

ELECTRIC TUMOR TREATMENT FIELD THERAPY

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[Instructions for Use](#) ⓘ

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Related Policy

- [Clinical Trials](#)

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package DME
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes ¹
Precertification with Medical Director Review Required	Yes ¹
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Other
Special Considerations	¹ Precertification with review by a Medical Director or their designee is required.

COVERAGE RATIONALE

The following is proven and medically necessary for treating newly diagnosed histologically-confirmed Supratentorial glioblastoma (GBM):

- The use of U.S. Food and Drug Administration (FDA) approved devices to generate electric tumor treatment fields (TTF) when used according to FDA labeled indications, contraindications, warnings and precautions, and when **all** of the following criteria are met:
 - Initial treatment with radiation therapy has been completed; **and**
 - Individual is receiving Temozolomide; **and**
 - Individual has a Karnofsky Performance Status (KPS) score of ≥ 60 ; **and**
 - 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.

The following is proven and medically necessary for treating radiologically confirmed recurrence of GBM in the Supratentorial region of the brain:

- The use of FDA approved devices to generate electric TTF after initial chemotherapy when used according to FDA labeled indications, contraindications, warnings and precautions and when **all** of the following criteria are met:
 - The device is used as a monotherapy; **and**
 - Individual has a KPS score of ≥ 60 ; **and**

- o Individual or caregiver has been trained and is willing and able to apply the device daily; **and**
- o Individual is willing to wear the device at least 18 hours daily.

When all of the above criteria are met for either newly diagnosed or recurrent GBM, an initial 3 months of electric TTF therapy will be approved.

Subsequent approval(s) for continuation of electric TTF is based on:

- MRI scan has been performed $\leq 2-4$ months prior to request and documents no evidence of disease progression; **and**
- KPS score of ≥ 60 ; **and**
- Documentation that the individual has been wearing the device at least 18 hours daily.

The use of devices to generate electric tumor treatment fields (TTF) is considered investigational, unproven, and not medically necessary when the criteria above are not met and for all other indications due to insufficient evidence of efficacy.

Computer software used for therapeutic radiology clinical treatment planning in conjunction with electric tumor treatment field (TFF) therapy is unproven and not medically necessary due to insufficient evidence of efficacy.

DEFINITIONS

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. (National Cancer Institute [NCI], 2018)

Supratentorial: The upper portion of the brain comprised of the cerebrum and the diencephalon. (NCI, 2018)

Temozolomide: An oral alkylating chemotherapy drug used in the treatment of some brain cancers. It is a first-line treatment for glioblastoma. (NCI, 2018)

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

CPT Code	Description
77299	Unlisted procedure, therapeutic radiology clinical treatment planning <i>CPT® is a registered trademark of the American Medical Association</i>
HCPCS Code	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

DESCRIPTION OF SERVICES

Electric tumor treatment field (TTF) therapy (also known as tumor-treating fields, TTFs, ETTFs) is based on the principle that low intensity, intermediate frequency electric fields (100 to 300 kHz) have an anti-mitotic effect which acts during late metaphase and anaphase, with specific frequencies affecting specific cell types. (Rulseh et al, 2012)

Alternating electrical fields within the human body that 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. TTF harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTF technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFs. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM). In contrast, the TTFs have not been shown to have an effect on cells that are not undergoing division. Since

most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTFs. (Novocure, 2018)

Glioblastoma multiforme (GBM) is the most prevalent and primary malignant brain tumor in adults, accounting for 54% of all gliomas. GBM is the most lethal brain tumor with only a third of patients surviving for one year and less than 5% living beyond 5 years. Unfortunately most glioblastomas recur (National Comprehensive Cancer Network [NCCN], 2018). It develops from star-shaped glial cells (astrocytes and oligodendrocytes) that support the health of the nerve cells within the brain.

The mainstay of 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 (such as motor skills, the ability to speak and walk, etc.). 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 those cells in the center of the tumor that may be resistant to radiation and/or chemotherapy and reduce intracranial pressure. [American Association of Neurological Surgeons (AANS), 2018]

The Optune[®], formerly the NovoTTF-100A System, (Novocure, Portsmouth NH) was approved by the FDA in April 2011, as a novel device to treat adults age 22 years or older with GBM that recurs or progresses after receiving chemotherapy and radiation therapy.

A supplemental FDA premarket approval was received in October 2015 for Optune[™] with Temozolomide in adult patients with newly diagnosed, Supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. For newly diagnosed GBM, Optune is not intended to be used as a substitute for standard treatments but rather as an adjunct therapy.

Refer to the [U.S. Food and Drug Administration \(FDA\)](#) section for additional information.

The Optune kit contains the portable electric field generator (Optune device), INE (insulated electrode) transducer arrays, power supply, and additional supplies. Prior to treatment, transducer arrays are placed on the patient's scalp according to the tumor's location, which are then covered by a lightweight white cap which resembles a bandage. The patient receives the noninvasive TTF treatment for at least 18 continuous hours per day for a minimum of 4 weeks. As the Optune device is portable, patients are able to carry out every-day activities.

Treatment parameters are preset by the manufacturer such that there are no electrical output adjustments available to the patient. The patient or caregiver must learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the transducer arrays need to be replaced once to twice a week and the scalp re-shaved in order to maintain optimal contact.

The NovoTAL[™] (transducer array layout) system is optional simulation software for use in clinical treatment planning with Optune therapy that may be leased from the manufacturer. Its purpose is to determine the optimal location of the transducer arrays based on the patient's most recent magnetic resonance imaging (MRI) scan, head size, and tumor location.

TTF technology is also being studied through ongoing clinical trials as a treatment for other solid tumors such as non-small cell lung cancer, brain metastasis, pancreatic cancer, ovarian cancer and mesothelioma.

CLINICAL EVIDENCE

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline for Central Nervous System Cancers, anaplastic gliomas/glioblastoma includes standard brain radiation therapy (RT) + concurrent temozolomide and adjuvant temozolomide + alternating electric field therapy for patients with good performance status and either methylated or unmethylated/indeterminate MGMT promoter status, in whom resection was not feasible with the following footnote: "Alternating electric field therapy is only an option for patients with supratentorial disease" (category 1). For recurrence of GBM (GLIO-5), the guideline includes consideration of alternating electric treatment fields for glioblastoma after surgery, radiation and chemotherapy (category 2B). (NCCN, 2018)

Stupp et al. (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 TTFields-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 TTFields-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 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.

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.

In a multinational, open-label, randomized phase III trial (EF-14 trial), 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 TTFields 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 TTFields 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 TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

Stupp et al. (2012) 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 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 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 $\geq 75\%$ (≥ 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 cm², 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.

Wong et al. (2015) conducted a retrospective chart review from a single institution on patients treated with NovoTTF-100A and bevacizumab between November 2011 and December 2013. The patients were segregated into two cohorts: (i) those treated with NovoTTF-100A and bevacizumab only and (ii) those treated with NovoTTF-100A, bevacizumab and TCCC. Response to treatment was measured according to the Response Assessment in Neuro-Oncology criteria. Progression-free survival (PFS) and OS were measured from the time of application of these treatments to death or last follow up. The cohort treated with NovoTTF-100A, bevacizumab, and TCCC ($n = 3$) did not differ significantly from the rest of the cohort treated with NovoTTF-100A and bevacizumab only ($n = 34$). Potential reasons for this include baseline clinical characteristics and dexamethasone use. The authors note limitations with this review to be the number of patients treated with NovoTTF-100A, bevacizumab, and TCCC is small and therefore they cannot recommend this combination as standard clinical practice. However, they commented that the findings in their patients are notable and it can serve as a basis for future clinical trials. Second, it is unclear what the relative contribution of immunosuppression in the periphery versus the tumor microenvironment has on treatment resistance in recurrent glioblastomas. Therefore, they conclude that combination treatment, rather than single-agent monotherapy, will more likely affect meaningful clinical results.

Wong et al. (2014) analyzed the characteristics of responders and nonresponders in both cohorts of the phase III trial which compared NovoTTF-100A Best Physician's Choice (BPC) chemotherapy for recurrent glioblastoma to determine the characteristics of response and potential predictive factors. Their analysis showed that a significantly higher proportion of NovoTTF-100A responders, five of 14 (36%), had prior low-grade histologies while none of seven (0%) BPC responder had this type of histological characteristics, suggesting that secondary glioblastoma may be more responsive to NovoTTF-100A treatment. Because primary and secondary glioblastomas have different genetic alterations, notably *EGFR* and *MDM2* amplifications together with *p16* deletion in primary glioblastomas and mutation, *IDH1* mutation and *PDGFR* amplification in secondary glioblastomas, the distinct genetic makeup in these two subtypes of glioblastomas could make secondary glioblastomas more susceptible to NovoTTF-100A treatment. Secondary glioblastomas and low dexamethasone usage are associated with a higher proportion of NovoTTF-100A responders but not BPC chemotherapy responders. The authors surmise that during treatment with NovoTTF-100A, this slower rate of tumor progression might allow enough time for the efficacy of TTFs to emerge because it may take multiple mitotic cycles to reduce the number of tumor cells and the size of the glioblastoma. The authors recommend that future clinical trials on the NovoTTF-100A device must include stratification of potential predictive factors of response that include both genetic and epigenetic determinants.

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.

Rulseh et al. (2012) reported the long-term survival of patients with glioblastoma multiforme treated with tumor-treating fields in a small pilot study of 20 individuals. The inclusion criteria of the study included a KPS \geq 70% and age \geq 18 years, and the patients were divided into two groups. The first group consisted of 10 patients diagnosed with recurring GBM after failing temozolomide treatment that were treated with TTF therapy alone, and the second group consisted of 10 newly diagnosed GBM patients at least four weeks post radiation therapy (with adjuvant temozolomide) that received TTF therapy combined with maintenance temozolomide. The treatment duration in individual patients varied between one and one and a half years, and all histological samples were independently examined in two laboratories in two countries. Twenty percent of the participants in the pilot study (4 out of 20) survived until the time of their report, roughly seven years. The individuals showed no clinical or radiological signs of recurrence and were no longer receiving any treatment. The authors suggest that in order to increase the probability of response to TTF therapy and subsequent long term survival, TTF treatment should be continued even in the face of initial radiologic tumor growth.

There is a lack of published evidence from randomized controlled trials examining the long-term safety and effectiveness of TTF as a treatment for tumors other than GBM, including non-small cell lung brain metastasis, pancreatic cancer, ovarian cancer and mesothelioma.

NovoTAL™ Simulation System

There is limited published clinical available evidence related to the NovoTAL™ simulation system, and insufficient data to support improved long-term health outcomes with its use. This includes a small case series (Connelly et al., 2016), human head model (Wenger et al., 2015), and a user group survey. (Chaudry et al., 2015) A framework for the use of NovoTAL in treatment planning has been proposed by Trusheim et al. (2016)

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

The Optune is categorized by the FDA as a stimulator, low electric field, tumor treatment; see the following website for the initial Premarket Approval information:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034S013> (Accessed July 5, 2018)

Refer to the following website for additional information on supplemental FDA approvals for the Optune using product code NZK: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>. (Accessed July 16, 2018)

NovoTAL simulation software is not regulated by the FDA.

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2019T0582D]

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	<ul style="list-style-type: none">Simplified coverage rationale (no change to guidelines)Archived previous policy version CANCER 039.3 T2

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.