Cigna Medical Coverage Policy

Subject: Convection-Enhanced Delivery of Therapeutic Agents to the Brain

Effective Date: 4/15/2015
Next Review Date: 4/15/2016
Coverage Policy Number: 0476

Table of Contents
Coverage Policy: 1
General Background: 1
Coding/Billing Information: 3
References: 3

Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain standard Cigna benefit plans. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, 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 supersedes 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. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2015 Cigna

Coverage Policy
Cigna does not cover convection-enhanced delivery of therapeutic agents to the brain for any indication because it is considered experimental, investigational or unproven.

General Background
Brain tumors account for 85–90% of all primary central nervous system (CNS) tumors. Effective treatment of glioblastoma (GBM), the most common and most malignant glioma, represents one of the most formidable challenges in oncology. Despite the use of extensive surgery, radiation therapy, and chemotherapy, the prognosis for patients with GBM remains poor, with a median survival of 12–15 months. It is the infiltrative nature of these tumors that eliminates the possibility of curative surgical resection.

Drug delivery directly into the CNS has been an actively investigated field of study for the treatment of primary brain tumors. Approaches to local drug delivery have included the use of implantable, controlled-release polymer systems, delivery into the cerebrospinal fluid (CSF) or a cyst cavity (often using an implanted reservoir), and catheter-based convection-enhanced delivery (CED).

Convection-Enhanced Delivery (CED)
CED involves continuous positive-pressure infusion of a solute containing a therapeutic agent. It relies on pressure-driven bulk flow as a means for delivering therapeutic agents to the CNS. The bulk flow mechanism is created by a small pressure gradient from a pump that pushes solute through a catheter targeted within the CNS. There are several potential advantages of CED as compared with traditional delivery methods: (i) CED bypasses the blood brain barrier (BBB) and can be used to infuse therapeutic agents with large or small molecular weights via bulk interstitial flow; (ii) CED provides targeted delivery to the region into which the
catheter is placed and the potential for real-time monitoring of distribution, which would allow intelligent adjustment of flow rates; (iii) and unlike diffusion-limited delivery, CED provides pressure-driven delivery that enhances interstitial drug distribution. This form of localized delivery limits the potential for neurotoxicity because the infused doses do not need to be as high as those needed for diffusion-mediated delivery (Vogelbaum and Aghi, 2015; National Cancer Institute, 2014).

**Literature Review**

The majority of studies evaluating CED method are non-human feasibility trials. However, there are a few human studies evaluating the use of CED for the treatment of malignant glioma.

Kunwar et al. (2007) published an aggregate summary of three Phase I clinical trials investigating the use of intracerebral CED of cintredekin besodotox (NeoPharm, Inc., Lake Forest IL) in the treatment of recurrent malignant glioma. Cintredekin besodotox, also referred to as IL-13PE38QQR, received U.S. Food and Drug Administration (FDA) orphan drug status in 2001 for the treatment of malignant glioma. It is a recombinant protein consisting of interleukin-13 (IL-13) and a truncated form of Pseudomonas exotoxin (PE38QQR). The three trials evaluated the use of cintredekin besodotox along with tumor resection in 51 patients with malignant glioma. A total of 48 of these patients had glioblastoma multiforme, a devastating glioma with a median survival of six months after recurrence. The trials were designed to assess the tolerability of various concentrations and infusion durations and to evaluate tissue distribution and methods to optimize delivery. All patients had tumor resection followed by intraparenchymal placement of one to three silicone barium-impregnated catheters in areas at risk for residual infiltrating tumor. In some cases catheter placement was deferred until one to three days after tumor resection. CED of cintredekin besodotox was administered sequentially in some patients, 3–21 days prior to surgery and 24–48 hours after surgery. Other patients received a single infusion 24–72 hours after tumor resection. Cintredekin besodotox was administered by CED at a fixed rate for 48–96 hours. Procedure-related adverse events were primarily CNS related, and included headache, sensory disturbance, aphasia, weakness, convulsion, and hemiparesis. The overall median survival after treatment was 45.9 weeks. Several patients had prolonged progression-free survival of more than one or two years, most without any additional treatment. The authors concluded that cintredekin besodotox appears to have a favorable risk-benefit profile, and that CED is a complex delivery method requiring catheter placement via a second procedure to achieve accurate catheter positioning, better drug distribution, and better outcome.

PRECISE, an acronym for Phase III Randomized Evaluation of Convection-Enhanced Delivery of IL10-PE38QQR with Survival Endpoint, is a randomized controlled trial conducted at 52 neurosurgery centers (n=296). The trial was designed to compare treatment with CED of cintredekin besodotox to treatment with the Gliadel Wafer® (MGI Pharma, Minneapolis, MN) in patients with a first recurrence of glioblastoma multiforme. The Gliadel Wafer is an FDA-approved treatment for newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation, and for recurrent glioblastoma multiforme as an adjunct to surgery. Patients in the PRECISE trial were randomized to receive cintredekin besodotox (CB) administered over 96 hours via 2–4 intraparenchymal catheters placed 2–7 days following tumor resection (n=183) or to Gliadel Wafers (GW) placed immediately following tumor resection (n=93). There was no significant difference between the two groups in the primary endpoint, overall survival from the time of randomization. Median survival was 36.4 weeks (9.1 months) in the CB group and 35.3 weeks (8.8 months) in the GW group (p=.476). Although safety profiles were similar between the two groups in most measures, there was a higher incidence of pulmonary embolism in the CED group. The authors noted that drug distribution was not evaluated and should be incorporated into future CED-based therapeutics (Kunwar et al., for the PRECISE Study Group, 2010).

Other therapeutic agents for the treatment of brain tumors via CED are being investigated in clinical trials. IL-4 Pseudomonas toxin fusion protein IL-4(38-37) (Protox Therapeutics, Vancouver, BC) received orphan drug status in 2000 and is currently under evaluation for the treatment of astrocytic glioma. Topotecan hydrochloride (GlaxoSmithKline, London, UK), a chemotherapeutic agent previously approved for treatment of other types of cancer, is also being evaluated for the treatment of primary and recurrent brain tumors via CED.

**Professional Societies/Organizations**


**Use Outside the U.S.**
Convection-enhanced delivery of therapeutic agents is not mentioned in European Society of Medical Oncology clinical practice guideline for the diagnosis, treatment and follow-up of high grade malignant glioma (Stupp et al., 2014).

**Summary**
Convection-enhanced delivery is being investigated as a strategy to circumvent the blood brain barrier by delivering therapeutic agents directly to the brain. Convection-enhanced delivery of therapeutic agents is a promising technique in the treatment of malignant glioma, but further research is needed to define effective agents and treatment parameters and to compare this treatment to standard medical and surgical care. Convection-enhanced delivery is also being explored in the treatment of other disorders affecting the central nervous system, including Parkinson’s disease and Gaucher disease. There is insufficient evidence in the medical literature to demonstrate the safety and efficacy of this technique for any indication.

**Coding/Billing Information**

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Experimental/Investigational/Unproven/Not Covered:**

<table>
<thead>
<tr>
<th>CPT®* Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0169T</td>
<td>Stereotactic placement of infusion catheter(s) in the brain for delivery of therapeutic agent(s), including computerized stereotactic planning and burr hole(s)</td>
</tr>
</tbody>
</table>


**References**


The registered marks "Cigna" and the "Tree of Life" logo are owned by Cigna Intellectual Property, Inc., licensed for use by Cigna Corporation and its operating subsidiaries. All products and services are provided by or through such operating subsidiaries and not by Cigna Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, Cigna Health and Life Insurance Company, Cigna Behavioral Health, Inc., Cigna Health Management, Inc., and HMO or service company subsidiaries of Cigna Health Corporation.