Molina Clinical Policy
Electric Tumor Treatment Fields for Glioblastoma: Policy No. 353

Last Approval: 2/8/2023
Next Review Due By: February 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Glioblastoma (or glioblastoma multiforme, astrocytoma, GBM) is a rare, complex, deadly, treatment-resistant cancer that comprises 49.1% of all primary malignant brain tumors. Over 13,000 people are expected to be diagnosed with glioblastoma in the United States in 2022, with glioblastoma with a mean age at diagnosis of 64 and rare occurrence in children (National Brain Tumor Society, 2022). The risk of glioblastoma increases significantly with age; however, the incidence has remained stable over the last 20 years among older adults. Overall incidence was 13.16 per 100,000 between 2000 and 2017. A majority (84%) were non-Hispanic Whites, and the incidence among males was 1.62 times higher (Chen et al., 2021). Approximately 10,000 people in the United States die annually. The survival rate for glioblastoma is under 7%, with an average survival time of only approximately 8 months, which has remained stable for decades (National Brain Tumor Society, 2021). The five-year survival rate for patients diagnosed with malignant tumors was 36% overall, reflecting the low survival for glioblastoma (Miller et al., 2021). In the United States, rates are slightly higher among men than women. Caucasians have the highest rate of glioblastoma diagnoses compared to other African Americans, Asians, and American Indians (NORD, 2019).

Glioblastomas are graded on a scale from I to IV to determine the rate of tumor growth; grade I is indicative of slow growth, whereas grade IV is the result of rapid growth. It is common for glioblastomas to begin as grade IV tumors and absent of earlier lower grade tumors. Typically, glioblastomas do not spread from the brain; however, they can be located anywhere in the brain (NORD, 2019). Symptoms include headaches, seizures, confusion, memory loss, muscle weakness, visual changes, language deficits, and cognitive changes. Treatment options include a combination of surgery, chemotherapy, radiation therapy, and alternating electric field therapy (NORD, 2019). While glioblastoma was identified in the medical literature in the 1920s, only four drugs and one device have been approved by the Food and Drug Administration (FDA); none of the available treatments have successfully extended a patient's life beyond a few additional months. These treatments can impact parts of the brain that control cognition, mood, behavior, and all other functions of every organ and body part. As a result, patients lose the ability to work and carry out daily activities that contribute to their independence and sense of self (National Brain Tumor Society, 2021).

The standard of care for newly diagnosed patients with glioblastoma is debulking surgery followed by combination chemotherapy using temozolomide and radiation therapy. Essentially all newly diagnosed patients relapse despite the best available treatment (median time to recurrence of approximately 7 months). At the time of recurrence, treatment options for patients are limited; approximately 20% of patients may undergo repeat surgery. Carmustine polymer wafers may be placed intraoperatively in the surgical cavity during repeat surgery. Rarely, patients may undergo reirradiation. For the majority of recurrent patients, chemotherapy is indicated. In the United States, combination treatment with chemotherapy and the angiogenesis inhibitor bevacizumab has been approved for recurrent glioblastoma and certain other cancers. However, 40-60% of recurrent patients are either unresponsive to bevacizumab or experience serious adverse events following treatment ([1] Bacthelor, 2022).

Electric Tumor Treatment Fields, also known as alternating electric field therapy and tumor treatment field therapy (TFT), is a non-invasive anticancer modality that is comprised of low-intensity (1–3 V/cm) and intermediate-frequency (100–300 kHz), alternating electric fields delivered via cutaneous transducer arrays that are configured to provide optimal tumor-site coverage (Rominiyi et al., 2021). The procedure is performed using Novocure (Optune™ or NovoTFF-100A System), which emits alternating electric fields that disrupt the rapid cell division exhibited by cancer

cells. Novocure has been approved for use in patients with recurrent glioblastoma or as a concomitant treatment with temozolomide in patients with newly diagnosed glioblastoma. The Optune™ TTF system is intended to treat patients with glioblastoma by using transducer arrays placed on the patient's scalp according to the tumor's location. Patients use the device on an outpatient basis for at least 18 hours per day for 4 weeks to several months. Intended benefits include stabilizing the disease, having fewer treatment-related adverse events, and improving quality of life. A potential disadvantage is skin irritation. ([1-3] Optune).

Regulatory

The NovoTTF-100A (Novocure/Optune) device received premarket approval from the Food and Drug Administration (FDA) on April 8, 2011 as a Class 3 device under Product Code NZK (stimulator, low electric field, tumor treatment) for the treatment of patients with recurrent glioblastoma multiforme (FDA, 2011). Approval was extended to patients with newly diagnosed glioblastoma in combination with emozolomide in 2015 (FDA, 2015).

COVERAGE POLICY

Electric Tumor Treatment Fields (TTF) when used according to FDA labeled indications, contraindications, warnings and precautions **may be considered medically necessary** when **ALL** of the following criteria are present ([1-5] NCCN, 2021; Hayes, 2021; MCG, 2021; [1-2] Bacthelor, 2021; [3] Bacthelor, 2020; Farrell et al., 2020; NCI, n.d.; ECRI, 2015; [1] Olson et al., 2014; [2] Olson et al., 2014):

1. Initial request is for 90 days of TTF therapy; **AND**
2. Member is age 22 years or older; **AND**
3. Member can adhere to therapy that includes treatment to be provided by a trained individual or caregiver that can apply the device daily and Member is willing to wear the device at least 18 hours per day; **AND**
4. Member has a diagnosis of glioblastoma with a World Health Organization (WHO) grade IV astrocytoma that is **newly diagnosed** as indicated by **ALL** of the following:
    a. Administered in combination with temozolomide;** **AND**
    b. Initial treatment with maximal debulking surgery (when feasible), followed by chemotherapy and radiotherapy; **AND**
    c. Supratentorial disease.**
5. Karnofsky Performance Status (KPS)** score of 60 or higher; **AND**
6. Member has none of the following contraindications:
    a. Cardiac pacemaker or implantable defibrillator
    b. Deep brain, spinal cord, or vagus nerve stimulator
    c. Major skull defect (e.g., missing section of calvarium)
    d. Metal within brain (e.g., aneurysm clip, bullet fragment)
    e. Programmable ventriculoperitoneal shunt
    f. Pregnancy
    g. Known sensitivity to conductive hydrogels (e.g., gels used on electrocardiogram [ECG] stickers or transcutaneous electrical nerve stimulation [TENS] electrodes)

**** Definitions (NCI, n.d.)**

- **Karnofsky Performance Status (KPS):** A standard way of measuring the ability of cancer patients to perform ordinary tasks; KPS scores range from 0 to 100 (a higher score means a person is better able to carry out daily activities). For example, a KPS of 60 means a person requires occasional assistance but is able to care for most of their personal needs. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function, or to decide if a patient could be included in a clinical trial.
- **Response Assessment in Neuro-Oncology (RANO):** Progression criteria is defined as ≥ 25% increase in enhancing disease or worsening neurologic status in the setting of stable or increasing steroid use.
- **Supratentorial:** The upper portion of the brain comprised of the cerebrum, ventricles, choroid plexus, hypothalamus, pineal gland, pituitary gland, and optic nerve. Examples of tumors that form in the supratentorium are glioblastomas, pineal region tumors, and ependymomas.
- **Temozolomide:** Also called Temodar. An oral alkylating chemotherapy drug used in the treatment of some brain cancers and is considered a first-line treatment for glioblastoma.

Recurrent Glioblastoma **(NCCN, 2021; Mrugala et al., 2014; Stupp et al., 2012)**

Electric TTF **may be considered medically necessary** for recurrent glioblastoma for an initial three-month period when the above criteria are met.

Continuation of TTF for recurrent glioblastoma is dependent **ALL** of the following:

- Member has had an MRI ≤ 2 months prior to the request and there is no evidence of disease progression; **AND**
- Member with newly diagnosed glioblastoma continues to receive Temozolomide; **AND**
- KPS score of ≥ 60 or ECOG Performance Status ≤ 2; **AND**
- Documentation indicating that the Member has been using the device at ≥ 18 hours a day.

Continuation of Therapy

Continued treatment beyond the first THREE months (90 days) after initiating therapy **may be considered medically necessary** when the following criteria is met (CMS; AMR, 2020; [1-5] NCCN, 2021):

1. Member must have a face-to-face clinical re-evaluation by the treating Provider that indicates benefit from the treatment as documented by **ALL** of the following:
   a. MRI scan performed two (2) to four (4) months prior to request and shows no evidence of disease progression; **AND**
   b. KPS score of ≥ 60; **AND**
   c. Documentation of compliance that the Member has been compliant and wears the device at least 18 hours per day.

Limitations and Exclusions

Electric TTF **is considered experimental and investigational** due to a lack of evidence for any indication not listed above. This includes, but is not limited to:

- Treatment of tumors other than GBM; or
- Use of electric TTF therapy with concurrent medical therapy (e.g., bevacizumab or chemotherapy) for treatment of recurrent GBM.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The body of evidence is sufficient to determine that TTFT in patients with newly diagnosed glioblastoma demonstrates a health benefit. Clinical trials have shown that TTFT with temozolomide have a median overall survival that is longer than temozolomide alone. Medical literature for TTFT is insufficient to determine net health benefits in recurrent glioblastoma. Evidence is limited to small and individual studies with serious limitations, including lack of a control or comparator group, high loss to follow-up, and lack of statistical comparisons. Randomized controlled trials and cohort studies of sufficient size and design are needed to further investigate the safety and efficacy of TTFT in patients with recurrent glioblastoma.

Rominiyi et al. (2021) reviewed the mechanisms by which TTF mediate anticancer effects. There is minimal research on the pediatric population with respect to the use of chemotherapy and radiotherapy. Research shows that TTF show a broad mechanism of action by interrupting a multitude of biological processes (DNA repair, cell permeability and immunological responses, to elicit therapeutic effects). Efficacy was also found in pediatric patients diagnosed with glioblastoma. One study demonstrated that TTFwere tolerable in five pediatric patients with high-grade glioma between the ages 10-20. Three demonstrated partial responses when TTF was paired with chemotherapy and/or radiation. For adults with newly diagnosed glioblastoma, improvements lead to an expected survival of under two years. Ghiaseddin

et al. (2020) reported on the efficacy and tolerance of TTF in patients with glioblastoma that were studied in two large phase 3 trials. Adherence was reported 75% of the time despite the need for patients to regularly shave their head. Increased survival corresponds with level of usage. Shah et al. (2020) conducted a systematic review that evaluated prior studies on the efficacy of TTF in patients with high-grade gliomas. A total of 852 studies conducted through February 2019 were initially reviewed for inclusion however, nine were included in the final review (two pilot clinical trials, two randomized clinical trials, and five retrospective studies). There were 1191 patients identified who received TTF. Increased survival was noted among newly diagnosed glioblastoma patients however, this increase was not noted for recurrent glioblastoma patients.

Toms et al. (2019) analyzed compliance data from TTF and temozolomide patients in a subgroup analysis of the phase 3 EF-14 trial by Stupp et al. (2017). The aim was to correlate TTF compliance with progression free survival (PFS), overall survival and to identify potential lower boundary for compliance with improved clinical outcomes. Compliance was assessed by usage data from the NovoTTF-100A device and calculated as percentage per month of TTF delivery. TTF/temozolomide patients were segregated into subgroups by percent monthly compliance. A Cox proportional hazard model controlled for sex, extent of resection, MGMT methylation status, age, region, and performance status was used to investigate the effect of compliance on PFS and overall survival. A threshold value of 50% compliance with TTF/temozolomide improved PFS and overall survival versus temozolomide alone with improved outcome as compliance increased. With a compliance of >90%, median survival was 24.9 months (28.7 months from diagnosis); the five-year survival rate was 29.3%. In conclusion, a compliance threshold of 50% with TTF/temozolomide correlated with significantly improved outcome survival and PFS versus temozolomide alone. Hence, the evidence supports that the use of TTF in recurrent GBM is associated with improved OS when used consistently with a trend towards higher levels of survival associated with increasing compliance.

In a secondary analysis of the Stupp et al. (2017) trial, Taphoorn et al. (2018) examined the association of TTF therapy with progression-free survival and health-related quality of life (HRQoL) among patients with glioblastoma. Of the 695 patients in the study, 639 (92%) completed the baseline HRQoL questionnaire. Of these, 437 (68%) were men; mean age was 54.8 (11.5) years. The HRQoL did not differ significantly between treatment arms except for itchy skin. Deterioration-free survival was significantly longer with TTF for global health (4.8 vs 3.3 months); physical (5.1 vs 3.7 months) and emotional functioning (5.3 vs 3.9 months); pain (5.6 vs 3.6 months); and leg weakness (5.6 vs 3.9 months). These likely related to improved progression-free survival. Time to deterioration (reflecting the influence of treatment) did not differ significantly except for itchy skin (TTF worse; 8.2 vs 14.4 months) and pain (TTF improved; 13.4 vs 12.1 months). Role, social, and physical functioning were not affected by TTF. Addition of TTF to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for increased itchy skin, an expected consequence from the transducer arrays.

NovoTTF System

Kanner et al. (2014) conducted a treatment-based analysis of data from the pivotal phase III trial of the NovoTTF-100A System™ versus best physician's choice (BPC) chemotherapy in patients with recurrent glioblastoma multiforme. Emphasis was on the efficacy in patients using NovoTTF therapy as intended. Median overall survival was compared for recurrent glioblastoma patients receiving at least one full cycle of treatment with NovoTTF-100A System or BPC chemotherapy (modified intention-to-treat [mITT] population). The relationship between NovoTTF-100A System compliance and overall survival was evaluated in the ITT population. Kaplan-Meier analyses examined treatment-related differences in overall survival for various patient subgroups. Median overall survival was significantly higher in patients receiving≥1 course of NovoTTF therapy versus BPC (7.7 v 5.9 months; hazard ratio, 0.69; 95% confidence interval, 0.52-0.91; P = .0093). Median overall survival was also significantly higher in patients receiving NovoTTF therapy with a maximal monthly compliance rate≥75% (≥18 hours daily) versus those with a <75% compliance rate (7.7 v 4.5 months; P = .042), and Kaplan-Meier analysis demonstrated a significant trend for improved median overall survival with higher compliance. Additional post hoc analysis showed significantly higher median overall survival with NovoTTF therapy than with BPC for patients with prior low-grade glioma, tumor size ≥18 cm(2), Karnofsky performance status≥80, and those who had previously failed bevacizumab therapy. This contrasts with the equivalent efficacy reported previously based on analysis of all randomized ITT subjects, including many who did not receive a full cycle of treatment. The authors summarized those results from the present study suggest that when used as intended, NovoTTF Therapy provides efficacy superior to that of chemotherapy in a heterogeneous population of patients with recurrent glioblastoma. Post hoc analyses identified subgroups of patients who may be particularly good candidates for NovoTTF Therapy, pending further confirmatory studies.

Mrugala et al. (2014) evaluated data collected from all adult patients with recurrent glioblastoma who began commercial Novocure TTF therapy through the Patient Registry Dataset (PRiDe), a post-marketing registry of all recurrent glioblastoma glioblastoma patients who received NovoTTF therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data from 457 recurrent glioblastoma patients who received Novocure TTF therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received Novocure TTF therapy for first recurrence (33% versus 9%) and had received prior bevacizumab therapy (55.1% versus 19%). Median overall survival was significantly longer with Novocure TTF therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 versus 6.6 months; HR, 0.66; 95% CI, 0.05 to 0.86). One- and two-year overall survival rates were more than double for Novocure TTF therapy patients in PRiDe than in the EF-11 trial (one-year: 44% versus 20%; two-year: 30% versus 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the Novocure TTF therapy transducer arrays. It was concluded that results from PRiDe, together with those previously reported in the EF-11 trial, indicate that Novocure TTF therapy offers clinical benefit to patients with recurrent glioblastoma, has high patient tolerability and favorable safety profile in the real-world, clinical practice setting. Future investigations may need to include NovoTTF Therapy in combination with other recurrent glioblastoma treatments, which together may have additive or synergistic effects on patient outcomes.

Studies

Two related studies are currently recruiting in the United States. The first study is titled *Temozolomide with Radiation Therapy and Tumor Treating Fields Therapy in Treating Participants for Glioblastoma*. This involves the use of the NovoTTF-200A device. Study location is the Sidney Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, Pennsylvania. A second study, *Niraparib/TTF in GBM*, is also recruiting in Philadelphia at the Hospital of the University of Pennsylvania. This involves the Optune device (ClinicalTrials.gov, 2021).

National and Specialty Organizations

The **National Comprehensive Cancer Network (NCCN)** (2022) has published a clinical practice guideline related to cancers of the central nervous system. Sections are included for Adult Low-Grade (WHO Grade 1 or 2) Glioma, Adult Medulloblastoma, Anaplastic Gliomas, Anaplastic Gliomas/Glioblastoma, and Glioblastoma. Nabors et al. (2020) note that the guidelines focus on the management of CNS cancers in adults, including noninvasive and surgically curable pilocytic astrocytomas to metastatic brain disease. The NCCN aims to have an interdisciplinary team involved in the patient's treatment including neurosurgeons, radiation therapists, oncologists, neurologists, and neuroradiologists. Nabors et al. outline NCCN recommendations for the following WHO grade gliomas:

- Grade I (pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, subependymal giant cell astrocytoma)
- Grade II (diffuse astrocytoma and oligodendroglioma)
- Grade III (anaplastic astrocytoma and oligodendroglioma)
- Grade IV (glioblastoma)

Treatment recommendations for brain tumors include surgical resection, radiation therapy and/or chemotherapy as treatment options. Current standard treatment for newly diagnosed glioblastoma consists of tumor resection followed by daily low dose temozolomide administered concurrently with external beam radiotherapy followed by adjuvant temozolomide with alternating electric field therapy (NCCN, 2022).

The use of adjuvant alternating electric field therapy when used as an initial therapy along with temozolomide for individuals with anaplastic gliomas/ glioblastoma with good performance status following standard radiotherapy and concurrent temozolomide is a NCCN category 1 recommendation.

For recurrent glioblastoma, NCCN gives alternating electrical field therapy a 2B rating (consensus based upon lower-level evidence). There is no established second-line therapy for recurrent gliomas (NCI, 2022; NCCN, V2.2022). The NCCN panel designates a 2B recommendation for alternating electric field therapy in the treatment of recurrent GBM.

The **American Society of Clinical Oncology** endorsed the **ASTRO** (2016) *Guideline on Radiation Therapy for Glioblastoma.* A systematic literature review investigated the following questions:

1. Is radiation therapy indicated after biopsy/resection of glioblastoma and how does systemic therapy modify its effects?
2. What is the optimal dose-fractionation schedule for external beam radiation therapy after biopsy/resection of glioblastoma and how might treatment vary based on pretreatment characteristics such as age or performance status?
3. What are ideal target volumes for curative-intent external beam radiation therapy of glioblastoma?
4. What is the role of reirradiation among glioblastoma patients whose disease recurs following completion of standard first-line therapy?

The guideline recommends that following biopsy or resection, glioblastoma patients with reasonable performance status who are up to 70 years of age should receive conventionally fractionated radiation therapy (e.g., 60 Gy in 2-Gy fractions) with concurrent and adjuvant temozolomide. Routine addition of bevacizumab to is not recommended. Older patients (≥ 70 years of age) with reasonable performance status should receive hypofractionated radiation therapy (e.g., 40 Gy in 2.66-Gy fractions); preliminary evidence may support adding concurrent and adjuvant temozolomide to this regimen. Partial brain irradiation is the standard paradigm for radiation delivery. A variety of acceptable strategies exist for target volume definition, generally involving 2 phases (primary and boost volumes) or 1 phase (single volume). For recurrent glioblastoma, focal reirradiation can be considered in younger patients with good performance status.

SUPPLEMENTAL INFORMATION

None.

CODING & BILLING INFORMATION

NOTE: CMS does not have a National Coverage Determination (NCD) for electric tumor treatment field therapy however, there is a Local Coverage Determination (LCD) (L34823) for Tumor Treatment Field Therapy (TTFT). Effective 10/1/2015; revision effective date 1/1/2020.

CPT Codes – N/A

HCPCS Codes

HCPCS	Description
A4555	Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

02/08/2023 Policy reviewed, no changes to criteria, updated references.
02/09/2022 Policy reviewed; TTF now covered for recurrent glioblastoma; updated Summary of Medical Evidence and Reference sections.
02/08/2021 Policy reviewed, no changes to criteria.
04/23/2020 New policy. IRO Peer Review in January 2020 by a practicing, board-certified neurologist.

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APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*