CIGNA MEDICAL COVERAGE POLICY

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

Subject **Percutaneous Ethanol Injection (PEI) for Liver Cancer**

Effective Date 12/15/2008
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INSTRUCTIONS FOR USE

*Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant'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 participant'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 participant'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 group 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 percutaneous ethanol injection (PEI) as medically necessary for the treatment of unresectable hepatocellular liver cancer.

General Background

Liver cancer, also known as hepatocellular carcinoma (HCC), is the fifth most common cancer in the world. In the United States, liver cancer occurs more frequently in Asians, African-Americans and Hispanics than in other racial and ethnic groups. In 2008, the American Cancer Society (ACS) estimates that 21,370 new cases will be diagnosed, and 18,410 deaths will occur from this disease. Liver cancer incidence has been linked to the prevalence of chronic hepatitis B virus, through the mutation of this viral genome within the cells of the liver. Liver cancer can also develop as a result of the hepatitis C virus, cirrhosis, alcohol abuse, or aflatoxin B1 exposure (National Cancer Institute [NCI], 2008).

In patients with underlying liver disease, a rise in the biological marker (alpha-fetoprotein [AFP]) and/or alkaline phosphatase, or a rapid deterioration of hepatic function, may be the only signs of the presence of a neoplasm.

The biological marker AFP is useful in the diagnosis of liver cancer. It is estimated that 50–70% of patients with liver cancer in the United States have elevated levels of AFP. This biological marker is also a prognostic indicator, as patients who are AFP-negative have a significantly longer median survival time than patients who are AFP-positive. Other prognostic indicators include: performance status, liver function, the presence or absence of cirrhosis, and the severity of any cirrhosis. There are several staging systems that can be used, e.g., the Child-Pugh Classification shown below, but no one staging is superior to the others (Blum, 2005; NCI, 2005).

Child-Pugh Classification

	A	B	C
HCC/mass	Solitary/< 50%	Multifocal/<50%	Multifocal/>50%
AFP (ng/ml)	< 400	≥ 400	≥ 400
Portal vein thrombosis	No	Yes	Yes
Points (presence or absence of cirrhosis)	0	1	2

The United Network for Organ Sharing (UNOS), a nonprofit charitable organization, operates the Organ Procurement and Transplantation Network (OPTN) under a Federal contract. In 2002, OPTN/UNOS implemented a change in the system for prioritizing patients waiting for liver transplants. The new system is based on statistical formulas that predict the probability of death within three months from listing.

The MELD (Model for End Stage Liver Disease) is used for patients age 12 and older. The MELD score uses a mathematical formula based on levels of serum creatinine and bilirubin, together with International normalized ratio (INR). MELD scores can range from 6–40 (MELD scores greater than 40 receive a score of 40). The PELD (Pediatric End Stage Liver Disease) Model is used for pediatric patients under the age of 12. The PELD score formula includes bilirubin level, INR, albumin level, growth failure, and the patient's age when placed on the waiting list. PELD scores can range from negative values to very high numbers. Additional points can be requested by transplant centers for patients with localized hepatocellular carcinoma and hepatoblastoma, based on their increased risk for metastasis while on the waiting list.

The exact scores are calculated according to the following formulas:

MELD score =
$\{[0.957 \times \text{Log}_e(\text{creatinine mg/dL})] + [0.378 \times \text{Log}_e(\text{bilirubin mg/dL})] + [1.120 \times \text{Log}_e(\text{INR})] + 0.643\} \times 10$
This result is then rounded to the nearest whole number.
Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD score calculation.

The maximum serum creatinine considered within the MELD score equation is 4.0 mg/dL. For patients receiving dialysis twice within a week prior to the serum creatinine test, the serum creatinine is valued at 4.0 mg/dL.

PELD Score =
$\{[0.480 \times \text{Log}_e(\text{bilirubin mg/dL})] + [1.857 \times \text{Log}_e(\text{INR})] - [0.687 \times \text{Log}_e(\text{albumin g/dL})] + (0.436$ if patient is less than one year old) + (0.667 if the patient has growth failure of < –2 Standard deviation)$\} \times 10$
The result is then rounded to the nearest whole number.

Laboratory values less than 1.0 are set to 1.0 for the purposes of the PELD score calculation. The age score for a patient listed for liver transplantation before the patient's first birthday continues to include the value assigned for age (< 1 year) until the patient reaches the age of 24 months.

The natural course of the disease and the median survival of patients are dependent on the stage of the disease at the time of diagnosis. Once diagnosed, curative treatments for liver cancer include surgical resection or liver transplantation; these treatments are only appropriate for a small group of patients. When hepatic resection or transplant is not a treatment option, alternative treatment interventions include radiofrequency ablation (RFA),

transarterial embolization (TAE), transarterial chemoembolization (TACE), cryoablation and systemic chemotherapy. Newer treatments that are currently being studied include gene therapy and immunotherapy.

Percutaneous Ethanol Injection (PEI)
PEI has been proposed as an alternative to liver resection when an individual has a single localized mass less than 5 cm in diameter or several small tumors measuring 3–4 cm in diameter. Patients are typically not candidates if they have evidence of extrahepatic metastases. By injecting pure alcohol (i.e., ethanol) through the skin via ultrasonic or computerized tomographic (CT) guidance into the tumor bed, blood flow to the cancer is blocked. The alcohol induces tumor destruction by drawing water out of the tumor cells (dehydrating them) and denaturing the structure of the cellular proteins. It may take several injections to completely destroy the tumor. This procedure can be done under local anesthetic and on an outpatient basis.

Due to the relation of PEI effectiveness to tumor size, PEI therapy is generally appropriate only in those patients with fewer than four lesions, each less than 3–4 cm in size or with a small single lesion less than 5 cm. PEI is most frequently used for treatment of primary HCC, because the multifocal nature of the disease and the common association with cirrhosis often make resection of even small amounts of liver prohibitively high risk (Cancer Medicine, 2003).

Tumor response rates to PEI have been reported to be 90–100% in HCCs smaller than 2 cm in diameter, 70% in HCCs of 3 cm in diameter, and 50% in HCCs of 5 cm in diameter (Blum, 2005). According to this author, PEI may be appropriate for patients with any of the following:

- a single HCC lesion smaller than 5 cm in diameter
- up to three lesions smaller than 3 cm in diameter that are localized but unresectable due to the location in the liver, concomitant medical considerations (cirrhosis), or even limited bilateral tumors (NCI, 2005; Blum, 2005)
- a lesion surrounded by a shell consisting of scar tissue (fibrous encapsulation) and
- not near the surface of the liver

The most common side effect of PEI therapy is leakage of alcohol onto the surface of the liver and into the abdominal cavity, causing pain and fever. Blood vessels and/or bile ducts that are adjacent to a tumor should be defined and protected from accidental injection or injury (Fong, 2002).

Literature Review
Evidence in the published, peer-reviewed scientific literature supports the use of PEI for the treatment of small HCC. A number of uncontrolled studies have reported overall survival rates ranging from 70%–85% at three years and 40%–60% at five years (Ebara, et al., 2005; Sung, et al., 2006). Comparative studies have reported similar survival rates among PEI and resection patients. Livraghi et al. (1995) reported three-year survival rates of 79% for patients who underwent hepatic resection versus 71% for patients who received PEI. A study by Gournay et al. (2002) found that PEI therapy had survival probabilities at one, three and five years of 87.7%, 69.6% and 44.2%, respectively, while patients who underwent HR had survival probabilities of 79.7%, 61.7% and 44.2%, respectively. However, both Wakai et al. (2006) and Cho et al. (2007) reported a trend toward better survival rates for patients who had hepatectomy versus PEI.

A randomized, controlled three-armed study of 157 patients with HCC conducted by Lin et al. (2004) compared the clinical outcomes of RFA, conventional PEI and higher-dose PEI. The rate of complete tumor necrosis for patients receiving conventional PEI was 88%; local tumor progression at one, two and three years for the PEI group was 23%, 45% and 45%, respectively. The overall survival rates for the PEI groups at one, two and three years were 85%, 61%, and 50% in the conventional PEI group and 88%, 63% and 55% in the higher-dose PEI group, respectively. Cancer-free survival for the PEI groups was 61%, 42% and 17% for the conventional dose group; 63%, 45%, and 20% for the higher-dose PEI group; and 78%, 59% and 37% for the RFA group. Study results suggest that PEI delivered conventionally (single injection) or at a higher dose (multiple sites, simultaneous injections) is equivalent to RFA in the treatment of patients with lesions measuring 3–5 cm in diameter.

In a systematic review, Lopez and colleagues (2006) analyzed 16 RCTs published from 2002 to 2005 assessing percutaneous ablation, other loco-regional therapies and systemic therapies. Percutaneous treatments (i.e., PEI and RFA) were evaluated in six of these studies. The authors stated that the best outcomes associated with the use of PEI and RFA have been reported in Child-Pugh A patients with small single tumors that are usually < 2 cm in diameter. Treatment with PEI or RFA was noted to provide five-year survival rates of 40–70% for HCC patients. However, surgery continues to be the mainstay of treatment for HCC. "Resection and transplantation achieve the best outcomes in well selected candidates with a five-year survival rate of 60–70%" (Lopez, et al., 2006).

Professional Societies/Organizations
According to the National Comprehensive Cancer Network (NCCN) guidelines for hepatobiliary cancers, the treatment of choice for HCC patients without cirrhosis is resection whenever possible. Resection of liver tumors in patients with cirrhosis is more controversial. In cirrhotic patients, the best indication for resection is the presence of small peripheral lesions and preserved liver function (i.e. Child-Pugh class A). If deemed unsafe for resection, small HCC tumors in a patient with cirrhosis may be treated with ablation or liver transplantation. Alternative therapies for patients with unresectable disease, or those who decline surgery include ablative therapy (e.g., RFA, alcohol, cryotherapy, microwave), chemoembolization, chemotherapy and clinical trial. Patients with inoperable disease are those who should not undergo surgery because of performance status, comorbidity or extent of liver disease (NCCN, 2008).

The NCI states that, along with RFA, chemoembolization and cryosurgery, PEI is a standard treatment option for small (< 5 cm), localized, unresectable tumors in patients with primary liver cancer (NCI, 2008).

The British Society of Gastroenterology (BSG) care guidelines for the diagnosis and treatment of HCC state that nonsurgical therapy should only be used on HCC patients who are not candidates for surgery. According to the guidelines, PEI has been shown to produce necrosis of small HCCs. The BSG notes that PEI is best suited to peripheral lesions, less than 3 cm in diameter. Although PEI has not been subjected to randomized controlled trials, several large studies have shown complete response rates of 75% in lesions ≤ 3 cm, with five-year survival rates of 35–75% (Ryder, 2003).

Summary
Evidence in the published, peer-reviewed scientific literature in the form of uncontrolled studies and limited RCTs indicates that percutaneous ethanol injection (PEI) is a safe and effective alternative for the treatment of hepatocellular carcinoma (HCC) that is unresectable, small in lesion size and localized. This procedure is one of several minimally invasive standard treatment options available to patients with unresectable, localized primary liver cancer that are recommended by the National Cancer Institute (NCI). Studies have shown that PEI and hepatic resection (HR) yield similar tumor response rates and tumor-free survival times for a subset of patients with HCC.

Coding/Billing Information

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

Covered when medically necessary:

CPT®* Codes	Description
	No specific codes

HCPCS Codes	Description
	No specific codes

ICD-9-CM Diagnosis Codes	Description

155.0	Malignant neoplasm of the liver, primary, hepatocellular

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	5/15/2008	0364	Percutaneous Ethanol Injection (PEI) for Liver Cancer