer the best supportive care for palliative therapy in esophageal cancer, but PDT may be an option for patients who are not candidates for the stents if the goal is to relieve dysphagia. They noted that the recommendation is based on expert opinion. In a second guideline (Malthaner, et al., Jun 2006) regarding the use of PDT for ablation of HGD with Barrett's esophagus, the CCO stated that surgery alone should be the treatment of choice in suitable surgical candidates. For patients who have contraindications to surgery, PDT could be considered a treatment option.

Lung Cancer
The NCI classifies lung cancers as small-cell lung cancer (SCLC), comprising 25% of all cases and non-small cell lung cancer (NSCLC), comprising 75% of all cases. Early-stage disease includes both stage 0 and stage 1, or carcinoma in situ, which are superficial lesions. While surgery is the conventional treatment for patients with early-stage NSCLC, a significant number of these patients also have chronic obstructive disease, limited pulmonary function, cardiovascular disease, and/or poor cardiac function that precludes surgical resection. PDT appears particularly applicable to the treatment of early-stage NSCLC, since it preserves lung function, can be repeated as additional tumors appear, and does not preclude ultimate surgical intervention if deemed necessary. The intent of PDT is to limit the extent of resection and convert inoperable lung cancers into operable cancers (Awan and Tarin, 2006).

Literature Review: Although the number of studies is limited, PDT is an established treatment alternative for a subgroup of patients with NSCLC. Systematic reviews (Maziak, et al., 2004) and case series (Furukawa, et al., 2005; Friedberg, et al., 2004) support the safety and efficacy of the use of PDT for the treatment of early-stage NSCLC. A five-year survival rate of up to 72% following PDT has been reported.

Professional Societies/Organizations: The NCI (2011) lists PDT as a standard treatment option for patients with stage 0 NSCLC. They also list PDT as a treatment option for highly selected patients with stage 1 NSCLC patients, indicating that its use is still under investigation.

In their guidance on NSCLC, the NCCN® Clinical Practice Guidelines in Oncology (2010d) stated that PDT "offers a simple and effective alternative to conventional techniques for palliative debridement of endobronchial obstructions". They also stated PDT is a treatment option for severe hemoptysis and for recurrence when a tumor in situ is present.

In November 2005, NICE published an interventional procedure guidance on PDT for the treatment of localized inoperable endobronchial cancer and supported its use for the treatment of NSCLC confined within the bronchial wall with no evidence of lymph node involvement. NICE defined inoperable cancer as those patients unsuitable

for lung resection due to bilateral lung cancer with impaired respiratory function secondary to chronic obstructive pulmonary disease. These patients had previous resection for primary cancer and are high-risk surgical candidates or refused surgery. In an August 2004 interventional procedure guidance regarding the use of PDT as a treatment option for advanced bronchial cancer, NICE stated that the current evidence on the safety and efficacy of PDT for advanced bronchial carcinoma is adequate to support the use of this procedure to treat patients with inoperable NSCLC.

From the available evidence in the literature, the Ontario Lung Cancer Disease Site Group (DSG) (Maziak, et al., 2005) concluded that PDT could be considered a treatment option for patients with medically inoperable early-stage disease that is accessible by bronchoscopy. PDT may be most effective in small (≤ 1 cm) superficial airway lesions. PDT can also contribute to relief of airway obstruction and hemoptysis in locally advanced and symptomatic patients. The Lung Cancer DSG further stated that the relative safety and effectiveness of PDT compared with radiotherapy, an alternative treatment for patients with inoperable early-stage disease, remains undefined.

Head and Neck Cancer
Cancer of the upper aerodigestive tract, referred to as head and neck cancer, includes cancer of the lips, oral cavity, pharynx, larynx, paranasal sinuses, nasal cavity, ear, and salivary glands. Treatment options include surgical excision, and/or chemotherapy and/or radiation therapy. Although PDT has been proposed for the treatment of these cancers, the therapy is problematic because the laser light cannot pass through more than one centimeter of tissue, limiting the size of lesion it can destroy. PDT remains under investigation for the treatment of head and neck cancers including the use of newer photosensitizing agents, such as Temoporfin (Foscan®, Biolitec Pharma Ltd., Scotland) and 5-ALA (Levulan®, DUSA Pharmaceuticals, Inc., Valhalla, NY).

Literature Review: There is insufficient evidence in the published peer-reviewed literature to support PDT for the treatment of head and neck cancer. Studies have primarily been in the form of case series (Rossi, et al., 2004; Rigual et al., 2009) and retrospective reviews (Chen, et al., 2004) with small patient populations and short-term follow-up.

Fayter et al. (2010) conducted a systematic review of randomized and nonrandomized clinical trials investigating PDT for the treatment of various cancerous and precancerous conditions. The review of 88 studies included one pilot randomized controlled trial (n=30) comparing PDT to chemotherapy and three abstracts of nonrandomized studies (n=246) for the treatment of head and neck cancer. Cancer sites included nasopharynx, larynx, laryngeal part of the pharynx and the mouth, respectively. There was insufficient data to assess the effectiveness of PDT alone or compared to other treatment options.

Rigual et al. (2009) conducted a prospective case series (n=26) to evaluate the use of PDT for the treatment of laryngeal and oral cavity premalignant and malignant disease of the head and neck. The study included two cohorts of patients. One group included patients with tumor grade T1 squamous call carcinoma (n=14), and the second group included patients with dysplasia and carcinoma in situ (n=12). Twelve patients had persistent or recurrent disease after previous surgery or radiotherapy, and 14 patients had primary disease. Follow-up ranged from 7–52 months (mean 15 months). Twelve patients in the dysplasia group and 12 in the T1 group experienced complete response. One T1 patient experienced partial response and one experienced no response following PDT. Three patients with oral dysplasia had recurrence within 90 days and one T1 patient developed a second invasive primary cancer. Adverse effects included pain, edema, hoarseness and phototoxicity.

Cholangiocarcinoma
Cholangiocarcinoma (CC) is a rare adenocarcinoma of the bile duct (i.e., 3% of all gastrointestinal tumors). The standard treatment is surgical excision and chemotherapy and/or radiation therapy. There are a limited number of studies with small patient populations that have investigated PDT with the use of various photosensitizers as an adjunctive and palliative therapy. Preliminary results suggested that PDT may be instrumental in extending survival when used in conjunction with biliary stenting as palliative therapy in unresectable patients without metastases. PDT may destroy cancer cells and induce tumor thrombosis to aid in biliary obstruction. However, due to the lack of randomized controlled trials, PDT is not recommended for the treatment of biliary tract cancers (Fayter, et al., 2010; Aljiffry, et al., 2009; Blechacz and Gores, 2008; Joyce and Heiss, 2008; Kahaleh et al., 2008; Saito, et al., 2008; Zoepf, 2008).

Literature Review: Fayter et al. (2010) conducted a systematic review of randomized and nonrandomized clinical trials investigating PDT for the treatment of various cancerous and precancerous conditions. A total of 88 clinical trials met inclusion criteria and included two randomized controlled trials (n=71), two nonrandomized trials (n=239), and one abstract (n=32) on PDT for the treatment of cholangiocarcinoma. The authors concluded that PDT with stenting may improve survival in patients with cholangiocarcinoma compared to stenting alone, but additional data are needed to provide more definitive evidence that is generalisable to a broader cholangiocarcinoma patient population and to define the PDT treatment procedures including the most suitable photosensitizers.

Gao et al. (2009) conducted a systematic review of the published, peer-reviewed literature to determine the safety and efficacy of PDT for the treatment of cholangiocarcinoma. Twenty studies met inclusion criteria (n=1–184) and included patients with various stages of cancer. Different types of photosensitizers (e.g., photofrin, photosan, delta-aminolevulinic acid) were used in the trials. Median survival rates increased for up to one year following PDT. Complications included bacterial cholangitis (27.5%) and skin phototoxicity (10.5%). Limitations of the studies included: small heterogeneous patient populations, various inclusion criteria, short-term follow-up, retrospective study designs, and the use of various photosensitizers and endoprostheses. According to the authors, the general conclusion from the studies was that PDT had a therapeutic effect on patients with nonresectable cholangiocarcinoma. However, PDT is not universally available and whether the results achieved in tertiary centers can be generalized to other clinical settings is unknown. It is also unclear if PDT can enhance the effect of chemotherapy and/or radiation therapy.

Kahaleh et al. (2008) prospectively compared survival in patients (n=48) with unresectable cholangiocarcinoma who underwent endoscopic retrograde cholangiopancreatography (ERCP) with Porfimer sodium PDT and stent replacement (n=19) to those who underwent ERCP and stent replacement alone (n=29). Patients had Bismuth I-IV tumors (type I are below the confluence of the left and right hepatic ducts; type IV are multicentric or involve the confluence and both the right and left hepatic ducts). The PDT group had a median 3.0 ERCP procedures (range 1–8) and a mean 1.6 PDT sessions (range 1–3). The stent group underwent a median 2.0 ERCP procedures (range 1–13). The PDT group experienced significantly longer survival rates compared to the stent-only group ($p<0.004$). The mortality rate at three, six and 12 months was 0%, 16%, 56%, respectively for the PDT group compared to 28%, 52% and 82%, respectively for the stent-only group. Both groups experienced a significant decrease in bilirubin levels, but the difference between the two groups was not significant. Eight PDT patients and two stent patients were alive at last analysis. Ten patients in the stent group developed cholangitis with two deaths, and four developed pancreatitis. Seven PDT patients developed cholangitis. The authors noted that although the PDT group had better outcomes, it is unknown if the effect was due to the PDT or to the number of ERCP session.

Professional Societies/Organizations: In their hepatobiliary practice guidelines NCCN (2010c) stated that PDT is a relatively new therapy for local treatment of cholangiocarcinoma and small studies have reported improvement in patients who were treated with PDT and biliary stenting. NCCN makes no recommendations regarding its use.

NICE's 2005 guidance document on PDT for bile duct cancer stated the current evidence on safety and efficacy is not adequate for the procedure to be used without special consent and audit or research.

Other Malignancies
PDT has been proposed as a treatment option for many other types of cancer. Studies have been primarily in the form of phase I or II trials with heterogeneous patient populations, and used various types of photosensitizers and light sources. There is a lack of evidence in the peer-reviewed, published scientific literature to support the safety and efficacy of PDT in the treatment of other malignancies including, but not limited to: anal squamous neoplasms, bladder, brain, cervical, colon, gastric, hepatobiliary, rectal, pancreatic, parotid, and prostate cancers (Moore, et al., 2009; Blechacz and Gores, 2008; Fleshner, et al., 2008; Hillemanns, et al., 2008; NICE, 2008; Zaak, et al., 2008; Zoepf, 2008).

Literature Review: A systematic review (Fayker, et al., 2010) of PDT for the treatment of cancerous and precancerous conditions (n=88 total studies) included one randomized controlled trial and one nonrandomized trial investigating PDT for the treatment of brain cancer. Both studies were of poor methodology and included less than 30 patients per study. The authors noted that with brain cancer, stem cells may be outside the clinical

target volume and focal treatment would be ineffective if all zones were not included. The role of PDT for the treatment of brain cancer is unknown.

Professional Societies/Organizations: NICE investigated PDT for the treatment of malignant parotid tumors (2008) and brain tumors (2009) and concluded that the evidence on safety and efficacy was inadequate to support its use for the treatment of these cancers.

Summary
The evidence in the published peer-reviewed scientific literature supports photodynamic therapy (PDT) as a safe and effective treatment option for carefully selected individuals with Barrett's esophagus, esophageal cancer, and non-small cell lung cancer. Although PDT has been proposed for the treatment of various other types of cancers (e.g., head and neck, cholangiocarcinoma, prostate), there is insufficient evidence in the form of well-designed large, randomized controlled trials to support the safety and efficacy of PDT for other cancers.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
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 esophagus)
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 esophagus)
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
31641	Bronchoscopy, (rigid or flexible); with destruction of tumor or relief of stenosis by any method other than excision (eg, laser therapy, cryotherapy)

HCPCS Codes	Description
J9600	Porfimer sodium, [Photofrin], 75mg

ICD-9-CM Diagnosis Codes	Description
150.0-150.9	Malignant neoplasm of esophagus
162.2-162.9	Malignant neoplasm of bronchus, and lung
197.0	Secondary malignant neoplasm of lung
230.1	Carcinoma in situ of esophagus
231.2	Carcinoma in situ of bronchus and lung
530.85	Barrett's esophagus

Experimental/Investigational/Unproven/Not Covered when used to report Photodynamic Therapy with light-activated porfimer sodium (Photofrin):

ICD-9-CM Diagnosis Codes	Description

140.0-140.9	Malignant neoplasm of lip
142.0-142.9	Malignant neoplasm of major salivary glands
145.9	Malignant neoplasm of mouth, unspecified
149.0	Malignant neoplasm of pharynx, unspecified
151.0-151.9	Malignant neoplasm of stomach
153.0-153.9	Malignant neoplasm of colon
154.0-154.8	Malignant neoplasm of rectum, rectosigmoid junction, and anus
155.0-155.2	Malignant neoplasm of liver and intrahepatic bile ducts
156.0-156.9	Malignant neoplasm of gallbladder and extrahepatic bile ducts
157.0-157.9	Malignant neoplasm of pancreas
160.0	Malignant neoplasm of nasal cavities
160.1	Malignant neoplasm of auditory tube, middle ear and mastoid air cells
160.9	Malignant neoplasm of accessory sinus, unspecified
161.0-161.9	Malignant neoplasm of larynx
171.0	Malignant neoplasm of head, face and neck
173.2	Other malignant neoplasm of skin of ear and external auditory canal
180.0-180.9	Malignant neoplasm of cervix uteri
185	Malignant neoplasm of prostate
195.0	Malignant neoplasm of head, face and neck
230.0-230.9	Carcinoma in situ of digestive organs
233.1	Carcinoma in situ of cervix uteri
233.4	Carcinoma in situ of prostate
233.7	Carcinoma in situ of bladder
	All other codes

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	02/15/2008	0023	Photodynamic Therapy for Cancer