

## Electric Tumor Treatment Field Therapy for the Treatment of Glioblastoma Multiforme

**Policy MP-042**

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### Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial, and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.

### Description:

Glioblastoma multiforme (GBM) is a fast-growing type of central nervous system tumor usually occurs in adults and affects the brain more often than the spinal cord. Glioblastoma multiforme also called GBM, glioblastoma, and grade IV astrocytoma can arise in the brain "de novo" or evolve from star-shaped glial cells (astrocytomas or oligodendrogliomas) that support the health of nerve cells within the brain. (American Association of Neurological Surgeons [AANS], 2019). The National Cancer Institute (NCI) estimates 23,820 new cases and 17,760 deaths resulting from brain and other nervous system cancers in 2019.

The mainstay treatment for GBM is surgery, followed by radiation and chemotherapy. The primary objective of surgery is to remove as much of the tumor as possible without injuring the surrounding healthy brain tissue needed for normal neurological function. However, GBMs are surrounded by a zone of migrating, infiltrating tumor cells that invade surrounding tissues, making it impossible to ever remove the tumor entirely. Surgery provides the ability to reduce the amount of solid tumor tissue within the brain, remove cells in the center of the tumor that may be resistant to radiation and/or chemotherapy and reduce intracranial pressure (AANS, 2019). Chemotherapy is intended to treat residual tumor cells.

Optune® is an additional therapy which produces alternating electrical fields within the human body proposed to disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp. The special characteristics and geometrical shape of dividing cells make them susceptible to the effects of the alternating electric tumor treating fields. The electric fields alter the tumor cell polarity at a particular frequency specific to the cell type being treated.

Treatment parameters are preset by Novocure® such that there are no electrical output adjustments available to the patient. The patient will learn to change and recharge depleted device batteries that last about 2-3 hours, and connect to an external power supply overnight. In addition, the electrodes (transducer arrays) need to be replaced at least every 4 days and the scalp re-shaved in order to maintain optimal contact. Patients carry the device in an over-the-shoulder bag or backpack, which weighs about 2.7 lbs., to receive continuous treatment without changing their daily routine.

## **Policy Statement and Criteria**

### **1. Commercial Plans**

**U of U Health Plans may cover tumor treatment field therapy for the treatment of glioblastoma multiforme in limited circumstance when the following criteria are met (treatment is *limited* to 6 month increments):**

- A. Tumor Treatment field therapy is being used in one of the following Food and Drug Administration (FDA) approved indications:
  - i. Histologically-confirmed glioblastoma multiforme (GBM), following histologically- or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy.
  - ii. The device is intended to be used as a monotherapy, and is being used as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.
  - iii. Use with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.
- B. Device must be FDA approved;
- C. The member is 22 years of age or older;
- D. The member does not have an active implanted medical device (i.e., deep brain stimulator, spinal cord stimulator, pacemaker, defibrillator, etc.);
- E. There are no bullet fragments in the area;
- F. Member has no intraventricular shunts;
- G. Member has no skull defects (i.e., missing bone with no replacement).

*(Continued on next page)*

**U of U Health Plans may re-authorize tumor treatment field therapy for the treatment of glioblastoma multiforme if the above criteria have been met and the following:**

- A. The device has been used for a minimum of 18 hours per day by patient documentation; and
- B. Evidence for disease stabilization or improvement has been confirmed by MRI.

**U of U Health Plans does NOT cover tumor treatment field therapy devices or indications that are not approved by the FDA.**

**U of U Health Plans does NOT cover tumor treatment field therapy for any other tumor type, location or circumstances as current evidence in other malignancies is insufficient to reach conclusions regarding efficacy and safety.**

## **2. Medicaid Plans**

**Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at <http://health.utah.gov/medicaid/manuals/directory.php> or the [Utah Medicaid code Look-Up tool](#)**

## **3. Medicare Plans**

**Coverage is determined by the Centers for Medicare and Medicaid Services (CMS); if a coverage determination has not been adopted by CMS and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicare policies and coverage, please visit their search website at: <http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?from2=search1.asp&> or [the manual website](#)**

## **Clinical Rationale**

The evidence as to the efficacy and safety of tumor treatment field therapy is limited to a few studies. This is supported by a 2019 Hayes a Directory Report/systematic review regarding Tumor Treating Fields. This review noted clinical trials suggest the use of Novocure<sup>®</sup> monotherapy in adult patients (aged 22 years and older), with recurrent glioblastoma (GBM) following surgery and radiotherapy, is at least comparable with chemotherapy, although the low body of evidence and individual studies have serious limitations, including but not limited to; high loss follow-up, lack of statistical comparisons and control or comparator groups. Novocure shows potential even though it has unproven benefit. As for treatment of newly diagnosed adults, there is very low quality evidence and very low/insufficient evidence for

treatment of other cancers. Hayes concluded that further RCTs and cohort studies of sufficient size and design are needed to further investigate the safety and efficacy of Novocure in patients with recurrent or newly diagnosed GBM and other cancers.

Studies supporting tumor treatment fields have been competed by several researcher, the most prominent is Stupp. In 2012 Stupp et al. completed a phase III randomized trial (EF-11 trial) of chemotherapy-free treatment of Novo tumor treatment fields (TTF) (20-24h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. The primary end-point was improvement of overall survival. Patients (median age 54 years (range 23- 80), Karnofsky performance status 80% (range 50-100) were randomized to TTF alone (n=120) or active chemotherapy control (n=117). Number of prior treatments was two (range 1-6). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66-1.12]; p=0.27), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% (p=0.13), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, p=0.19). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% (p=0.022) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favored TTF therapy in most domains. Although no improvement in overall survival was demonstrated, the authors conclude that the efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma and that toxicity and quality of life favored TTF.

A treatment-based analysis of data from the pivotal phase III trial of the NovoTTF-100A System™ versus best physician's choice (BPC) chemotherapy was also conducted by Kanner et al. (2014) 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 NovoTTF100A 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.

A multinational, open-label, randomized phase III trial (EF-14 trial) by Stupp et al. (2015) compared Optune® in combination with temozolomide to temozolomide alone in 700 patients age 18 and over with newly diagnosed GBM. The interim report revealed that in the intent-to-treat population, patients treated with TTFIELDS plus temozolomide showed a statistically significant increase in progression free survival (PFS), the primary endpoint, compared to temozolomide alone (median PFS 7.1 months versus 4.0 months, hazard ratio=0.62, p=0.0013). In the per-protocol population, patients treated with TTFIELDS

plus temozolomide demonstrated a statistically significant increase in OS, a powered secondary endpoint, compared to temozolomide alone (median OS 20.5 months versus 15.6 months, hazard ratio=0.64,  $p=0.0042$ ). In the intent-to-treat population, the median OS was 19.6 months versus 16.6 months, respectively, hazard ratio=0.74 ( $p=0.0329$ ). The two-year survival rate was 50 percent greater with TTFs plus temozolomide versus temozolomide alone: 43 percent versus 29 percent. The trial's independent data monitoring committee concluded that the study met its endpoints at its pre-specified interim analysis of the first 315 patients with 18 months or more of follow-up. The committee recommended that the trial be terminated early for success and that all control patients be offered TTFs therapy even prior to progression. In addition, the authors reported that the trial showed Optune could be safely combined with temozolomide. There was no significant increase in systemic toxicities from Optune reported in combination with temozolomide versus temozolomide alone. The most common adverse reaction from Optune treatment was mild to moderate skin irritation, which according to the authors was easily managed, reversible and did not result in treatment discontinuation. This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFs plus temozolomide group, TTFs were to be continued, and thus, more detailed treatment information has been tracked for this group.

Stupp et al. lastly in 2017 reported final outcomes from the randomized, open-label trial of 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) and Optune therapy. Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFs-temozolomide group and 4.0 months in the temozolomide alone group (HR, 0.63; 95% CI, 0.52-0.76;  $P < .001$ ). Median overall survival was 20.9 months in the TTFs-temozolomide group vs 16.0 months in the temozolomide alone group (HR, 0.63; 95% CI, 0.53-0.76;  $P < .001$ ). Systemic adverse event frequency was 48% in the TTFs-temozolomide group and 44% in the temozolomide alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFs-temozolomide vs no patients who received temozolomide alone. In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFs 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.

Based on a post hoc analysis of the 2015 Stupp et. al. EF-14 trial, Kesari et. al. analyzed the same patient population in 2017 by comparing adjuvant therapy with temozolomide following definitive treatment of glioblastoma to the combination of temozolomide plus tumor treating fields, to see what happened when they progressed. Some patients continued their TTF and had chemotherapy added while others went on to chemotherapy alone. There were also a few patients who had had temozolomide alone and receive TTF along with the second line chemotherapy. The authors concluded that the continuation of TTF with the second line chemotherapy was superior to second line chemotherapy alone. However, this is not a prospective randomized trial but is a retrospective study of the patient population. In addition, the improvement with the continuation of TTF (or with the addition of TTF to second line therapy) was marginal with a P value of  $P = 0.0049$ . This study was the basis of the FDA approval for Optune.

In a secondary analysis of the Stupp et al. (2017) trial, Taphoorn et al. (2018) examined the association of TFields 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 TFields 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 (TFields worse; 8.2 vs 14.4 months;  $P < .001$ ) and pain (TFields improved; 13.4 vs 12.1 months;  $P < .01$ ). Role, social, and physical functioning were not affected by TFields. The addition of TFields 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.

The FDA-approved label for newly diagnosed GBM indicates it as treatment for adult patients (22 years of age or older) with histologically-confirmed GBM. Another indication for Optune® is with temozolomide for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines on Central Nervous Systems Tumors (v.1.2019) recommend TTF therapy in conjunction with standard brain radiation therapy and current/adjuvant temozolomide for primary treatment in patients with supratentorial disease with good performance status. The panel conceded that data regarding TTF therapy is limited to evidence from a phase III clinical trial which demonstrated similar survival in between groups. In addition, in the background section, the panel indicated that TTF therapy may be considered as a treatment option for recurrent GBM but the panel was divided due to a lack of clear efficacy data. The NCCN guideline does not advocate for the use of TTF therapy in the recommendation section for patients with recurrent disease.

## **Applicable Coding**

### **CPT Codes**

No applicable codes

### **HCPCS Codes**

- |              |   |
|--------------|---|
| <b>A4555</b> | Electrode/transducer for use with electrical stimulation device used for cancer treatment, replacement only |
| <b>E0766</b> | Electrical stimulation device used for cancer treatment, includes all accessories, any type                 |

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