Electric Tumor Treatment Field Therapy

Policy Number: 2020T0582F
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Instructions for Use

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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:
  - Treatment with radiation therapy has been completed; and
  - Individual is receiving Temozolomide as the only cancer drug; and
  - Individual has a Karnofsky Performance Status (KPS) score of ≥ 60 or Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2; and
  - Individual has been counselled that the device must be worn 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 the only treatment; and
  - Individual has a KPS score of ≥ 60 or ECOG Performance Status ≤ 2; and
  - Individual has been counselled that the device must be worn 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:

- Magnetic resonance imaging (MRI) scan has been performed ≤ 2 months prior to request and documents no evidence of disease progression; and
- KPS score of ≥ 60 or ECOG Performance Status ≤ 2; and

- Documentation that the individual has been using the device at least 18 hours daily

Due to insufficient evidence of efficacy, the use of devices to generate electric TTF is unproven and not medically necessary when the criteria above are not met and for all other indications including but not limited to the following:

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

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

Documentation Requirements

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 documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

CPT/HCPCS Codes*	Required Clinical Information
Electric Tumor Treatment Field Therapy	

77299
E0766
	Treatment of Newly Diagnosis Glioblastoma
	• Physician order
	• Diagnosis
	• Physician notes to include the following:
	  ○ Documenting prior treatment with Radiation Therapy
	  ○ Provide results of the *Karnofsky Performance Status (KPS)* or *Eastern Cooperative Oncology Group (ECOG) Performance Status*
	  ○ Documentation that the member has been counselled that the device must be worn at least 18 hours daily
	  ○ Documentation that member is only taking Temozolomide for cancer drug
	
	Treatment of a Reoccurrence of Glioblastoma
	• Physician order
	• Diagnosis
	• Physician notes to include the following:
	  ○ Provide results of the *Karnofsky Performance Status (KPS)* or *Eastern Cooperative Oncology Group (ECOG) Performance Status*
	  ○ Documentation that the member has been counselled that the device must be worn at least 18 hours daily
	  ○ Documentation that member is only taking Temozolomide for cancer drug
	
	Request to Continue Therapy
	• Results of MRI imaging 2-4 months prior to the request to continue therapy
	• Provide results of the *Karnofsky Performance Status (KPS)* or *Eastern Cooperative Oncology Group ECOG Performance Status*
	• Documentation that the member has been wearing the device for at least 18 hours per day

**For code description, see the Applicable Codes section.*

Definitions

Eastern Cooperative Oncology Group (EGOG) Performance Status: A measurement of performance status that describes an individual's level of functioning. Individuals who have a worse performance status and limited functional capacity tend to have more difficulty tolerating rigorous cancer treatments. This scale may also be referred to as the WHO or Zubrod score.

- A score of zero indicates the individual is fully active and has no restrictions
- A score of one indicates that the individual is restricted in physically strenuous activity but is completely ambulatory and cares for self
- A score of two indicates the individual is ambulatory more than 50% of the time and is capable of all self care but unable to carry out any work activities
- A score of three indicates that the individual is ambulatory 50 percent or less of the time and is capable of only limited self-care
- A score of four indicates bedbound (cannot perform any self-care and is totally confined to bed or chair)

(West and Jin, 2015; ECOG-ACRIN Cancer Research Group)

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], 2019; West and Jin, 2015).

Supratentorial: A term used to describe the upper portion of the brain comprised of the cerebrum, ventricles, choroid plexus, hypothalamus, pineal gland, pituitary gland, and optic nerve (NCI, 2019).

Temozolomide: An oral alkylating chemotherapy drug used in the treatment of some brain cancers. It is a first-line treatment for glioblastoma (NCI, 2019).

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 and Guidelines may apply.

CPT Code	Description
77299	Unlisted procedure, therapeutic radiology clinical treatment planning

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HCPCS Code	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

Description of Services

Electric tumor treatment field (TTF) therapy (also known as tumor-treating fields, TTFields, ETTFs) is based on the principle that low intensity, intermediate frequency electric fields (100 to 300 kHz) disrupt cell division and may destroy proliferating cells in brain tumors (Rulseh et al, 2012).

Glioblastoma multiforme (GBM) is the most prevalent and primary malignant brain tumor in adults. The mainstay of treatment for GBM is surgery, followed by radiation and chemotherapy.

The Optune® Treatment Kit, formerly the NovoTTF-100A System, (Novocure) 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. The Optune Treatment Kit has also been approved by the FDA in combination with Temozolomide in adult patients with newly diagnosed, Supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy.

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 individual's scalp according to the tumor's location, which are then covered by a lightweight white cap which resembles a bandage. The individual 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, individuals 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 individual being treated. The individual being treated 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 individual'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

Glioblastoma

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 (Karnofsky Performance Status (KPS) ≥60) and either methylated or unmethylated/indeterminate MGMT promoter status, in whom maximal, safe 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). The guideline recommends that follow-up magnetic resonance imaging (MRI) of the brain be done 2 to 8 weeks after RT, then every 2–4 months for 3 years, then every 3–6 months indefinitely (NCCN, 2020).

Marenco-Hillembrand et al. (2020) conducted a systematic review to describe the current status and advances in the survival of patients with glioblastoma by analyzing median overall survival through time and between treatment modalities. Full-text glioblastoma papers with human subjects ≥ 18 years old and n ≥ 25 were included for evaluation. The central tendency of median overall survival (MOS) was 13.5 months (2.3-29.6) and cumulative 5-year survival was 5.8% (0.01%-29.1%), with a significant difference in survival between studies that predate versus postdate the implementation of temozolomide and radiation, [12.5 (2.3-28) vs 15.6 (3.8-29.6) months, P < 0.001]. Within clinical trials, the highest MOS involved tumor treating fields (TTF) with 20.7 (range 20.5–20.9) months. According to the authors, therapies such as TTF provide a means of prolonging the survival of glioblastoma patients.

Kim et al. (2020) reported on Korean newly diagnosed GBM patients who participated in the EF-14 trial. Thirty-nine participants of the EF-14 trial were enrolled at 8 sites in South Korea. Patients (24 TTFields/TMZ; 14 TMZ alone) received: TTFields (200 kHz) for > 18 h/day; TMZ at 120-150 mg for 5 days per a 28 day cycle. Safety and efficacy were assessed. Patient baseline characteristics were balanced in the 2 arms and the mean age was 52.1 years, 66.7% were male with a mean KPS of 90. Safety incidence was comparable between the 2 arms. In the TTFields/TMZ arm, 30% suffered from skin irritation versus 52% in the entire study population. No TTFields-related serious adverse events were reported. The median progression-free survival (PFS) in the TTFields/TMZ arm was 6.2 months (95% CI 4.2-12.2) versus 4.2 (95% CI 1.9-11.2) with TMZ alone (p = 0.67). Median overall survival was 27.2 months (95% CI 21-NA) with TTFields/TMZ versus 15.2 months (95% CI 7.5-24.1; HR 0.27, p = 0.01) with TMZ alone. The authors concluded that median overall survival and 1- and 2-year survival rates were higher with

TTFields/TMZ and similar to the entire EF-14 population. According to the authors, these results demonstrate the efficacy and safety of TTFields in in this population of newly diagnosed glioblastoma patients.

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.

Magouliotis et al. (2018) performed a systematic review on the literature for patients with glioblastoma treated with tumor-treating fields (TTFields) plus radio chemotherapy or conventional radio chemotherapy alone, to compare the efficacy and safety of the two methods. Six studies met the inclusion criteria incorporating 1806 patients for the qualitative analysis and 1769 for the quantitative analysis. This study reveals increased median overall survival at 1 year and 2 years and median progression-free survival along with progression-free survival at 6 months for the patients treated with TTFields. Survival at 3 years was comparable between the two groups. TTFields were associated with fewer adverse events compared to chemotherapy along with similar incidence of skin irritation. The authors indicated that this review suggests that TTFields are a safe and efficient novel treatment modality.

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 TTFields-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 TTFields-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.

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.

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 (monotherapy) 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.

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 TTFields 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.

Tumors Other Than Glioblastoma

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.

Ceresoli et al. (2019) conducted a prospective, single-arm, phase 2 trial (STELLAR study) with the aim to test the activity of tumor treating fields (TTFields) delivered to the thorax in combination with systemic chemotherapy for the front-line treatment of patients with unresectable malignant pleural mesothelioma. Patients were at least 18 years old, had an Eastern Cooperative Oncology Group performance status of 0-1, and at least one measurable or evaluable lesion according to modified Response Evaluation Criteria in Solid Tumors for mesothelioma. Patients received continuous TTFields at a frequency of 150 kHz to the thorax and concomitant chemotherapy with intravenous pemetrexed (500 mg/m2 on day 1) plus intravenous platinum (either cisplatin 75 mg/m2 on day 1 or carboplatin area under the curve 5 on day 1) every 21 days for up to six cycles. Patients not progressing after completion of chemotherapy received TTFields as maintenance treatment until progression, patient or physician decision, or unacceptable toxic effects. The primary endpoint of the trial was overall survival. Survival analyses were done in the intention-to-treat population, and safety analyses were done in all patients who received at least 1 day of TTFields treatment. A total of 80 patients were enrolled in the study. Median follow-up was 12·5 months. Median overall survival was 18·2 months (95% CI 12·1-25·8). The most common grade 3 or worse adverse events were anaemia (nine [11%] patients), neutropenia (seven [9%]), and thrombocytopenia (four [5%]). Skin reaction was the only adverse event associated with TTFields and was reported as grade 1-2 in 53 (66%) patients, and as grade 3 in four (5%) patients. No treatment-related deaths were observed. According to the authors, the trial showed encouraging overall survival results, with no increase in systemic toxicity. TTFields (150 kHz) delivered to the thorax concomitant with pemetrexed and platinum was an active and safe combination for front-line treatment of unresectable malignant pleural mesothelioma. The lack of a comparison group limits the conclusions that can be drawn from the study. The authors indicated that further investigation in a randomized trial is warranted.

NovoTAL™ Simulation System

There is limited published clinical 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., 2016), 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)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

The Optune Treatment Kit, formerly the NovoTTF-100A System, (Novocure) was approved by the FDA in April 2011, as a novel device to treat adults age 22 years or older with glioblastoma (GBM) that recurs or progresses after receiving chemotherapy and radiation therapy. 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=P100034. (Accessed July 24, 2020)

A supplemental FDA premarket approval was received in October 2015 for Optune with Temozolomide in adults with newly diagnosed, Supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. See the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100034S013. (Accessed July 24, 2020)

The FDA has approved a humanitarian device exemption (HDE) application for the NovoTTF™-100L System for mesothelioma. See the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf18/H180002B.pdf. (Accessed July 29, 2020)

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 24, 2020)

NovoTAL simulation software is not regulated by the FDA.

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for electric tumor treatment field therapy. Local Coverage Determinations (LCDs)/ Local Coverage Articles (LCAs) exist; see the LCDs/LCAs for Tumor Treatment Field Therapy (TTFT).

For any item to be covered by Medicare, it must 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. Refer to the Medicare Benefit Policy Manual, Chapter 15, §110 - Durable Medical Equipment - General.
(Accessed August 10, 2020)

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Policy History/Revision Information

Date	Summary of Changes
12/01/2020	Coverage Rationale *Proven/Medically Necessary* Newly Diagnosed Histologically-Confirmed Supratentorial Glioblastoma (GBM) • Revised language to indicate the use of U.S. Food and Drug Administration (FDA) approved devices to generate electric TTF when used according to FDA labeled indications, contraindications, warnings and precautions, and when all of the following criteria are met:

Date	Summary of Changes
	○ Treatment with radiation therapy has been completed; and ○ Individual is receiving Temozolomide *as the only cancer drug*; and ○ Individual has a Karnofsky Performance Status (KPS) score of ≥ 60 *or Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2*; and ○ *Individual has been counselled that the device must be worn at least 18 hours daily* **Radiologically Confirmed Recurrence of GBM in the Supratentorial Region of the Brain** • Revised language to indicate 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 *the only treatment*; and ○ Individual has a KPS score of ≥ 60 *or ECOG Performance Status ≤ 2*; and ○ *Individual has been counselled that the device must be worn at least 18 hours daily* **Subsequent Approval(s) for Continuation of Electric TTF** • Revised language to indicate subsequent approval(s) for continuation of electric TTF is based on: ○ Magnetic resonance imaging (MRI) scan has been performed ≤ *2* months prior to request and documents no evidence of disease progression; and ○ KPS score of ≥ 60 *or ECOG Performance Status ≤ 2*; and ○ Documentation that the individual has been *using* the device at least 18 hours daily ***Unproven/Not Medically Necessary*** • Added language to indicate the use of devices to generate electric tumor treatment fields (TTF) is unproven and not medically necessary when the [proven and medically necessary] criteria [in the policy] are not met and for all other indications *including but not limited to the following*: ○ *Treatment of tumors other than GBM* ○ *Use of electric TTF therapy with concurrent medical therapy (e.g., bevacizumab or chemotherapy) for treatment of recurrent GBM* **Documentation Requirements** • Updated required clinical information **Definitions** • Added definition of "Eastern Cooperative Oncology Group (EGOG) Performance Status" • Updated definition of "Supratentorial" **Supporting Information** • Updated *Clinical Evidence*, *FDA*, *CMS*, and *References* sections to reflect the most current information • Archived previous policy version 2019T0582E

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare 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 reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Medical 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.