

Subject: Electric Tumor Treatment Field (TTF)
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Description

This document addresses electrical fields known as “tumor treatment fields (TTF)” that are created by low-intensity, intermediate frequency (100–200 kilohertz [kHz]) electric currents delivered to the malignant tumor site by insulated electrodes placed on the skin surface. TTF are felt to cause tumor cell death (apoptosis) by disrupting the assembly of microtubules during later stages of cell division.

Clinical Indications

Medically Necessary:

The use of FDA approved devices to generate electric tumor treatment fields (TTF) to treat histologically-confirmed supratentorial glioblastoma (known also as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) is considered **medically necessary as adjunctive treatment** when all of the following criteria below are met:

- A. Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant temozolomide and radiotherapy has been completed with no documented tumor progression*; **and**
- B. TTF is used in combination with temozolomide; **and**
- C. TTF is initiated within 7 weeks from final dose of temozolomide and radiotherapy; **and**
- D. Individual has Karnofsky Performance Status score of 70 or higher **or** Eastern Cooperative Oncology Group (ECOG) performance status 0-1; **and**
- E. Individual or caregiver has been trained and is willing and able to apply and maintain the device at least 18 hours every day.

Continuation of TTF therapy beyond the initial 90 days is considered **medically necessary** when *both* of the following criteria are met:

- Documentation of compliant use must be reported every 90 days as evidenced by the device monitor report showing the individual is using the device at least 18 hours every day; **and**
- There is no documented tumor progression*.

*See discussion section for MacDonald criteria

Not Medically Necessary:

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Electric Tumor Treatment Field (TTF)

The use of devices to generate electric tumor treatment fields (TTF) is considered **not medically necessary** when the criteria above are not met and for all other malignant tumors.

The use of enhanced computer treatment planning software (such as NovoTal) is considered **not medically necessary** in all cases.

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

77299 Unlisted procedure, therapeutic radiology clinical treatment planning [when specified as plan for using a medically necessary electrical stimulation device for TTF for GBM]

HCPCS

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 Diagnosis

C71.0-C71.9 Malignant neoplasm of brain
Z85.841 Personal history of malignant neoplasm of brain

When services are Not Medically Necessary:

For the procedure and diagnosis codes listed above when criteria are not met, and for all other diagnoses not listed.

When services are also Not Medically Necessary:

CPT

77299 Unlisted procedure, therapeutic radiology clinical treatment planning [when specified as treatment planning for use of an electrical stimulation device for TTF using enhanced computer software (e.g., NovoTal)]

ICD-10 Diagnosis

All diagnoses

Discussion/General Information

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Glioblastoma Multiforme (GBM)

Glioblastoma (WHO grade IV astrocytoma), also known as GBM (NCI, 2021), has a peak incidence between the ages of 45 and 70 years. GBM is the most frequently occurring brain tumor accounting for approximately 12% to 15% of all brain tumors and 50% to 60% of all astrocytic tumors. Giant cell glioblastoma and gliosarcoma are two histologic variants of GBM. The 5-year survival rate for GBM is between 1% and 19%, depending upon age (NCCN, 2022).

NovoTTF™-100A System (NovoCure™ Ltd., Portsmouth, NH; Haifa, Israel) received U.S. Food and Drug Administration (FDA) premarket approval (PMA) in 2011. The device is now marketed as Optune® (NovoCure Ltd., Portsmouth, NH, Haifa, Israel). Optune, a portable, non-invasive device designed for the delivery of TTF to the head, should be worn at least 18 hours a day in order to obtain the best treatment response. The device was originally approved as a novel device to treat adults aged 22 years or older with GBM that recurs or progresses after receiving chemotherapy and radiation therapy. On October 5, 2015, the FDA approved the use of Optune in combination with temozolomide for the treatment of adults with newly diagnosed, supratentorial GBM following maximal debulking surgery and radiation therapy.

Newly diagnosed GBM

Current standard treatment for newly diagnosed GBM 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). Radiochemotherapy is followed by adjuvant temozolomide given for 6 to 12 months. The prognosis for individuals with GBM is poor, with a 1-year survival rate of less than 40%.

Stupp and colleagues (2015) evaluated the safety and efficacy of TTF in individuals with newly diagnosed GBM following chemoradiation therapy. In a multi-center clinical trial, 695 individuals were randomized (2:1) to either TTF (worn at least 18 hours/day) with temozolomide or temozolomide alone. The primary endpoint was identified as progression-free survival (PFS) time in the intent-to-treat (ITT) population (significant threshold, $p \leq 0.01$).

Tumor progression, based on Macdonald criteria was defined as *at least one* of the following:

- Tumor growth of greater than 25% of the product of 2 perpendicular diameters compared to the smallest tumor area measured
- Appearance of one or more new tumors in the brain (diagnosed radiologically as GBM).

An interim analysis conducted on the first 315 participants who had completed at least 18 months of follow-up revealed median PFS in the TTF plus temozolomide group of 7.1 months (95% confidence interval [CI], 5.9-8.2 months) compared to 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide group (Hazard Ratio [HR] 0.62; 98.7% CI, 0.43-0.89; stratified log-rank, $p=0.001$). Median overall survival (secondary endpoint) in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTF plus temozolomide group versus 15.6 months (95% CI, 13.3-19.1 months) (HR, 0.64; 99.4% CI, 0.42-0.98; $p=0.004$) in the temozolomide alone group. Based on the interim analysis results, the study was terminated and individuals in the control group were offered

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TTF in addition to temozolomide. A total of 11 individuals crossed over and began using TTF. With the exception of a higher incidence of localized skin reactions in the TTF plus temozolomide group, the incidence, distribution, and severity of adverse events (AEs) were similar across both treatment groups. This trial does contain a few limitations. As enrollment was not initiated until following radiochemotherapy, this initial phase of treatment is subject to variability. Participants were excluded from participation for progression during early radiotherapy; therefore, those with a very poor prognosis were not included in the sample population. In addition, as TTF was continued beyond tumor progression, there was additional data on this group, increasing the potential for reporting bias. The final analysis of the data was consistent with the interim analysis results (Stupp, 2017).

Results from an industry-sponsored pilot study of TTF alone and TTF in combination with chemotherapy for individuals with diagnosed GBM were reported (Kirson, 2009b). In this single arm study, the first group included 10 individuals with recurrent GBM after failure of maintenance temozolomide, and 10 individuals with newly diagnosed GBM treated with TTF combined with temozolomide were in the second cohort. All 20 individuals were treated for an average of 1 year (range 2.5-24 months) continuously. The first group was compared to a matched group of 18 concurrent controls who received salvage chemotherapy for relapsed/recurrent GBM. The TTF-chemotherapy group was compared to a matched group of 32 concurrent controls who received temozolomide alone. In addition, OS for both cohorts was compared to matched historical control data. Data for the first group were reported by Kirson and colleagues in 2007. For the group of 10 individuals with newly diagnosed GBM, PFS was significantly different (HR 3.32; 95% CI, 1.9-5.9; $p=0.0002$) between the TTF-chemotherapy group compared to the matched concurrent and historical controls. The difference in OS was also significant ($p=0.0018$). The authors concluded TTF may also be an effective sensitizer when used concurrently with chemotherapeutic agents.

The Optune device is designed to be used at least 18 hours every day in order to maximize treatment benefit. Continuous application is needed to reach and maintain therapeutic efficacy (Regev, 2021). The compliance rate, the number of days in which the minimum 18 hours daily use is reached, is associated with the survival rate. In a systematic review and meta-analysis (Regev, 2021) reported on the pooled effect of compliance on OS rates of those with a TTF daily compliance of 75% or more (10.3 months) compared to those with a TTF daily compliance of less than 75% (5.7 months). The 6, 9, and 12-month OS rates of those who used the TTF device 75% or more improved compared to those who used the TTF device less than 75% (73.5% (95%CI = 67.5-80), 54.3% (95%CI = 47.7-61.9), and 44.4% (95%CI = 37.9-51.9) compared to 48% (95%CI = 41-56.2), 40.6% (95%CI = 33.7-49), and 32.5% (95%CI = 25.8-40.9), respectively). An internal log file monitors compliance with therapy.

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.

Recurrent or Progressive GBM

Stupp and associates (2012) conducted a phase III, multinational, randomized controlled pivotal clinical trial upon which the initial PMA was based. Between September 2006 and May 2009, 28 clinical centers enrolled 237 adult participants with relapsed or progressive GBM despite conventional therapy (e.g., surgery and chemo-radiotherapy followed by chemotherapy). A total of 120 participants were randomized in a 1:1 ratio to receive monotherapy with NovoTTF treatment and 117 participants were randomized to the group treated with available best standard care

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(BSC) chemotherapies as practiced at each of the participating clinical centers. Chemotherapy agents considered as BSC during the trial included platinum-based chemotherapy (i.e., carboplatin); nitrosureas (BCNU); procarbazine; combination of procarbazine, lomustine and vincristine (PCV); temozolomide; and bevacizumab. A period of 28 days of treatment with NovoTTF was considered one full treatment course. Participants treated with NovoTTF were allowed to take breaks from treatment up to an hour, twice per day for personal needs such as showers. The primary endpoint of the study was OS. Secondary endpoints included PFS at 6 months (PFS6), time-to-progression (TTP), 1-year survival rate, quality of life (QOL), and radiological response. Participants were seen in clinic monthly, and magnetic resonance imaging (MRI) was performed after 2, 4, and 6 months from initiation of treatment and subsequent MRIs were done according to local practice until disease progression. Medical follow-up continued for 2 months after disease progression. Monthly telephone interviews with the participants' caregivers were used to assess participant mortality rates.

Of the 237 enrollees, 8 participants (4 in each group) did not receive the assigned therapy. A total of 97% (116) of 120 enrollees in the NovoTTF group started treatment and 93 participants (78%) completed 1 cycle (4 weeks) of therapy. Discontinuation of TTF occurred in 27 participants due to noncompliance or the inability to handle the device. For each TTF treatment month, the median compliance was 86% (range 41-98%), which equaled a mean use of 20.6 hours per day. In the BSC (active control) group, 113 (97%) of the 117 assigned participants received chemotherapy and all completed 1 full treatment course with the exception of 1 individual. In the BSC cohort, 21 participants did not return to the site and details on disease progression and toxicity were not available. Stupp and colleagues (2012) noted the median survival of 6.6 months in the TTF group was marginally higher than 6 months in the BSC group (HR 0.86, 95% CI, 0.66-1.12; $p=0.27$). For both groups, 1-year survival was 20%. The survival rates for 2 and 3 years were 8% (95% CI: 4, 13) and 4% (95% CI: 1, 8) versus 5% (95% CI: 3, 10) and 1% (95% CI: 0, 3) for the TTF cohort compared to the BSC cohort, respectively. With a median follow-up of 39 months, 93% (220 participants) had died. Objective radiological responses (partial response [PR] and complete response [CR]) were noted in 14 participants in the TTF group and 7 in the BSC group, with a calculated response rate of 14.0% (95% CI, 7.9-22.4%) compared to 9.6% (95% CI, 3.9-18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with topical steroids. BSC participants experienced grade 2-4 events by organ system related to the pharmacologic activity of chemotherapy agents utilized. QOL data were available in 63 participants (27%). Based on the Quality of Life Questionnaire-Core 30 (QLQ C-30) and Brain Cancer Module (BN-20) questionnaires, 5 out of 6 general scales and 7 of 9 symptom scales including nausea, vomiting, diarrhea, constipation and pain, QOL was consistently higher in NovoTTF than in the control group. There were no meaningful differences observed between the domains of global health and social functioning. The BSC cohort had a larger decrease in the negative effects of seizures than the TTF cohort. The self-reporting of QOL indicators may be influenced by bias for the treatment group (FDA Label, 2011; Stupp, 2012). Although the NovoTTF-100A device has received FDA approval, the pivotal trial did not achieve the primary endpoint of the study, which was improved survival with NovoTTF treatment in comparison to chemotherapy. The study was not sufficiently powered to evaluate for a non-inferiority determination.

Vymazal and colleagues (2015) analyzed the response patterns in individuals with recurrent GBM who exhibited an objective response in two previous studies in order to evaluate the baseline characteristics of those individuals who responded and to evaluate the relationship between compliance with use and efficacy outcomes. The analysis was completed on one pilot study ($n=10$) and a phase III trial ($n=237$) in which TTF was compared to standard chemotherapy. Between both studies, TTF was administered as monotherapy in 130 individuals. Across both trials,

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there was a 15% response rate (16/110 with a 4% CR rate). There were no significant differences in baseline characteristics between the responder and non-responder groups. In those in which a response was noted, there was frequently a delayed response; the tumor would initially continue to grow before responding to treatment. Analysis supported that an increase in compliance was associated with better treatment response and longer OS. The extent of treatment response in those who exhibited a response was significantly dependent on compliance.

Treatment recommendations for brain tumors published by the National Comprehensive Cancer Network® (NCCN, 2022) and the National Cancer Institute (NCI, 2022) include surgical resection, radiation therapy and/or chemotherapy as treatment options. In 2014, the NCCN clinical practice guideline for CNS Tumors was updated and the consideration for alternating electric field therapy for individuals with recurrent, diffuse or multiple GBM was changed to a category 3 from the previous 2B level of evidence. This revision denoted a major disagreement on the appropriateness of the intervention, with NCCN members noting similar survival in both arms of the RCT trial. In May 2015, the NCCN clinical practice guideline was again revised to change the recommendation to consider alternating electric field therapy for GBM from a category 3 back to a category 2B for recurrent disease. The NCI Adult Brain Tumors Treatment (PDQ®) (2022) does not include TTF treatment for recurrent GBM.

The evidence does not support that TTF is effective in the treatment of recurrent GBM. The evidence is limited to an RCT, a retrospective review and several prospective studies (Kirson, 2009b; Mrugala, 2014; Rulseh, 2012; Stupp, 2012). The RCT did not meet its primary endpoint of demonstrating an improvement in survival in this population.

Malignant Pleural Mesothelioma

Pleural mesothelioma cancer develops in the mesothelial surface of the lungs and is primarily associated with asbestos exposure. Malignant mesothelioma is rare in the United States, with approximately 2500 new cases diagnosed each year. Pleural mesothelioma accounts for more than 75% of mesothelioma cases. Most individuals present with advanced disease limiting treatment options available. Median overall survival is 1 year with a 5-year overall survival of about 10% (NCCN, 2022).

In May 2019, the FDA approved the use of a modified version of the TTF device (Optune Lua™ previously known as NovoTTF™-100L) for the first-line treatment of adults with unresectable, locally advanced or metastatic malignant pleural mesothelioma to be used concurrently with pemetrexed and platinum-based chemotherapy. The device was approved under the Humanitarian Device Exemption (HDE) and identifies the specific population that the modified device is intended to treat. The HDE was not reviewed by the FDA advisory panel, but was approved based upon the previous review and approval of the similar GBM device. The Optune Lua operates on the same principle as the device used to treat GBM, but includes different technological characteristics and area of application.

Ceresoli and colleagues (2019) evaluated the activity of TTF used in combination with systemic chemotherapy in treating Stage IV unresectable malignant pleural mesothelioma (STELLAR study). Participants in the Phase II, prospective, single arm study (n=80) were treated with pemetrexed and cisplatin or carboplatin in combination with TTF to the thorax until radiological disease progression or unacceptable toxicity was seen. The primary endpoint was overall survival (OS) time from diagnosis until the date of death. The median OS was 18.2 months (95% CI,

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12.1-25.8). The 1-year survival rate was 62% and the 2-year survival rate was 42%. This OS was compared to the OS reported in two recent randomized trials involving malignant pleural mesothelioma chemotherapy regimens. These studies evaluated the addition of bevacizumab or nintedanib to a standard cisplatin and pemetrexed regimen. Both studies reported increased OS in the study groups compared to control groups, 18.8 months (95% CI, 15.9-2.6) and 18.3 months (15.2-28.8) compared to 16.1 months (14.0-17.9) and 14.2 months (95% CI 12.3-20.9) respectively. A total of 32 individuals (40%) reported severe AEs during the study, with anemia and neutropenia being unrelated to device use. Device-related AEs primarily consisted of skin reactions and were reported in 66% of the individuals, with 5% of these reactions being severe enough to result in treatment interruption. Randomized trials which compare standard chemotherapy with and without concurrent TTF therapy are needed to further evaluate any potential incremental benefit of this therapy over the current standard of care.

In summary, the available evidence regarding the use of TTF in treating stage IV non-curative mesothelioma in combination with standard chemotherapy does not demonstrate that use provides cost effective, therapeutically equivalent outcomes over the use of standard chemotherapy therapy alone.

Other Solid Tumors

In addition to TTF treatment for GBM, phase III trials are underway in other types of malignancies, including brain metastasis, non-small cell lung cancer (NSCLC), ovarian cancer and pancreatic carcinoma. The FDA has granted breakthrough device designation to the NovoTTF-200T for liver cancer. This designation was granted based upon the unpublished results of a phase 2 study evaluating the safety and efficacy of the TTF device when used with sorafenib to treat advanced liver cancer. At this time, there are no studies which support the use of tumor treating fields for conditions other than GBM. The NCCN clinical practice guidelines do not include any recommendations regarding the use of electric TTF treatment for any condition other than GBM.

Treatment Planning Software

In 2013, the FDA approved NovoTal through a PreMarket Approval (PMA) supplement. NovoTal is an algorithmic software package which allows treating physicians, who have completed a certification program, to create individualized treatment maps. The standard treatment plan developed by the manufacturer uses post-contrast MRI sequences to develop a treatment plan. Treating physicians using NovoTal are able to incorporate additional imaging data and other clinical considerations into TTF treatment planning (Connelly, 2016). There is a paucity of literature reporting on planning approaches in TTF treatment and their effect on clinical outcomes. Connelly and colleagues (2016) reported on the use of NovoTal in a case series of 8 individuals with grades 2-4 GBMs. In addition to contrast enhancing MRI imaging, other clinical considerations, such as the heterogeneity in contrast enhancement in tumors, were taken into account during the planning process. The authors discuss the use of alternative MRI sequences during the planning stage of treatment, but do not report on clinical outcomes, noting:

this case series demonstrates that treatment planning beyond the extent of contrast enhancement is clinically feasible and should be prospectively compared to standard treatment planning in a clinical trial setting, in order to determine the impact on patient outcomes.

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Chaudhry and associates (2015) compared physician performance using the NovoTal system to conduct transducer array layout mapping to the mapping laid out by the Novocure in-house clinical team. Neuro-oncologists, medical oncologists and neurosurgeons (n=14) evaluated 5 cases of recurrent GBM and developed treatment plans. While the study demonstrated a high level of concordance in transducer array layout planning between NovoTal certified physicians and the Novocure in-house clinical team, the study did not address whether clinical outcomes were affected. The evidence does not support that the use of enhanced treatment planning software is considered effective in the use of TTF treatment.

Definitions

Cytokinesis: The cytoplasmic changes accompanying mitosis. The cleavage of the cytoplasm into daughter cells following nuclear division.

Eastern Cooperative Oncology Group (ECOG) Performance Status: A scale used to determine the individual's level of functioning. This scale may also be referred to as the WHO or Zubrod score which is based on the following scale:

- 0 Fully active, able to carry on all pre-disease performance without restriction
- 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 Dead

Glioblastoma multiforme: Stage IV glioblastoma, which includes WHO recognized variants, giant cell glioblastoma and gliosarcoma.

Karnofsky Performance Status Score: A 10-point scale used by healthcare providers to quickly evaluate how an individual is feeling on any given day.

- 100 Able to work. Normal; No complaints; No evidence of disease.
- 90 Able to work. Able to carry on normal activity; Minor symptoms.
- 80 Able to work. Normal activity with effort; Some symptoms.
- 70 Independent; not able to work. Cares for self; Unable to carry on normal activity.
- 60 Disabled; dependent. Requires occasional assistance; cares for most needs.
- 50 Moderately disabled; dependent. Requires considerable assistance and frequent care.
- 40 Severely disabled; dependent. Requires special care and assistance.
- 30 Severely disabled. Hospitalized, death not imminent.
- 20 Very sick. Active supportive treatment needed.
- 10 Moribund. Fatal processes are rapidly progressing

Macdonald criteria for disease progression is defined as *at least one* of the following:

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Electric Tumor Treatment Field (TTF)

- Tumor growth of greater than 25% of the product of 2 perpendicular diameters compared to the smallest tumor area measured
- Appearance of one or more new tumors in the brain (diagnosed radiologically as GBM).

Mitosis: The process by which a single parent cell divides to make two new daughter cells. Each daughter cell receives a complete set of chromosomes from the parent cell, allowing the body to grow and replace cells.

Progressive disease: Disease that is growing, spreading or getting worse.

Recurrent disease or recurrence: Disease that has recurred (come back), usually after a period of time during which the disease could not be detected. In the case of cancer, the disease may come back to the same place as the original (primary) tumor or to another place in the body (metastatic).

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History

Status	Date	Action
Reviewed	08/11/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion and References sections.
Revised	08/12/2021	MPTAC review. Added medically necessary indications for continuation therapy. Updated Discussion and References sections.
Revised	08/13/2020	MPTAC review. Revised definition of tumor progression to refer reader to Discussion section. Updated Discussion and References sections. Reformatted Coding section.
Reviewed	08/22/2019	MPTAC review. Updated Discussion and References sections.
Revised	03/21/2019	MPTAC review.
Revised	03/20/2019	Hematology/Oncology Subcommittee review. Added a not medically necessary statement for treatment mapping and planning computer software. Updated Discussion and References sections.
New	05/03/2018	MPTAC review.
New	05/02/2018	Hematology/Oncology Subcommittee review. Initial document development. Moved content of DME.00035 Electric Tumor Treatment Field (TTF) to new clinical utilization management guideline document with the same title.

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