Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Infusion of Therapeutic Agents to the Brain (Convection-Enhanced Intraparenchymal Delivery)

Description/Background

Convection–enhanced delivery (CED) is a drug delivery technique used to bypass the blood brain barrier (BBB) for the administration of therapeutic agents directly into targeted brain tissue. The brain is naturally protected from harmful agents by the BBB, which is a barrier made up of cells that selectively controls the movement of molecules between the circulating blood and the neuronal tissue. It allows the movement of substances essential to metabolic function but restricts the passage of large molecules (proteins and microorganisms). This capacity to block the entrance of large molecules has made the delivery of drugs directly to brain tissue nearly impossible.

A way around the BBB is to infuse substances directly into the brain, which is a very invasive procedure. In most procedures for intraparenchymal infusion or injection, the delivery device is stereotactically guided to its intracranial target through a burr hole. For slow infusion processes (in humans, typically <0.3ml/hr), the catheter might be left indwelling for several days.

Conventional magnetic resonance imaging (MRI) or computed tomography (CT) scanning studies are typically used preoperatively to estimate the optimal insertion trajectory. The final details of the implantation procedure are usually specific to the design of the delivery device, the rate at which the infusion or injection is to occur, and the number of devices that must be inserted and/or passes that must be made to obtain adequate therapeutic coverage of the targeted volume. Infusion methodologies for both framed and frameless stereotaxy have been developed, with forms for the latter being optimized for use in the interventional MR imaging context. Once the cannula is inserted, a solution containing the antineoplastic or other drug can be infused through the cannula using a microinfusion pump. Once the solution is in the brain, it needs to be distributed throughout the intended target. There are two mechanisms for dispersion: diffusion and convection.

Diffusion is the process in which the drug molecules move from regions of high concentration at the cannula opening, to regions of lower concentration. Diffusion works very slowly through spontaneous motion because the temperature of the infusion must be tolerable for living tissue. This concentration profile drops off very rapidly and results in limited spreading of the drug.

As an alternative to diffusion, NIH researchers proposed to use the pressure built-up in the cannula to force the solution containing the drug through the free spaces that exist in the surrounding tissue.[1-8] In this method, the solution spreads further. This is known as convection-enhanced delivery (CED)

According to the World Health Organization estimates, there are 100 different types of brain tumors. There were an estimated 18,500 new cases of primary brain tumors in 2005. Of these, 50% were glial and 50% of all gliomas were glioblastomas (GBM). Glioblastoma multiforme is a biologically aggressive tumor that presents a unique treatment challenge due to the following characteristics:

- Localization of tumors in the brain
- Intrinsic resistance of these lesions to conventional therapy
- Limited capacity of the brain to repair itself
- The spread of malignant cells into brain parenchyma
- The variably disrupted blood-brain barrier complicating drug delivery
- Tumor capillary leakage, with resultant peritumoral edema and intracranial hypertension
- The limited response to therapy
- The neurotoxicity of treatments directed at gliomas

Many tumors continue to be refractory to standard therapies, such as surgery, radiotherapy and conventional chemotherapy. Newly engineered compounds such as recombinant cytotoxins, antiangiogenesis factors and genetic delivery vectors have been developed. These new agents are all dependent on an effective distribution method in order to bypass the blood-brain barrier. Convection–enhanced delivery (CED) allows for the administration of targeted toxins and other agents directly into the brain at the site of a tumor via catheters placed with the aid of stereotactic image-guided surgery. After significant testing in preclinical animal studies, this method of delivery was followed by the successful demonstration of *in vivo* efficacy in Phase I and II clinical trials. Currently, this technique is being used in the investigational setting at academic medical centers where investigators are starting to define the best practice for CED. The fundamental issues in this method of delivery are rate of infusion, cannula size, infusate concentration and tissue-cannula sealing time.

Several intratumoral drug delivery systems have been or are in clinical trials. Interstitial diffusion-based drug delivery systems such as controlled-release polymer implants (Gliadel wafers) are limited by a small volume of distribution within the tumor and the brain surrounding it and by high and heterogeneous drug concentration that may be sub-therapeutic or toxic. In contrast, CED can deliver drugs over a large brain volume with relatively uniform concentrations by a high flow microinfusion that generates a positive pressure gradient propelling the drug through the extracellular matrix. The CED procedure, at present, uses a targeted therapy that binds to an overexpressed receptor specific to glioma cell. The rationale for CED is that it is a cytotoxic therapy that works independently of apoptotic factors, is not cell cycle-specific, functions in a hypoxic environment, is independent of cell signaling pathways, is not subject to drug efflux mechanisms and does not induce drug resistance.

A targeted anti-neoplastic that is administered by CED is cintredekin besudotox, a novel cytotoxin-based therapy that is being investigated for the treatment of recurrent glioblastoma multiforme (GBM). Cintredekin besudotox is a recombinant protein consisting of a single molecule composed of 2 parts: (i) interleukin-13, which binds to receptors on tumor cells; and (ii) pseudomonas exotoxin (PE), a cytotoxin, which causes destruction of the tumor cell once the molecule is absorbed. Interleukin-13 receptors are present in substantial numbers on malignant glioma cells, but only a minimal amount on healthy brain cells. Hence, cintredekin besudotox has the potential to target tumor cells, with minimal impact on surrounding normal brain tissue. Because of its large size, cintredekin besudotox cannot cross the BBB. In clinical studies, cintredekin besudotox has been administered by CED. Catheters are placed following tumor resection, in areas of microscopic tumor spread or at risk of tumor spread around the tumor resection cavity. Because of the need to achieve homogenous distribution of cintredekin besudotox throughout the tumor infiltrated tissue, the catheters cannot be placed in any previous resection cavity. Once the patient is stable, approximately 2 weeks following craniotomy with tumor resection, the patient is admitted for catheter placement and anti-neoplastic infusion. Catheters are strategically placed by neurosurgeons, taking into account the location of residual non-resectable tumor, brain anatomy, and fluid dynamics. Anywhere from 2 to 4 catheters are placed during a surgical procedure lasting several hours. Cintredekin besudotox is then slowly infused through the catheter directly into the brain over 96 hours.

Neurological disabilities limit the daily activities of thousands of Americans each year. The infusion devices that have been developed are designed to treat brain tumors and various other conditions such as Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke and vasospasm. This technique has been described in published pre-clinical and early clinical studies.

Regulatory Status

Therapeutic agents administered via convection-enhanced drug delivery is an ongoing area of research in the treatment of brain disease. At the present time, there are therapeutic agents that have received orphan drug designation by the U.S. Food and Drug Administration and are currently being studied in clinical trials. These drugs include, but may not be limited to: IL4-Pseudomonas toxin fusion protein IL-4(38-37)-PE38KDEL for the treatment of astrocytic glioma, and cintredekin besudotox or IL13-PE38QQR and trabedersen for the treatment of malignant gliomas.

Medical Policy Statement

The infusion of therapeutic agents to the brain by convection-enhanced delivery is experimental/investigational. It has not been scientifically demonstrated to be safe and effective or to result in improved patient outcomes.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

64999

Rationale

At present, the pharmacokinetics of CED are poorly understood. Sampson et al (2007) compared intratumoral bolus injection and convection-enhanced delivery of radiolabeled antitenascin monoclonal antibodies in patients with recurrent glioblastoma.[34] They demonstrated that CED is as good as or better than delivery of bolus injections, and that bolus injections would probably not be able to achieve the distributions predicted. Based on the small number of tumors that have been resected post-infusion, there appears to be a heterogeneous distribution within the tumor with CED. The authors found a significant crossover effect that suggests that as fluids are infused into the brain, expected neurological and physiological changes would influence a subsequent infusion course. More research is needed to determine the optimal catheter location to distribute a drug to target tumor cells within the tumor mass and in the infiltrated adjacent parenchyma. Optimal catheter design is being researched to minimize backflow, to maximize distribution in the brain, and to account for the need to maintain patient mobility.

Hall et al (2006) found convection-enhanced delivery of targeted toxins represents a new modality for glioblastoma multiforme and it is not influenced by the blood-brain barrier because of the unique route of administration.[18] Drug delivery using pump-assisted CED has led to a number of new, potential treatments for malignant glioma.

A study in which a targeted antineoplastic is delivered by the convection-enhanced method with Cintredekin besudotox was found to have a favorable risk-benefit profile. The medication is a cytotoxin-based therapy and is being investigated for the treatment of recurrent glioblastoma multiforme. The catheter placement via a second procedure is utilized to achieve accurate catheter positioning, better drug distribution and better outcome. Survival results from the early phase studies are encouraging and warrant further evaluation. A Phase III Randomized Evaluation of Convection-Enhanced Delivery of IL 10-PE38QQR with Survival Endpoint, (PRECISE) is currently underway.

Several questions about CED of therapeutic agents remain. They include determining the optimal catheter location to distribute a drug to target tumor cells not only within the tumor mass but also in the infiltrated adjacent parenchyma, the selection of molecule-targeted therapies, catheter design to minimize backflow, etc., and the appropriate form of drug delivery.

Raghavan et al (2006) identified several factors that affect the disposition of an agent infused under positive pressure into the brain parenchyma and are essentially unpredictable and man-made which are[32]:

- Influx: Determined by flow rate and duration.
- Transport: Determined by convection, diffusion, conductivity and surfaces/sulci.
- Efflux: Determined by binding and capillary permeability.
- Distribution

Further studies aimed at optimizing catheter design and infusion parameters should identify modifications capable of effectively addressing these issues now that the potential utility of this approach has been established in humans.

In 2008, Sampson et al determined the maximum tolerated dose (MTD), dose-limiting toxicity (DLT), and intra-cerebral distribution of a recombinant toxin (TP-38) targeting the epidermal growth factor receptor in patients with recurrent malignant brain tumors using the intra-cerebral infusion technique of CED.[35] Twenty patients were enrolled and stratified for dose escalation by the presence of residual tumor from 25 to 100 ng/ml in a 40-ml infusion volume. In the last 8 patients, co-infusion of (123)I-albumin was performed to monitor distribution within the brain. The MTD was not reached in this study. Dose escalation was stopped at 100 ng/ml due to inconsistent drug delivery as evidenced by imaging the co-infused (123)I-albumin. Two DLTs were seen, and both were neurological. Median survival after TP-38 was 28 weeks (95 % confidence interval: 26.5 to 102.8). Of the 15 patients treated with residual disease, 2 (13.3 %) demonstrated radiographical responses, including 1 patient with glioblastoma multiforme who had a nearly complete response and remains alive for over 260 weeks after therapy. Co-infusion of (123) I-albumin demonstrated that high concentrations of the infusate could be delivered over 4 cm from the catheter tip. However, only 3 of 16 (19 %) catheters produced intra-parenchymal infusate distribution, while the majority leaked infusate into the cerebrospinal fluid spaces. Intra-cerebral CED of TP-38 was well-tolerated and produced some durable radiographical responses at doses less than or equal to 100 ng/ml. The authors concluded that CED has significant potential for enhancing delivery of therapeutic macromolecules throughout the human brain. However, the potential efficacy of drugs delivered by this technique may be severely constrained by ineffective infusion in many patients. Further studies are needed.

A 2009 review by Bidros et al noted the increased pressure gradient within a tumor versus the normal brain along with the heterogeneity of drug distribution within the tumor itself are potential "limiting factors in drug delivery by this method."[7]

Kunwar et al (2010) reported results of a phase III multicenter study of 296 participants randomized to either postoperative intraparenchymal cintredekin besudotox (CB) or Gliadel wafer (GW) to treat first recurrence of glioblastoma multiforme (GBM).[22] There was no significant difference in the primary endpoint of overall survival. The median survival for CB was 9.1 months and 8.8 months for GW (P= 0.476; hazard ratio 0.89; 95% confidence interval (CI) = 0.67 – 1.18). There were no statistically significant differences between cohorts for adverse events (AE) except for a higher incidence of vascular disorders (P < 0.001). The predominant vascular AE was due to the rate of pulmonary embolism in the CB group compared to the control group (8% vs. 1%, respectively; P= 0.014). The actual distribution of the drug was not evaluated in this trial.

Bidros et al (2009) stated that CED has emerged as a leading investigational delivery technique for the treatment of brain tumors. Clinical trials utilizing these methods have been completed, with mixed results, and several more are being initiated. However, the potential effectiveness of drugs delivered by CED may be severely constrained by poor drug distribution.[7]

A retrospective analysis of catheter positioning and drug distribution utilizing computer software that was not available during the phase III PRECISE trial was performed by Sampson et al (2006).[36] The reviewers were blinded to the identity of the institution and the neurosurgeon responsible for catheter placement. Out of 174 participants with sufficient data, only 49.8% of the catheters placed met all criteria for positioning. The investigators also noted from simulations that the amount of target tumor tissue covered by adequately placed catheters was small. The authors concluded additional trials were necessary to determine optimized CED catheter placement; verification of drug delivery and distribution along with safety and effectiveness.

Buonerba et al (2011) stated that GBM is the most frequent and aggressive malignant glioma (MG), with a median survival time of 12 to15 months, despite current best treatment based on surgery, radiotherapy and systemic chemotherapy.[11] Many potentially active therapeutic agents are not effective by systemic administration, because they are unable to cross the BBB. As intra-cerebral administration bypasses the BBB, it increases the number of drugs that can be successfully delivered to the brain, with the possibility of minor systemic toxicity and better effectiveness. These researchers summarized the results of the extensive clinical research conducted on intra-cerebral therapy. Biodegradable drug carriers, implantable subcutaneous reservoirs and CED represent the main techniques for intra-cerebral delivery, while conventional chemotherapy agents, radiolabeled antibodies and receptor-targeted toxins are the main classes of drugs for intra-cerebral therapy. At the present time, biodegradable carmustine wafers, commercialized as Gliadel, are the only FDA-approved treatment for intra-cerebral chemotherapy of MG, but intra-cavitary delivery of mitoxantrone and radiolabeled anti-tenascin antibodies via implantable reservoirs has yielded promising results in uncontrolled trials. The pressure-driven flow generated by CED can potentially distribute convected drugs over large volumes of the brain, independently on their intrinsic diffusivity. Nevertheless, prominent technical problems, like backflow, are yet to be properly addressed and contributed to the disappointing results of 2 phase III trials that investigated CED of cintredekin besudotox and TransMid in patients with recurrent GBM.

White et al (2012) described a single-center, phase I, dose-escalation clinical trial of carboplatin administered by CED to patients with recurrent or progressive GBM despite full standard treatment. This trial will incorporate 6 cohorts of 3 patients each.[42] Cohorts will be treated in a sequential manner with increasing doses of carboplatin, subject to dose-limiting toxicity not being observed. This protocol should facilitate the identification of the maximum-tolerated infused concentration of carboplatin by CED into the supratentorial brain. This should facilitate the safe application of this technique in a phase II trial, treating patients with GBM, as well as for the treatment of other forms of malignant brain tumors, including metastases.

Barua and colleagues (2013) noted, "Effective CED depends upon a number of parameters - the diameter of the catheter, the catheter implantation method, the rate of infusion, the physicochemical characteristics of the infusate, and the cytoarchitecture of the targeted brain tissue or structure."[44] Preliminary studies evaluating whether techniques such as

intraoperative MRI can be used to improve accuracy in the targeting and placing of the CED cannula are needed.[46] However, at this time, due to the paucity of comparative clinical trials, the safety and efficacy of the CED procedure have not been determined.

Zhou and colleagues (2017) noted that CED is a technique designed to deliver drugs directly into the brain or tumors.[46] Its ability to bypass the BBB has made it a promising drug delivery method for the treatment of primary brain tumors. A number of clinical trials utilizing CED of various therapeutic agents have been conducted to treat patients with supra-tentorial high-grade gliomas. Significant responses have been observed in certain patients in all of these trials. However, the insufficient ability to monitor drug distribution and pharmacokinetics hampers CED from achieving its potentials on a larger scale. Brainstem CED for DIPG treatment is appealing because this tumor is compact and has no definitive treatment. The safety of brainstem CED has been established in small and large animals, and recently in early stage clinical trials. There are a few current clinical trials of brainstem CED in treating DIPG patients using targeted macromolecules such as antibodies and immunotoxins. Future advances for CED in DIPG treatment will come from several directions including: choosing the right agents for infusion; developing better agents and regimen for DIPG infusion; improving instruments and technique for easier and accurate surgical targeting and for allowing multi-session or prolonged infusion to implement optimal time sequence; and better understanding and control of drug distribution, clearance and time sequence. The authors concluded that CED-based therapies for DIPG will continue to evolve with new understanding of the technique and the disease.

Jahangiri and colleagues (2017) noted that glioblastoma is the most common malignant brain tumor, and it carries an extremely poor prognosis.[47] Attempts to develop targeted therapies have been hindered because the BBB prevents many drugs from reaching tumors cells. Furthermore, systemic toxicity of drugs often limits their therapeutic potential. A number of alternative methods of delivery have been developed, one of which is CED. The authors described CED as a therapeutic measure and review pre-clinical studies and the most prominent clinical trials of CED in the treatment of glioblastoma. Moreover, they outlined numerous technical challenges that need to be met to overcome the issues encountered with the use of CED to treat glioblastoma to date. Another consideration that will be important to prioritize going forward is that durable CED efficacy might require long-term convection at set intervals for months, as is often required for systemically administered chemotherapy to be effective for non-brain tumors. The success of such a strategy may require implantable ports that can be cannulated to receive CED in an out-patient setting. In addition, they stated that before one can evaluate the effectiveness of an agent delivered via CED, technical reproducibility must be achieved. The authors concluded that discouraging results from the 2 randomized phase III studies conducted to date revealed technical shortcomings that need to be addressed to allow CED to fulfill its therapeutic potential; CED holds promise for treating glioblastoma and warrants further pre-clinical and clinical development.

Saito and Tominaga (2017) noted that CED circumvents the BBB by delivering agents directly into the tumor and surrounding parenchyma; CED can achieve large volumes of distribution by continuous positive-pressure infusion.[48] Although promising as an effective drug delivery method in concept, the administration of therapeutic agents via CED is not without challenges. Limitations of distribution remain a problem in large brains, such as those of humans. Accurate and consistent delivery of an agent is another challenge associated with CED. Similar to the difficulties caused by immunosuppressive environments associated with gliomas, there are

several mechanisms that make effective local drug distribution difficult in malignant gliomas. These investigators discussed methods for local drug application targeting gliomas with special emphasis on CED. The authors concluded that although early clinical trials have failed to demonstrate the efficacy of CED against gliomas, CED potentially can be a platform for translating the molecular understanding of glioblastomas achieved in the laboratory into effective clinical treatments. They noted that several clinical studies using CED of chemotherapeutic agents are ongoing; successful delivery of effective agents should prove the efficacy of CED in the near future.

Sasaki and colleagues (2020) examined the efficacy of enhancer of zeste homolog-2 (EZH2) inhibitor by CED against human DIPG xenograft models.[49] The concentration of EZH2 inhibitor (EPZ-6438) in the brainstem tumor was evaluated by liquid chromatography-mass spectrometry (LC/MS). These researchers treated mice-bearing human DIPG xenografts with EPZ-6438 using systemic (intra-peritoneal) or CED administration. Intra-cranial tumor growth was monitored by bioluminescence image, and the therapeutic response was evaluated by animal survival. LC/MS analysis showed that the concentration of EPZ-6438 in the brainstem tumor was 3.74 % of serum concentration following systemic administration. CED of EPZ-6438 suppressed tumor growth and significantly extended animal survival when compared to systemic administration of EPZ-6438 ($p = 0.0475$). The authors concluded that the findings of this study indicated that CED of an EZH2 inhibitor is a promising strategy to bypass the BBB and to increase the efficacy of an EZH2 inhibitor for the treatment of DIPG.

Bander and associates (2020) reported on the safety and experience in a group of pediatric patients who received sequential CED into the brainstem for the treatment of DIPG.[50] Patients in this study were enrolled in a single-center, phase-I clinical trial using 124I-8H9 monoclonal antibody (124I-omburtamab) administered by CED. A retrospective chart and imaging review were used to examine demographic data, CED infusion data, and post-operative neurological and surgical outcomes. MRI scans were analyzed using iPlan Flow software for volumetric measurements. Target and catheter coordinates as well as radial, depth, and absolute error in MRI space were calculated with the ClearPoint imaging software. A total of 7 patients underwent 2 or more sequential CED infusions. No patients experienced Clinical Terminology Criteria for adverse events (AEs) of grade-3 or greater deficits; 1 patient had a persistent grade-2 cranial nerve deficit after a 2nd infusion. No patient experienced hemorrhage or stroke post-operatively. There was a statistically significant decrease in radial error ($p = 0.005$) and absolute tip error ($p = 0.008$) for the 2nd infusion compared with the initial infusion. Sequential infusions did not result in significantly different distribution capacities between the 1st and 2nd infusions (volume of distribution determined by the PET signal/volume of infusion ratio [mean ± SD]: 2.66 ± 0.35 versus 2.42 ± 0.75; $p = 0.45$). The authors concluded that the findings of this study showed the ability to safely carry out sequential CED infusions into the pediatric brainstem. Past treatments did not negatively influence the procedural workflow, technical application of the targeting interface, or distribution capacity. These researchers stated that this limited experience provided a foundation for using repeat CED for oncological purposes.

Lambride et al (2022) noted that brain cancer therapy remains a formidable challenge in oncology; and CED is an innovative and promising local drug delivery method for the treatment of brain cancer, overcoming the challenges of the systemic delivery of drugs to the brain.[51] To improve the understanding regarding the effectiveness of CED and drug transport, these investigators presented an in-silico methodology for brain cancer CED treatment simulation. To achieve this, a 3D finite element (FE) formulation was used that employed a

brain model representation from clinical imaging data and was used to predict the drug deposition in CED regimes. The model encompasses biofluid dynamics and the transport of drugs in the brain parenchyma. Drug distribution was studied under various pathophysiological conditions of the tumor, in terms of tumor vessel wall pore size and tumor tissue hydraulic conductivity as well as for drugs of various sizes, spanning from small molecules to nanoparticles. By means of a parametric study, these researchers reported the impact of the size of the vascular wall pores and that of the therapeutic agent on drug distribution during and after CED. The authors concluded that the in-silico findings provided useful insights of the spatiotemporal distribution and average drug concentration in the tumor towards an effective treatment of brain cancer.

Rechberger et al (2023) noted that despite much progress, the prognosis for H3K27-altered diffuse midline glioma (DMG, formerly known as diffuse intrinsic pontine glioma) when located in the brainstem, remains dark and dismal.[52] Extensive research over the last 10 years has revolutionized the understanding of the molecular basis of DMG, showing potential targetable vulnerabilities for the treatment of this lethal childhood cancer. However, obstacles to successful clinical implementation of novel therapies remain, including effective delivery across the BBB to the tumor site. These investigators reviewed relevant literature and clinical trials and discussed direct drug delivery via CED as a promising treatment modality for DMG. They outlined a comprehensive molecular, pharmacological, and procedural approach that may offer hope for afflicted patients and their families. The authors concluded that challenges remain in successful drug delivery to DMG. While CED and other techniques offer a chance to bypass the BBB, the variables influencing successful intra-tumoral targeting are numerous and complex. These researchers discussed these variables and potential solutions that could lead to the successful clinical implementation of pre-clinically promising therapeutic agents.

Clinical trials continue to study alternative therapeutic agents along with imaging techniques to investigate CED as a method to provide therapies for brain tumors and other diseases affecting the brain. There is a severe lack of comparative clinical trials of CED versus standard therapeutic methods, making it impossible to determine the safety and efficacy of the convection-enhanced delivery procedure. Therefore, this technique is experimental/investigational.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this policy are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06666712	Chronic CED of TPT for Recurrent Malignant Glioma (TPT CED rHGG)	6	Jun 2028
Unpublished			
NCT04264143	CED of MTX110 newly diagnosed diffuse midline gliomas	9	Feb 2024
NCT05063357	131I-omburtamab delivered by convection enhanced delivery in patients with diffuse intrinsic pontine glioma	36	Jan 2025 (withdrawn)

NCT: national clinical trial

Government Regulations
National:

Medicare National Coverage Determinations Manual, Chapter 1, Part 2, (Sections 90-160.26) Coverage Determinations, Table of Contents (Rev. 67. 04-06-07), 110.20- Blood Brain Barrier Osmotic Disruption for Treatment of Brain Tumors (Issued: 04-06-07; Effective March 20, 2007; Implementation Date: 05-07-07); Rev. 200, 07/25/17.

The blood brain barrier (BBB) of the central nervous system is characterized by tight junctions between vascular endothelial cells, which prevent or impede various naturally occurring and synthetic substances (including anti-cancer drugs) from entering brain tissue. The BBB may be partly responsible for the poor efficacy of chemotherapy for malignant primary or metastatic brain tumors.

Nationally Non-Covered indications. Effective for services performed on or after March 20, 2007, the Centers for Medicare & Medicaid Services determines that the use of osmotic BBBD is not reasonable and necessary when it is used as part of a treatment regimen for brain tumors.

This NCD does not alter in any manner the coverage of anti-cancer chemotherapy.

Local:

There is no local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

1. Allard E, Passirani C, Benoit JP. Convection-enhanced delivery of nano-carriers for the treatment of brain tumors. Biomaterials 30 (2009) 2302–2318.
2. Anderson RC, Kennedy B, Yanes CL, et al. Convection-enhanced delivery of topotecan into diffuse intrinsic brainstem tumors in children. J Neurosurg Pediatr. 2013;11(3):289-295.
3. Angelov, L., et al., Blood-brain barrier disruption and intra-arterial methotrexate-based therapy for newly diagnosed primary CNS lymphoma: a multi-institutional experience. Volume 27. Number 21, 2009, pp. 3503-3510.
4. Asthagiri, Ashok R., MD, Advances in Brain Tumor Surgery. Neurologic Clinics. Vol. 25, Issue 4, November 2007, pp. 1-12.
5. Barua NU, Gill SS, Love S. Convection-enhanced drug delivery to the brain: Therapeutic potential and neuropathological considerations. Brain Pathol. 2014;24(2):117-127.

6. Biddlestone-Thorpe L, Marchi N, Guo K, Ghosh C, Janigro D, Valerie K, Yang H. Nanomaterial-mediated CNS delivery of diagnostic and therapeutic agents. Adv Drug Deliv Rev. 2011 Dec 8. [Epub ahead of print]
7. Bidros DS, Vogelbaum MA. Novel drug delivery strategies in neuro-oncology. Neurotherapeutics. 2009; 6:539-546.
8. Bobo RH, Laske DW, Akbasak A et al. Convection-enhanced delivery of macromolecules in the brain. Proc. Natd. Acad. Sci (91) 2076-2080, March 1994.
9. Brady ML, Raghavan R, Singh D, et al. In vivo performance of a microfabricated catheter for intraparenchymal delivery. J Neurosci Methods. 2014;229:76-83.
10. Bruce, JN et al., Regression of recurrent malignant gliomas with convection-enhanced delivery of topotecan, Neurology, 2011; 69(9): 1272-1279.
11. Buonerba C, Di Lorenzo G, Marinelli A, et al. A comprehensive outlook on intracerebral therapy of malignant gliomas. Crit Rev Oncol Hematol. 2011;80(1):54-68.
12. Cavaliere, Robert, et al. Novel Therapies for Malignant Gliomas. Neurologic Clinics, Vol. 25, 2007, pp. 1141-1171.
13. Centers for Medicare & Medicaid Services (CMS), Medicare National Coverage Determinations Manual, Blood Brain Barrier Osmotic Disruption for Treatment of Brain Tumors, Manual section Number 110.20, Effective March 20, 2007.
14. Chamberlin, Marc C., MD, Treatment Options for Glioblastoma. Neurosurgical Focus. Vol. 20, No. 4, July 12, 2006, pp. 1-9.
15. Doolittle, Nancy D., et al., Targeted Delivery in Primary and Metastatic Brain Tumors: Summary Report of the Seventh Annual Meeting of the Blood-Brain Barrier Disruption Consortium, Clinical Cancer Research, Vol. 8, June, pp.1702-1709.
16. Guarnieri, Carson M., Catheters for Chronic administration of Drugs into Brain Tissue; Methods in Molecular Biology. Vol. 437: 109-117.
17. Hall WA, Rustamzadeh E, Asher AL. Convection-enhanced delivery in clinical trials. Neurosurg Focus. 2003; 14(2):e2.
18. Hall WA, Sherr GT. Convection-enhanced delivery: targeted toxin treatment of malignant glioma. Neurosurg Focus. 2006; 20(4):E10.
19. Kawakami K, Nakajima O, Morishita R, Nagai R. Targeted anticancer immunotoxins and cytotoxic agents with direct killing moieties. Sci World J. 2006;6:781-790.
20. Kioi M, Husain SR, Croteau D, et al. Convection-enhanced delivery of interleukin-13 receptor-directed cytotoxin for malignant glioma therapy. Technol Cancer Res Treat. 2006;5(3):239-250.
21. Kunwar S. Convection enhanced delivery of IL13-PE38QQR for treatment of recurrent malignant glioma: presentation of interim findings from ongoing phase 1 studies. Acta Neurochir Suppl. 2003;88:105-111.
22. Kunwar S, Chang S, Westphal M, et al.; PRECISE Study Group. Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma. J Neurosurg. 2010; 113(2):301-309.
23. Kunwar S, Chang SM, Prados MD, et al. Safety of intraparenchymal convection-enhanced delivery of cintredekin besudotox in early-phase studies. Neurosurg Focus. 2006; 20(4):E15.
24. Kunwar S, Prados MD, Chang SM, et al.; Cintredekin Besudotox Intraparenchymal Study Group. 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; 25(7):837-844.
25. Lam, MF et al., Neurosurgical convection-enhanced delivery of treatments for Parkinson's disease, J Clin Neurosci, 2011; 18(9): 1163-1167.

26. Lonser RR, Schiffman R, Robison RA, et al. Image-guided, direct convective delivery of glucocerebrosidase for neuronopathic Gaucher disease. Neurology. 2007; 68(4):254-261.
27. Morrison, Paul F, et al. Focal delivery during direct infusion to brain: role of flow rate, catheter diameter, and tissue mechanics. Am J Physiol Regul Integr Comp Physiol. Volume 277, 1999, pp. 2118-1219.
28. 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; 5(3):201-213.
29. Neuwelt, Edward, et al., Strategies to advance translational research into brain barriers. Lancet Neurology. Vol. 7, January 2008, pp. 84-96.
30. Patel SJ, Shapiro WR, Laske DW, et al. Safety and feasibility of convection enhanced Cotara for the treatment of malignant glioma: initial experience in 51 patients. Neurosurgery. 2005; 5(6):1243-1253.
31. Prados M, et al. Final Results of Phase I/II Studies of IL13PE 38 QQR Administered Intratumorally and/or Peritumorally Via Convection-enhanced Delivery in Patients Undergoing Tumor Resection for Recurrent Malignant Glioma. 2005 (slides).
32. Raghavan, Raghu, PhD., et al. Convection-Enhanced Delivery of Therapeutics for Brain Disease, and Its Optimization. Neurosurgical Focus, Vol. 20, No. 4, July 2006, pp. 1-21.
33. Sampson JH, Akabani G, Archer GE, et al. Intracerebral infusion of an EGFR-targeted toxin in recurrent malignant brain tumors. Neuro Oncol. 2008; 10(3):320-329.
34. Sampson JH, Archer G, Pedain C, et al.; PRECISE Trial Investigators. Poor drug distribution as a possible explanation for the results of the PRECISE trial. J Neurosurg. 2010; 113(2):301-319.
35. Sampson JH et al., Clinical Utility of a patient-specific algorithm for simulating intracerebral drug infusions. Neuro-Oncology, Vol. 9, No. 3, 2007, pp. 343-353.
36. Sampson JH et al. Comparison of intratumoral bolus injection and convection-enhanced delivery of radiolabeled antitenascin monoclonal antibodies. Neurosurgical Focus, Vol. 20, No. 4, April 2006, pp. 1-4.
37. Sampson, John H., MD, PhD, et al. Induction of Hyperintense Signal on T2-Weighted MR images correlates with infusion distribution from intracerebral convection-enhanced delivery of a tumor-targeted cytotoxin. Neuroradiology. Vol., 188, March, pp. 703-709.
38. Shahar, T., Ram. Z/ and Kanner, AA. Convection-enhanced delivery catheter placements for high-grade gliomas: complications and pitfall. J Neurooncol, Nov 4, 2011 [Epub ahead of print].
39. Shimamura T, Husain SR, Puri RK. The IL-4 and IL-13 pseudomonas exotoxins: New hope for brain tumor therapy. Neurosurg Focus. 2006;20(4):E11.
40. Slevin JT, Gash DM, Smith CD, et al. Unilateral intraputaminal glial cell line-derived neurotrophic factor in patients with Parkinson disease: response to 1 year each of treatment and withdrawal. Neurosurg Focus. 2006; 20(5):E1.
41. Sonabend AM et al. Prolonged intracerebral convection-enhanced delivery of topotecan with a subcutaneously implantable infusion pump. Neuro-oncology 13(8): 886-893 August 2011.
42. White E, Bienemann A, Taylor H, et al. A phase I trial of carboplatin administered by convection-enhanced delivery to patients with recurrent/progressive glioblastoma multiforme. Contemp Clin Trials. 2012;33(2):320-331.
43. Yamashita Y, Krauze MT, Kawaguchi T, et al. Convection-enhanced delivery of a topoisomerase I inhibitor (nanoliposomal topotecan) and a topoisomerase II inhibitor (pegylated liposomal doxorubicin) in intracranial brain tumor xenografts. Neuro Oncol. 2007; 9(1):20-28.

44. Barua NU, Woolley M, Bienemann AS, et al. Convection-enhanced delivery of AAV2 in white matter—a novel method for gene delivery to cerebral cortex. J Neurosci Methods. 2013;220(1):1-8.
45. Chittiboina P, Heiss JD, Lonser RR. Accuracy of direct magnetic resonance imaging-guided placement of drug infusion cannulae. J Neurosurg. 2015;122(5):1173-9.
46. Zhou Z, Singh R, Souweidane MM, et al. Convection-enhanced delivery for diffuse intrinsic pontine glioma treatment. Curr Neuropharmacol. 2017;15(1):116-128.
47. Jahangiri A, Chin AT, Flanigan PM, et al. Convection-enhanced delivery in glioblastoma: A review of preclinical and clinical studies. J Neurosurg. 2017;126(1):191-200.
48. Saito R, Tominaga T. Convection-enhanced delivery of therapeutics for malignant gliomas. Neurol Med Chir (Tokyo). 2017;57(1):8-16.
49. Sasaki T, Katagi H, Goldman S, et al. Convection-enhanced delivery of enhancer of zeste homolog-2 (EZH2) inhibitor for the treatment of diffuse intrinsic pontine glioma. Neurosurgery. 2020;87(6):E680-E688.
50. Bander ED, Ramos AD, Wembacher-Schroeder E, et al. Repeat convection-enhanced delivery for diffuse intrinsic pontine glioma. J Neurosurg Pediatr. 2020;26(6):661-666.
51. Lambride C, Vavourakis V, Stylianopoulos T, et al. Convection-enhanced delivery in silico study for brain cancer treatment. Front Bioeng Biotechnol. 2022;10:867552.
52. Rechberger JS, Power BT, Power EA, et al. H3K27-altered diffuse midline glioma: A paradigm shifting opportunity in direct delivery of targeted therapeutics. Expert Opin Ther Targets. 2023;27(1):9-17.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2025, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/07	10/2/07	10/31/07	Joint medical policy established.
11/1/08	8/19/08	10/30/08	Routine maintenance
7/1/12	4/10/12	5/18/12	Update of noncovered service; references added.
3/1/14	12/10/13	1/6/14	Routine maintenance
1/1/16	10/13/15	10/27/15	Routine update of non-covered service
1/1/17	10/11/16	10/11/16	Routine policy maintenance. Updated rationale, references and clinical trials.
5/1/17	2/21/17	2/21/17	Deleted code 0169T, added code 64999. Routine policy maintenance.
5/1/18	2/20/18	2/20/18	Routine policy maintenance. No change in policy status.
5/1/19	2/19/19		Routine policy maintenance. No changes in policy status.
5/1/20	2/18/20		Updated rationale, added references 46-48. No change in policy status.
5/1/21	2/16/21		Routine policy maintenance.
5/1/22	2/15/22		Routine policy maintenance, no change in policy status.
5/1/23	2/21/23		Routine policy maintenance, no change in policy status. (ds)
5/1/24	2/20/24		Updated rationale, added references 49-52. No change in policy status. Vendor managed: N/A (ds)
5/1/25	2/18/25		Routine policy maintenance, no change in status. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INFUSION OF THERAPEUTIC AGENTS TO THE BRAIN (CONVECTION-ENHANCED INTRAPARENCHYMAL DELIVERY)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See government section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

N/A