Clinical Policy Bulletin:
Electric Tumor Treatment Fields

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Policy

Aetna considers devices to generate electric tumor treatment fields (ETTF) medically necessary as monotherapy for persons with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy.

Aetna considers devices to generate electric tumor treatment fields (ETTF) experimental and investigational for the treatment of other malignant tumors (e.g., breast, lung, melanoma, ovarian cancer, pancreatic cancer, and solid tumor brain metastases; not an all-inclusive list) and for all other indications because their effectiveness has not been established.

Background

Alternating electric fields, generated by insulated electrodes, have been reported to exhibit inhibitory effect on the growth rate of a variety of human and rodent tumor cell lines as well as malignant tumors in animals. This non-thermal effect selectively affects dividing cells while quiescent cells are left intact. There are 2 modes of action for these anti-tumoric effects: (i) arrest of cell proliferation, and (ii) destruction of cells while undergoing division. Both effects were observed when such fields were applied for 24 hours to cells undergoing mitosis that is oriented along the field direction. The 1st mode of action is manifested by interference with the proper formation of the mitotic spindle, while the 2nd mode of action results in rapid disintegration of the dividing cells. Both effects are consistent with the computed directional forces exerted by these specific fields on charges and dipoles within the dividing cells. In-vivo treatment of tumors in C57BL/6 and BALB/c mice resulted in significant slowing of tumor growth and extensive destruction of tumor cells within 3 to 6 days. These findings showed the potential applicability of alternating electric fields as a novel therapeutic modality for malignant tumors (Kirson et al, 2004).

Electric tumor treating fields (ETTF), also known as alternating electrical field therapy, are low-intensity (1 to 2 V/cm), intermediate-frequency (100 to 200 kHz), alternating electric fields employed for the treatment of malignant tumors. This novel treatment modality has shown promise in pilot clinical trials in patients with advanced stage solid tumors including glioblastoma (GBM). Current published evidence is primarily from a single investigator
Kirson et al (2007) reported the findings of a pilot clinical trial examining the effects of ETTF in 10 patients with recurrent GBM. Median time to progression (TTP) in these patients was 26.1 weeks and median overall survival (OS) was 62.2 weeks. The authors noted that these TTP and OS values were more than double the reported medians of historical control patients. No device-related serious adverse events (AEs) were seen after more than 70 months of cumulative treatment in all of the patients. The only device-related AE observed was a mild-to-moderate contact dermatitis beneath the field delivering electrodes. The authors concluded that ETTF are a safe and effective new treatment modality that effectively slows down tumor growth in-vitro, in-vivo, as well as in human cancer patients.

In a pilot study, Salzberg and colleagues (2008) evaluated the safety, tolerability, and effectiveness of ETTF treatment in patients with locally advanced or metastatic solid tumors using the NovoTTF-100A device. A total of 6 patients were heavily pre-treated with several lines of therapy; no additional standard treatment option was available to them. Electric tumor treating fields treatment using continuous NovoTTF-100A lasted a minimum of 14 days and was well-tolerated. No related serious AEs occurred. Outcomes showed 1 partial response of a treated skin metastasis from a primary breast cancer, 3 cases where tumor growth was arrested during treatment, and 1 case of disease progression. One mesothelioma patient experienced lesion regression near ETTF with simultaneous tumor stability or progression in distal areas. The authors concluded that although the number of patients in this study was small, the lack of therapy toxicity and the effectiveness observed in data gathered to date indicate the potential of ETTF as a new treatment modality for solid tumors, thus, warranting further investigation.

Kirson et al (2009) reported the findings of 20 GBM patients who were treated with ETTF for a median duration of 1 year. No ETTF-related systemic toxicity was observed in any of these patients, nor was an increase in temozolomide toxicity seen in patients receiving combined treatment. In newly diagnosed GBM patients, combining ETTF with temozolomide treatment led to a progression-free survival of 155 weeks and OS of 39+ months. The authors concluded that these results suggest that combining ETTF with chemotherapeutic cancer treatment may increase chemotherapeutic efficacy and sensitivity without increasing treatment related toxicity.

Recent reviews indicated the ETTF is a promising approach for the treatment of GBM and non-small cell lung cancer. Stupp and Weller (2010) noted that novel treatment approaches in recurrent GBM include anti-angiogenic agents (e.g., bevacizumab and cilengitide) as well as ETTF (NovoTTF). Furthermore, Pless and Weinberg (2011) reviewed in-vitro and in-vivo pre-clinical studies, showing the activity of ETTF both as a monotherapy as well as in combination with several cytotoxic agents. They also summarized the clinical experience with ETTF, mainly in 2 indications: (i) recurrent GBM: in a prospective randomized phase III trial, ETTF was compared with best standard care (BSC, including chemotherapy): ETTF significantly improved median OS compared with standard therapy (7.8 versus 6.1 months) for the patients treated per protocol (Stupp et al, 2010; published as an abstract). Importantly, quality-of-life was also better in the ETTF group (Ram et al, 2010); (ii) a phase II study of second-line treatment of non-small cell lung cancer, where ETTF was administered concomitantly with pemetrexed. This combination resulted in an excellent median OS of 13.8 months (Pless et al, 2010; published as an abstract). Interestingly, the progression-free survival (PFS) within the area of the ETTF was 28 weeks; however, outside the ETTF the PFS was only 22 weeks. This is an important finding because it can be assumed that in the same patient the higher tumor control within the TTFields area was a specific effect of TTFields. Median OS was 13.8
months and 1-year survival was 57%; 6 patients (14.6%) had a radiological partial remission and 16 patients had stable disease (39%). The authors stated that these results are promising and compare well with matched historical controls treated with pemetrexed alone in second-line treatment. The authors stated that the proof of concept of ETTF has been demonstrated in the pre-clinical setting, and the clinical data seem promising in various tumor types. The side effects of ETTF were minimal and in general consisted of skin reaction to the electrodes. The authors said that there are a number of ways in which ETTF could be further evaluated, for example, in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible. The authors concluded that while more clinical data are clearly needed, ETTF is an emerging and promising novel treatment concept (Pless and Weinberg, 2011).

On April 15, 2011, the Food and Drug Administration (FDA) approved the NovoTTF-100A System (Novocure, Portsmouth, NH) for the treatment of adults with GBM that recurs or progresses after receiving chemotherapy and radiation therapy. The NovoTTF-100A System is not intended to be used in combination with other cancer treatment. It should only be used after other treatments have failed. The FDA-approved indication for use is: "The NovoTTF-100A System is intended as treatment for adult patients (22 years of age or older) with histologically confirmed glioblastoma multiforme (GBM), following histologically or radiologically confined recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted."

The approval was based on data presented to the FDA from a multi-national, randomized, controlled study. The expedited pre-market approval (PMA) includes a requirement for a post-market non-randomized, unblinded, concurrent control study of NovoTTF-100A in patients with recurrent GBM. The primary question to be addressed by the study (FDA, 2011): "Is the overall survival of patients treated with NovoTTF-100A non-inferior to the survival of patients treated with the best standard of care (chemotherapy)?"

The first randomized clinical study of electric tumor treatment fields did not reach its primary end-point of improved survival compared to active chemotherapy (Stupp, et al., 2012; Novocure, 2012). This study was funded and sponsored by the device manufacturer, Novocure, Ltd. Subjects for this study were age 18 years or older with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) with radiologically confirmed disease progression. Patients had a Karnofsky performance status greater than or equal to 70 percent, and adequate hematologic, renal and hepatic function (absolute neutrophil count greater than or equal to 1000/mm3, hemoglobin greater than or equal to 100g/L, platelet count greater than or equal to 100,000/mm3, serum creatinine level less than or equal to 1.7 mg/dL, total serum bilirubin less than or equal to the upper limit of normal, and liver function values less than three times the upper limit of normal. Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temozolomide). Patients with infra-tentorial tumor location were excluded, as were patients with implanted electronic medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt). Patients were randomized in a 1:1 ratio to receive either NovoTTF-100A without chemotherapy or the physician's choice of active chemotherapy (active control). Chemotherapy agents considered as best standard care (BSC) during the study included platinum-based chemotherapy (i.e., carboplatin); nitrosoureas; procarbazine; combination of procarbazine, lomustine and vincristine; temozolomide; and bevacizumab. For patients assigned to Novo-TTF, uninterrupted treatment was recommended, although patients were allowed to take treatment breaks of up to an hour, twice per day, for personal needs (e.g. shower). In addition, patients assigned to Novo-TTF were allowed to take 2–3 days off treatment at the end of each of 4
week (which is the minimal required treatment duration for TTF therapy to reverse tumor growth). A period of 28 days of treatment with ETTF was considered 1 full treatment course. The primary end point of the study was overall survival. Secondary end points included progression free survival rates at 6-months; median time to progression (TTP), 1-year survival rate; quality-of-life; and radiological response. Subjects 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 subjects’ caregivers were used to evaluate subject mortality rates.

A total of 28 clinical centers enrolled 237 adult subjects with 120 subjects randomized to the NovoTTF treatment group and 117 subjects randomized to the BSC group (Stupp, et al., 2012; Novocure, 2012). A total of 30 subjects never started on trial (4 in the treatment group and 26 in the BSC group); 207 subjects started on trial, with 79 % discontinuation rate (n = 47 deaths; n = 49 deterioration of condition; and n = 68 study requirements of 2 additional clinic visits after disease progression were completed). Consent was withdrawn before completing 2 months of post-progression follow-up in 20 subjects. Adverse events led to 20 additional subject withdrawals. Non-compliance with follow-up was attributed to 3 subjects. The proportions were similar between the NovoTTF-100A group and the BSC group of subjects who did not complete the protocol-defined follow-up due to withdrawal of consent, non-compliance, or AEs. An average of 4.2 months of TTF treatment per subject was completed for the 116 subjects in the active treatment cohort. Complete vital statistics were known for 93 % (221 subjects) at the end of the study. There were 202 known deaths and 19 subjects (ETTF = 9; BSC = 10) were still alive 6 months after the last subject was randomized. Sixteen (7 %) subjects were lost to follow-up.

The trial did not reach its primary end-point of improved survival compared to active chemotherapy (Stupp, et al., 20112; Novocure, 2012). In addition, differences in response rates, progression-free survival at 6 months, and reduction in risk of death were not statistically significant. Quality of life analyses favored ETTF therapy in most domains. The differences in median overall survival between patients in the NovoTTF-100A group and the BSC group were not statistically significant. According to the FDA, the median OS is 6.3 months (95 % confidence interval [CI]: 5.6 to 7.8) in the NovoTTF-100A group and 6.4 months (95 % CI: 5.2 to 7.4) in the BSC group (log rank p = 0.98; Wilcoxon p = 0.72). The hazard ratio is 1.0 (95 % CI: 0.76 to 1.32) (test for proportional hazards p = 0.45). In the active chemotherapy control arm of the trial, survival was not significantly affected by the choice of chemotherapy. The Kaplan-Meier survival curve for the two treatment groups appeared to be very similar during the first 12 months of followup. Between 12 and 24 months, the survival curves separated slightly in favor or the BSC control group. There were no statistically significant differences in secondary endpoints of one-year survival, progression-free survival, radiologic response rates, and median time to tumor progression (TTP). Mild to moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16% of ETTF patients. Patients receiving active control chemotherapy experienced toxicity related to pharmacologic mechanism of the agents used: gastrointestinal (30% vs. 8%), hematological (19% vs. 4%) and infectious (12% vs. 4%). Longitudinal Quality of Life (QOL) was available in only 27 percent of subjects (63 patients) who remained on study therapy for three months and for whom QOL data were available. In the domains of global health and social functioning, no meaningful differences between chemotherapy and ETTF were observed. However, cognitive, emotional, and role functioning favored ETTF, whereas physical functioning favored chemotherapy. Symptom scale analysis is in accordance to treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea and vomiting were directly related to the
chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the ETTF treatment group.

Commenting on the trial by Stupp, et al., Debonis, et al. (2012) stated that the study was designed for superiority; although well conducted, it might not have shown it for a limited compliance in the ETTF group. Debonis, et al. (2012) stated that, even with this limitation, the trial by Stupp, et al. has shown at least equivalence of ETTF to chemotherapy, with a decreased toxicity and increased quality of life favoring ETTF.

The manufacturer initiated a subsequent randomized clinical trial enrolling newly diagnosed glioblastoma patients after completion of standard radiochemotherapy, parallel to starting the adjuvant or maintenance temozolomide chemotherapy (Stupp, et. al., 2012). Patients randomized to the experimental arm received ETTF in addition to maintenance temozolomide. In an abstract, Stupp, et al. (2014) reported on an interim analysis of this international, multicenter, prospective, randomized phase III trial in newly diagnosed GBM patients. After completion of radiotherapy (RT) with concomitant temozolomide (TMZ), patients were randomized (2:1) to adjuvant TMZ with NovoTTF or adjuvant TMZ alone. The primary endpoint was progression-free survival (PFS), with overall survival (OS) an important secondary endpoint. Analysis was by intention to treat. The investigators reported on a pre-specified interim analysis of the first 315 patients randomized, after a minimum follow-up of 18 months (range 18-60 months). Investigators randomized 210 patients NovoTTF/TMZ and 105 to TMZ alone. Patient characteristics were balanced: median age 57 and 58 years, tumor resection in 89 and 90%, KPS 90%, for the NovoTTF and the control arms, respectively. MGMT promoter methylation status was assessable centrally in 60% of patients; of these 39% and 41% were methylated. Adverse events (AE) were comparable between treatment arms. The most common device-related AE was skin irritation in 45% of patients (all grades, severe 2%). Severe seizures were observed at a frequency of 7% in both arms. Median PFS was 7.1 months [mo] (95% confidence interval [CI] 5.9-8.2) and 4.0 mo (CI 3.0-4.3; Hazard ratio 0.63, p = 0.001), OS was 19.6 mo (CI 16.5-24.1) and 16.6 mo (CI 13.5-19.1) (HR 0.75, p = 0.034), both favoring NovoTTF. This translates into a 24-mo survival rate of 43% (CI 36-50%) and 29% (CI 21-39%) for the NovoTFF/TMZ and the TMZ alone arm, respectively. The investigators stated that the trial met its primary and main secondary endpoints, and was closed to accrual after this interim analysis. The investigators concluded that adjuvant TMZ chemotherapy and NovoTTF provides a clinically and statistically significant improvement in progression-free and overall survival, and should become the new standard of care against GBM.

The National Comprehensive Cancer Network (NCCN, 2013) had a Category 2B recommendation to consider the use of ETTF for persons with local, diffuse or multiple recurrences of glioblastoma. This was changed to a Category 3 recommendation in 2014 (NCCN, 2014). NCCN guidelines explain that approval of tumor treating fields (TTF) for recurrent glioblastoma was based on results of a clinical trial that randomized 237 patients to TTF or chemotherapy. Similar survival was observed in the two arms, and TTF therapy was associated with lower toxicity and improved quality of life. Due to the lack of efficacy, not all NCCN Panelists recommended the treatment. This was subsequently changed to a category 2B recommendation in 2015 (NCCN, 2015).

Medicare Durable Medical Equipment Medicare Administrative Contractor (DME MAC) considers tumor treatment field therapy not reasonable and necessary for Medicare beneficiaries (NHIC, 2014).

Electric tumor treating fields technology is also being studied as a treatment for other solid tumors (e.g., melanoma and non-small cell lung cancer). However, there is a paucity of published evidence from randomized controlled trials examining the long-term safety and
effectiveness of ETTF as a treatment of tumors.

Davis et al (2013) stated that the anti-mitotic effect of tumor treating fields (TTFields) therapy has been demonstrated in multiple cell lines when the appropriate frequency was utilized. A phase III trial of TTFields monotherapy compared to active chemotherapy in recurrent glioblastoma patients established that TTFields therapy is associated with minimal toxicity, better quality of life, and comparable efficacy to chemotherapy. Ongoing and future trials will evaluate TTFields in newly diagnosed glioblastoma, solid tumor brain metastases, non-small cell lung cancer, and ovarian and pancreatic cancers.

CPT Codes / HCPCS Codes / ICD-9 Codes

HCPCS codes not covered for indications listed in the CPB:

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-9 codes not covered for indications listed in the CPB:

147.0 - 147.9  Malignant neoplasm of nasopharynx
150.0 - 150.9  Malignant neoplasm of esophagus
151.0 - 151.9  Malignant neoplasm of stomach
153.0 - 153.9  Malignant neoplasm of colon
154.0 - 154.8  Malignant neoplasm of rectum, rectosigmoid junction, and anus
155.1  Malignant neoplasm of intrahepatic bile duct
156.0 - 156.9  Malignant neoplasm of gall bladder and extrahepatic bile duct
157.0 - 157.9  Malignant neoplasm of pancreas
160.2 - 160.9  Malignant neoplasm of accessory sinuses (paranasal)
162.0 - 162.9  Malignant neoplasm trachea, bronchus, and lung
164.0  Malignant neoplasm of thymus
171.0 - 171.9  Malignant neoplasm of connective and other soft tissue
172.0 - 172.9  Malignant neoplasm of skin
174.0 - 174.9  Malignant neoplasm of female breast
175.0 - 175.9  Malignant neoplasm of male breast
176.1  Kaposi's sarcoma, soft tissue
180.0 - 180.9  Malignant neoplasm of cervix uteri
182.0 - 182.8  Malignant neoplasm of body of uterus
183.0  Malignant neoplasm of ovary
183.2  Malignant neoplasm of fallopian tube
185  Malignant neoplasm of prostate
189.0 - 189.9  Malignant neoplasm of kidney and other and unspecified urinary organs
191.0 - 191.9  Malignant neoplasm of brain [World Health Organization grade IV astrocytomas]
193  Malignant neoplasm of thyroid gland
198.3  Secondary malignant neoplasm of brain and spinal cord [solid tumor brain metastases]
230.0 - 234.9  Carcinoma in situ

The above policy is based on the following references:

11. U.S. Food and Drug Administration (FDA). FDA approves new medical device for form of brain cancer. FDA News. Rockville, MD: FDA; April 15, 2011. Available at:


28. NHIC, Inc. Local Coverage Determination (LCD) for Tumor Treatment Field Therapy (TTFT) (L34730). Durable Medical Equipment Medicare Administrative Contractor (DME MAC) Jurisdiction A. Hingham, MA: NHIC; June 6, 2014.

29. NHIC, Inc. Local Coverage Article for Tumor Treatment Field Therapy (TTFT) – Policy Article – Effective August 2014 (A52680). Durable Medical Equipment
Medicare Administrative Contractor (DME MAC) Jurisdiction A. Hingham, MA: NHIC; August 1, 2014.
