



CIGNA MEDICAL COVERAGE POLICY

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

Subject Convection-Enhanced Delivery of Therapeutic Agents to the Brain

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Hyperlink to Related Coverage Policies

Intensity-Modulated Radiation Therapy (IMRT)
 Proton Beam Therapy for Intracranial and Skull Base Tumors
 Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT)

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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

Convection-enhanced delivery (CED) of therapeutic agents to the brain was developed as a method to treat brain tumors by circumventing the normal limitations imposed by the blood brain barrier. Brain tumors account for 85–90% of all primary central nervous system (CNS) tumors. Malignant gliomas are particularly difficult to treat using standard therapies of surgery, radiotherapy and chemotherapy, and carry a poor prognosis. Anaplastic astrocytoma and glioblastoma multiforme are the most aggressive forms of malignant glioma. Although advances in neurosurgical techniques allow safe resection of many tumors that had previously been inaccessible, glial tumors are usually not completely resectable because of their highly infiltrative nature. Although most CNS tumors are partially responsive to radiotherapy, curative doses are usually not possible because of neural tissue toxicity. Results of traditional chemotherapy are also disappointing, due in large part to the blood brain barrier. The blood brain barrier acts as a physiologic and functional barrier due to unique features of the CNS microvasculature. Modification of brain capillaries by reduction in fenestration and tight cell-to-cell contacts prevents many substances from leaving the blood and crossing the capillary walls into the brain tissues. Delivery of chemotherapeutic agents to the brain by intravenous or oral routes is hampered by high systemic exposure and toxicity. Several alternative methods of drug delivery have been developed in an attempt

to overcome these systemic effects and achieve high concentrations of the drug in brain tumors. These strategies include blood brain barrier breakdown, infusions into cerebrospinal fluid, and several intraparenchymal delivery methods including bolus injections, slow release using biodegradable vehicles, and convection-enhanced delivery (CED) of macromolecules (DeVita, Principles and Practice of Oncology, 2008; National Cancer Institute [NCI], 2009; Vandergrift, et al., 2006).

Convection enhanced delivery (CED) requires the stereotactically-guided implantation of one to four delivery catheters directly into the residual tumor or around the resection cavity in order to deliver the targeted toxin to tumor cells to which it comes into contact. CED provides the ability to move large molecules through the interstitial tissues. The drug or agent is delivered by continuous infusion, with a goal of achieving a homogenous drug distribution in a circumferential pattern away from the point of infusion. CED of therapeutic agents to the brain has been evaluated in several preclinical and clinical trials focused on the treatment of brain tumors. Researchers are also exploring CED as a treatment option for other disorders affecting the central nervous system, including Parkinson's disease and Gaucher disease. Clinical trials are underway at academic health centers to define the best clinical practice for CED and to evaluate various therapeutic agents, including immunotoxins and radioisotope-labeled antibodies (Hall and Sher, 2006; Fiandaca et al., 2008).

Literature Review

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.

Centers for Medicare & Medicaid Services (CMS)

A Medicare National Coverage Determination (NCD) issued on April 6, 2007, states that CMS has determined that the use of osmotic blood brain barrier disruption is not reasonable and necessary when it is used as part of a treatment regimen for brain tumors (CMS, 2007).

Professional Societies/Organizations

Convection-enhanced delivery of therapeutic agents to the brain is not mentioned in the National Cancer Institute (NCI) PDQ® on treatment of adult brain tumors, nor is it mentioned in the National Comprehensive Cancer Network (NCCN) practice guideline for treatment of anaplastic astrocytoma, anaplastic oligodendroglioma, and glioblastoma multiforme.

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

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
0169T	Stereotactic placement of infusion catheter(s) in the brain for delivery of therapeutic agent(s), including computerized stereotactic planning and burr hole(s)

ICD-9-CM Diagnosis Codes	Description
191.0-191.9	Malignant neoplasm of brain
272.7	Lipidoses
332.0	Parkinson's disease, Paralysis agitans
	All other codes

*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

References

1. Abeloff: Abeloff's Clinical Oncology, 4th ed. Churchill Livingstone, an imprint of Elsevier; 2008.
2. American Cancer Society. Detailed guide: brain/CNS tumors in adults. What's new in brain and spinal cord tumor research and treatment? Revised Aug 12, 2010. Accessed Mar 9, 2011. Available at URL address: <http://www.cancer.org/Cancer/BrainCNSTumorsinAdults/DetailedGuide/index>
3. Bidros DS, Liu JK, Vogelbaum MA. Future of convection-enhanced delivery in the treatment of brain tumors. Future Oncol. 2010 Jan;6(1):117-25.

4. Centers for Medicare & Medicaid Services (CMS). Medicare Coverage Database. NCD for blood brain barrier osmotic disruption. 2007 Mar 20. Accessed Feb 19, 2010. Available at URL address: http://www.cms.hhs.gov/MCD/viewncd.asp?ncd_id=110.20&ncd_version=1&basket=ncd%3A110%2E20%3A1%3ABlood+Brain+Barrier+Osmotic+Disruption+for+Treatment+of+Brain+Tumors%28Effective+March+20%7C%7C+2007%29
5. ClinicalTrials.gov. Accessed Mar 9, 2011. Available at URL address: <http://clinicaltrials.gov/>
6. Fiandaca MS, Forsayeth JR, Dickinson PJ, Bankiewicz KS. Image-guided convection-enhanced delivery platform in the treatment of neurological diseases. *Neurotherapeutics*. 2008 Jan;5(1):123-7.
7. Hall WA, Rustamzadeh E, Asher AL. Convection-enhanced delivery in clinical trials. *Neurosurg Focus*. 2003 Feb 15;14(2):e2.
8. Hall WA, Sherr GT. Convection-enhanced delivery: targeted toxin treatment of malignant glioma. *Neurosurg Focus*. 2006 Apr 15;20(4):E10.
9. James CD, Louis DN, Cavenee. Neoplasms of the central nervous system. In: Devita VT, Lawrence TS, Rosenberg SA, editors. *Devita, Hellman & Rosenberg's cancer: principles & practice of oncology*, 8th ed. Lippincott Williams & Wilkins; 2008.
10. Kunwar S, Chang SM, Prados MD, Berger MS, Sampson JH, Croteau D, et al. Safety of intraparenchymal convection-enhanced delivery of cintredekin besudotox in early-phase studies. *Neurosurg Focus*. 2006 Apr 15;20(4):E15.
11. Kunwar S, Chang SM, Westphal M, Vogelbaum M, Sampson J, Barnett G, for the PRECISE Study Group. Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma. *Neuro-oncol* 2010 Feb 4 (advance access published). Accessed Mar 9, 2011. Available at URL address: <http://neuro-oncology.oxfordjournals.org/>
12. Kunwar S, Prados MD, Chang SM, Berger MS, Berger MS, Lang FF, et al. Direct intracerebral delivery of cintredekin besudotox (IL13-PE38QQR) in recurrent malignant glioma: a report by the Cintredekin Besudotox Intraparenchymal Study Group. *J Clin Oncol*. 2007 Mar 1;25(7):837-44.
13. Lonser RR, Schiffman R, Robison RA, Butman JA, Quezado Z, Walker ML, et al. Image-guided, direct convective delivery of glucocerebrosidase for neuronopathic Gaucher disease. *Neurology*. 2007 Jan 23;68(4):254-61. Epub 2006 Oct 25.
14. Muro K, Das S, Raizer JJ. Convection-enhanced and local delivery of targeted cytotoxins in the treatment of malignant gliomas. *Technol Cancer Res Treat*. 2006 Jun;5(3):201-13.
15. National Cancer Institute. Adult brain tumors (PDQ[®]): Treatment. Modified 2010 Jul. Accessed Mar 9, 2011. Available at URL address: <http://www.cancer.gov/cancertopics/pdq/treatment/adultbrain/healthprofessional>
16. NeoPharm website. Accessed Feb 20, 2010. Available at URL address: http://www.neopharm.com/index.php?option=com_content&task=view&id=13&Itemid=27
17. National Comprehensive Cancer Network. Practice guidelines in oncology. Central Nervous System Cancers, v 2.2011. Accessed Mar 9, 2011 Available at URL address: http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf
18. Patel SJ, Shapiro WR, Laske D, Jensen RL, Asher AL, Wessels B, et al. Safety and feasibility of convection-enhanced delivery of Cotara for the treatment of malignant glioma: initial experience in 51 patients. *Neurosurgery*. 2005 Jun;56(6):1243-52; discussion 1252-3.

19. Raghavan R, Brady ML, Rodriquez-Ponce MI, Hartlep A, Pedain C, Sampson JH. Convection-enhanced delivery of therapeutics for brain disease, and its optimization. *Neurosurg Focus*. 2006 Apr 15;20(4):E12.
20. Sampson JH, Akabani G, Archer GE, Berger MS, Coleman RE, Friedman AH, et al. Intracerebral infusion of an EGFR-targeted toxin in recurrent malignant brain tumors. *Neuro Oncol*. 2008 Jun;10(3):320-9. Epub 2008 Apr 10.
21. Sampson JH, Brady ML, Petry NA, Croteau D, Friedman AH, Friedman HS, et al. Intracerebral infusate distribution by convection-enhanced delivery in humans with malignant gliomas: descriptive effects of target anatomy and catheter positioning. *Neurosurgery*. 2007 Feb;60(2 Suppl 1):89-99.
22. Sampson JH, Akabani G, Friedman A, Bigner D, Kunwar S, Berger MS, Bankiewicz KS. Comparison of intratumoral bolus injection and convection-enhanced delivery of radiolabeled antitenascin monoclonal antibodies. *Neurosurg Focus*. 2006 Apr 15;20(4):E14.
23. U.S. Food and Drug Administration (FDA). Cumulative list of all orphan designated products. Accessed Feb 19, 2010. Available at URL address: <http://www.fda.gov/orphan/designat/alldes.rtf>
24. Vandergrift WA, Patel SJ, Nicholas JS, Varma AK. Convection-enhanced delivery of immunotoxins and radioisotopes for treatment of malignant gliomas. *Neurosurg Focus*. 2006 Apr 15;20(4):E13.
25. Vogelbaum MA. Convection enhanced delivery for the treatment of malignant gliomas: symposium review. *J Neurooncol*. 2005 May;73(1):57-69.
26. Vogelbaum MA, Sampson JH, Kunwar S, Chang SM, Shaffrey M, et al. Convection-enhanced delivery of cintredekin besudotox (interleukin-13-PE38QQR) followed by radiation therapy with and without temozolomide in newly diagnosed malignant gliomas: phase 1 study of final safety results. *Neurosurgery*. 2007 Nov;61(5):1031-7; discussion 1037-8.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	04/15/2007	0476	Convection-Enhanced Delivery of Therapeutic Agents to the Brain

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