Subject: Electric Tumor Treatment Fields for Glioblastoma		Original Effective Date: 4/23/20
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Contents

DISCLAIMER

This Molina clinical policy is intended to facilitate the Utilization Management process. 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 (i.e., 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 Molina clinical policy document and provide the directive for all Medicare members.[1]

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL [1-3 29-30]

Electric Tumor Treatment Fields also known as alternating electric field therapy and tumor treatment field therapy (TTFT) is done by a device called Novocure (Optune™ or NovoTFF-100A System) that 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 (GBM) or as a concomitant treatment with temozolomide (TMZ) in patients with newly diagnosed GBM. 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.

Glioblastoma also known as glioblastoma multiforme (GBM) is an aggressive type of brain cancer. It is rare, with an incidence of 3.21 cases per 100,000 population per year in the US. GBM develops from glial cells in the brain and is the most prevalent and malignant intracranial tumor, representing as much as 30% of primary brain tumors. The overall prognosis is poor, even with the best standard of care. With optimal treatment, the median survival time is approximately 10 to 14 months. Only a third of patients survive for 1 year following diagnosis of GBM, and < 5% live beyond 5 years. Patients with recurrent GBM have a median survival time of just 5 to 7 months.

The current standard of care for newly diagnosed GBM patients is debulking surgery, followed by combination chemotherapy using temozolomide (TMZ) and radiation therapy. Essentially all patients with newly diagnosed GBM relapse despite best available treatment, with a median time to recurrence of approximately 7 months. At the time of disease recurrence, treatment options for GBM 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 GBM patients, chemotherapy is indicated. In the United States, combination treatment with chemotherapy and the angiogenesis inhibitor bevacizumab has been approved for recurrent GBM and certain other cancers. However, approximately 40% to 60% of recurrent GBM patients are either unresponsive to bevacizumab or experience serious adverse events following treatment.

Food and Drug Administration (FDA): The NovoTTF-100A (Novocure/Optune) device received FDA premarket approval (PMA) 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 (GBM). This approval was extended to patients with newly diagnosed GBM in combination with temozolomide on October 5, 2015. [2-3]

RECOMMENDATION CLINICAL CRITERIA [1-6 7-28 31]

1. Electric Tumor Treatment Fields also known as alternating electric field therapy and tumor treatment field therapy (TTFT) when used according to FDA labeled indications, contraindications, warnings and precautions may be considered medically necessary when **ALL** of the following criteria are present: [ALL]
   - ❑ Initial request is for 90 days of TTF therapy; and
   - ❑ Age 22 years or older; and
   - ❑ Adherence to therapy that the treatment will be used for an average of 18 hours per day defined as:
     - Individual or caregiver has been trained and is willing and able to apply the device daily; and
     - Individual is willing to wear the device at least 18 hours daily
   - ❑ Glioblastoma (GBM) [World Health Organization grade IV astrocytoma]: **Newly diagnosed**, as indicated by all of the following: [ALL]
     - Administered in combination with temozolomide*; and
     - Initial treatment with maximal debulking surgery (when feasible), followed by chemotherapy and radiotherapy; and

- Supratentorial disease*

❑ Karnofsky Performance Status (KPS)* score of 60 or higher; and

❑ None of the following contraindications:

- cardiac pacemaker or implantable defibrillator
- deep brain, spinal cord, or vagus nerve stimulator
- major skull defect (eg, missing section of calvarium)
- metal within brain (eg, aneurysm clip, bullet fragment)
- programmable ventriculoperitoneal shunt
- pregnancy
- known sensitivity to conductive hydrogels (e.g., gels used on electrocardiogram
- [ECG] stickers or transcutaneous electrical nerve stimulation [TENS] electrodes)

2. Electric Tumor Treatment Fields also known as alternating electric field therapy and tumor treatment field therapy (TTFT) is considered experimental, investigational and unproven when used for the diagnosis of **recurrent GBM** based upon insufficient evidence in the peer reviewed medical literature.

3. Electric Tumor Treatment Fields also known as alternating electric field therapy and tumor treatment field therapy (TTFT) is considered experimental, investigational and unproven for all other conditions including but not limited other solid tumors (e.g., melanoma, pancreatic adenocarcinoma, malignant mesothelioma, and non-small cell lung cancer) based upon insufficient evidence in the peer reviewed medical literature.

***Definitions:** [5]

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.

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.

RANO: Response Assessment in Neuro-Oncology. Progression criteria is defined as ≥ 25% increase in enhancing disease or worsening neurologic status in the setting of stable or increasing steroid use.

Temozolomide: Also called Temodar is an oral alkylating chemotherapy drug used in the treatment of some brain cancers. It is considered a first-line treatment for glioblastoma.

CONTINUATION OF THERAPY [1-4 8-29 32]

❑ Continued treatment beyond the first three months (90 days) after initiating therapy may be considered medically necessary when all of the following criteria is met:

- The member must have a face to face clinical re-evaluation by the treating physician that indicates that there is benefit from the treatment documented by all of the following:
  - MRI scan has been performed ≤2-4 months prior to request and documents no evidence of disease progression; and

- KPS score of ≥60; and
- Documentation of compliance that the individual has been wearing the device at least 18 hours daily

SUMMARY OF MEDICAL EVIDENCE [7-28]

The body of evidence is sufficient to determine that TTFT in patients with newly diagnosed GBM demonstrates a net health benefit and clinical trials have shown that TTFT with temozolomide have a median overall survival longer than temozolomide alone. The body of literature for TTFT is insufficient to determine net health benefits in recurrent glioblastoma. The 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. RCTs and cohort studies of sufficient size and design are needed to further investigate the safety and efficacy of TTFT in patients with recurrent glioblastoma.

Glioblastoma Newly Diagnosed

Stupp et al. (2015) evaluated the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with newly diagnosed glioblastoma. This study was a multicenter, open-label, randomized, phase III trial of 695 adults with supratentorial glioblastoma who were progression free after debulking surgery or biopsy, had undergone standard chemoradiotherapy with temozolomide, and had a mean Karnofsky Performance Status score of 90 (range 60 to 100) evaluated treatment with alternating electric field therapy plus temozolomide maintenance vs temozolomide maintenance only. Interval analysis of 315 patients found, at a median follow-up of 38 months, that combined treatment was associated with an increased median progression-free survival (9.2 months vs 4.0 months, respectively) and overall survival (20.5 months vs 15.6 months, respectively) compared with temozolomide treatment only. The trial was terminated based on the results of the interim analysis. The authors note that the study was limited to patients who had completed radiochemotherapy without progression of disease, excluding patients with poor prognosis; patients with poor performance status were also excluded. [21] At a median follow-up of 40 months, alternating electric field therapy plus temozolomide vs temozolomide alone continued to be associated with increased median progression-free survival (6.7 months vs 4.0 months, respectively) and overall survival (20.9 months vs 16.0 months, respectively). In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis. [19]

Toms et al. (2019) analyzed compliance data from Tumor treating fields (TTFields)/ temozolomide (TMZ) patients in a subgroup analysis of the phase 3 EF-14 trial (Stupp et al., 2017) to correlate TTFields compliance with progression free survival (PFS) and overall survival (OS) and 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 TTFields delivery. TTFields/TMZ 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 OS. A threshold value of 50% compliance with TTFields/TMZ improved PFS and OS versus TMZ alone with improved outcome as compliance increased. At compliance > 90%, median survival was 24.9 months (28.7 months from diagnosis) and 5-year survival rate was 29.3%. The authors concluded that a compliance threshold of 50% with TTFields/TMZ correlated with significantly improved OS and PFS versus TMZ alone. Patients with compliance > 90% showed extended median and 5-year survival rates. [23]

In a secondary analysis of the Stupp et al. (2017) trial, Taphoorn et al. (2018) examined the association of TTFields therapy with progression-free survival and HRQoL among patients with glioblastoma. Of the 695 patients in the study, 639 (91.9%) completed the baseline HRQoL questionnaire. Of these patients, 437 (68.4%) were men; mean (SD) age, 54.8 (11.5) years. Health-related quality of life did not differ significantly between treatment arms except for itchy skin.

Deterioration-free survival was significantly longer with TTFields for global health (4.8 vs 3.3 months; P < .01); physical (5.1 vs 3.7 months; P < .01) and emotional functioning (5.3 vs 3.9 months; P < .01); pain (5.6 vs 3.6 months; P < .01); and leg weakness (5.6 vs 3.9 months; P < .01), likely related to improved progression-free survival. Time to deterioration, reflecting the influence of treatment, did not differ significantly except for itchy skin (TTFields worse; 8.2 vs 14.4 months; P < .001) and pain (TTFields improved; 13.4 vs 12.1 months; P < .01). Role, social, and physical functioning were not affected by TTFields. The addition of TTFields to standard treatment with temozolomide for patients with glioblastoma results in improved survival without a negative influence on HRQoL except for more itchy skin, an expected consequence from the transducer arrays. [22]

Recurrent Glioblastoma

Stupp et al. (2012) evaluated the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with recurrent glioblastoma. This study was a randomized phase III trial of 237 patients (median Karnofsky Performance Status score of 80) with recurrent supratentorial glioblastoma comparing alternating electric field therapy and physician's best choice chemotherapy found, at a median follow-up of 39 months, that there was no significant difference in median 1-year overall survival and 6-month progression-free survival between the treatment groups; however, patients treated with alternating electric field therapy reported fewer gastrointestinal, hematologic, and infectious side effects as compared with patients treated with chemotherapy. The authors noted that the study was designed to demonstrate superiority of the intervention; the findings were also limited by the heterogeneous patient population and prior exposures to chemotherapy. [21]

Kanner et al. 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 (GBM), with particular focus on efficacy in patients using NovoTTF therapy as intended. Median overall survival (OS) was compared for recurrent GBM 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 OS was evaluated in the ITT population. Kaplan-Meier analyses examined treatment-related differences in OS for various patient subgroups. Median OS 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 [CI], 0.52-0.91; P = .0093). Median OS 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 OS with higher compliance (P = .039). Additional post hoc analysis showed significantly higher median OS 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 that 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 GBM. Post hoc analyses identified subgroups of patients who may be particularly good candidates for NovoTTF Therapy, pending further confirmatory studies. [13]

Mrugala et al. (2014) evaluated data collected from all adult patients with recurrent GBM who began commercial Novocure TTF therapy through the Patient Registry Dataset (PRiDe), which is a post-marketing registry of all recurrent GBM patients who received NovoTTF therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data from 457 recurrent GBM 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% v 9%) and had received prior bevacizumab therapy (55.1% v 19%). Median OS was significantly longer with Novocure TTF therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 v 6.6 months; HR, 0.66; 95% CI, 0.05 to 0.86, P =

.0003). One- and 2-year OS rates were more than double for Novocure TTF therapy patients in PRiDe than in the EF-11 trial (1-year: 44% v 20%; 2-year: 30% v 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. The authors 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 GBM, 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 GBM treatments, which together may have additive or synergistic effects on patient outcomes. [17]

PROFESSIONAL SOCIETY GUIDELINES: [4-6]

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for Central Nervous System Cancers (2019) include alternating electric field therapy as a treatment option for patients with newly diagnosed glioblastoma as a category 1 recommendation in patients who are 70 years of age or younger with good performance scores (PS). These recommendations are based on the results of the EF-14 clinical trial that randomized 695 patients with newly diagnosed glioblastoma to TMZ alone or TMZ and alternating electric field therapy. (Stupp 2015).[21] For recurrent glioblastoma the guideline includes consideration of alternating electric treatment fields for glioblastoma after surgery, radiation and chemotherapy (category 2B) however concludes that panel is divided about recommending treatment for this group due to lack of clear efficacy based on the results of the EF-11 trial that randomized 237 patients with recurrent glioblastoma to electric field therapy or chemotherapy. (Stupp 2012).[22] The NCCN clinical practice guidelines do not include any recommendations regarding the use of electric TTF treatment for any condition other than GBM.[4]

CODING INFORMATION: THE CODES LISTED IN THIS CLINICAL POLICY ARE FOR INFORMATIONAL PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE AND INCLUSION OR EXCLUSION OF ANY CODES DOES NOT GUARANTEE COVERAGE. PROVIDERS SHOULD REFERENCE THE MOST UP-TO-DATE SOURCES OF PROFESSIONAL CODING GUIDANCE PRIOR TO THE SUBMISSION OF CLAIMS FOR REIMBURSEMENT OF COVERED SERVICES.

CPT	Description
	N/A

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

ICD-10	Description: [For dates of service on or after 10/01/2015]
C71.0-C71.9	Malignant neoplasm of brain [supratentorial glioblastomas (WHO grade IV astrocytomas)]

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REVISION/REVIEW HISTORY

4/23/20: New Policy
2/8/21:Policy reviewed, no changes to criteria. One new guideline found under reference #6 called: Congress of neurological surgeons systematic review and evidence-based guidelines update on the role of emerging developments in the management of newly diagnosed glioblastoma. This new guideline does not change our position.