MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**TUMOR–TREATMENT FIELD THERAPY FOR GLIOBLASTOMA**
Policy Number	**6.01.45**
Category	**Technology Assessment**
Effective Date	**05/28/15**
Revised Date	**08/18/16, 08/17/17, 04/19/18, 03/21/19, 03/19/20**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.* • *If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*

POLICY STATEMENT

I. Based upon our criteria and assessment of peer-reviewed literature, alternating electrical field therapy (Tumor-Treatment Field (TTF) therapy) using Optune® (Novocure Inc, Portsmouth, New Hampshire) for treatment of recurrent Glioblastoma multiforme (GBM) is considered **medically appropriate** when all of the following criteria have been met:
   A. First or second recurrence of GBM; and
   B. The patient has a Karnofsky Performance Status (KPS) of 90 or greater; and
   C. The patient has not received prior treatment with Bevacizumab; and
   D. The device is to be used as monotherapy after failure of standard medical therapy (e.g., chemotherapy, surgery, and radiation therapy); and
   E. There is documented evidence the patient is compliant with the TTF device during a one month trial period. Compliance is defined as use of the device for 18 hours or more per day during the one-month trial period.

II. Based upon our criteria and assessment of peer-reviewed literature, alternating electrical field therapy (Tumor-Treatment Field (TTF) therapy) using Optune® for treatment of newly diagnosed Glioblastoma multiforme (GBM) is considered **medically appropriate** when both of the following criteria have been met:
   A. The device is to be used as an adjunct with the chemotherapy drug temozolomide (TMZ); and
   B. The therapy follows standard treatments that include maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

POLICY GUIDELINES

I. The Optune® (Novocure Inc, Portsmouth, New Hampshire) will be allowable for up to six months if the patient is compliant with the regimen. Continued use after six months will require additional documentation to show no progression in the patient's condition.

II. The Optune® is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM).

III. The Optune® was approved by the U.S. Food and Drug Administration (FDA) in April 2011 to deliver TTF therapy. It is intended as a treatment for adult patients (22 years of age or older) with confirmed glioblastoma multiforme, following confirmed recurrence in an upper region of the brain (supratentorial) after receiving chemotherapy. The device is intended to be used as a stand-alone treatment, and as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.

IV. The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

V. The Optune® was approved by the FDA in October 2015 to deliver TTF therapy and is intended as a treatment for adult patients (22 years of age or older) with newly-diagnosed glioblastoma multiforme when given along with the chemotherapy drug temozolomide following standard treatments that include surgery, and radiation therapy and chemotherapy used together.

DESCRIPTION

Glioblastoma multiforme (GBM) is the most common and aggressive primary intracranial tumor with approximately 33% surviving one year and less than 5% surviving more than five years. Median survival with optimal therapy has been reported to be 10 to 15 months with most tumors recurring within seven to nine months despite multimodal treatment (e.g. repeat surgery, re-irradiation and chemotherapy). Choice of chemotherapy for treatment in the case of recurrence varies but may include alkylating agents (e.g., lomustine, carmustine, procarbazine), re-treatment with temozolomide, and more recently, bevacizumab either alone or in combination with other agents. Overall survival after recurrence is relatively short even with optimal therapy. New or novel treatments such as TTF therapy are being investigated to improve survival in patients with GBM.

TTF therapy is delivered via the Optune® which is a battery-powered, portable device that generates alternating low intensity, intermediate electrical fields (100-300 kHz) by four disposable electrode arrays (replaced one to two times per week) which are noninvasively attached to the patient's shaved scalp placed in such a way to encompass the tumor. The alternating low intensity electrical field is thought to disrupt cell division of the cancer cells so that either cell division does not occur or it is ineffective, resulting in death of the cancer cells without harming the normal healthy cells. The device is used by the patient at home on a continuous basis (20-24 hours per day) for the duration of treatment, which can last for several months. Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

RATIONALE

The FDA approval of the Optune® device NovoTTF-100A system, was based on a phase 3, multinational prospective RCT (Stupp et al., 2012). Participating in the study were 237 patients with relapsed or progressive glioblastoma multiforme (GBM), despite conventional radiotherapy who were randomized in a 1:1 ratio to receive TTF therapy (delivered by the NovoTTF-100A System) only (n=120) or the best standard of care chemotherapy (active control) (n=117). The choice of chemotherapy regimens varied, reflecting local practice at each of the 28 participating clinical centers which were across seven countries. Patient characteristics were balanced in both groups, with median age of 54 years and median Karnofsky Performance Status (KPS) score of 80%. More than 80% of participants had failed two or more prior chemotherapy regimens, and 20% had failed bevacizumab prior to study enrollment. Ninety-seven percent (116) of 120 participants in the TTF group started treatment and 93 participants (78%) completed one cycle (four weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%) 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 active control group, 113 (97%) of the 117 assigned participants received chemotherapy, and all but one individual completed a full treatment course. Twenty-one participants (18%) in the active control group did not return to the treating site and details on disease progression and toxicity were not available. This RCT did not reach its primary end point of improved survival compared with active chemotherapy. With a median follow-up of 39 months, 220 participants (93%) had died. Median survival was 6.6 months in the TTF group compared with 6.0 months in the active control group (hazard ratio, 0.86; 95% confidence interval [CI], 0.66 to 1.12; p=0.27). For both groups, one-year survival was 20%. The survival rates for two- and three-year survival were 8% and 4%, respectively, for the TTF group versus 5% and 1%, respectively, for the active control group. PFS rate at six months was 21.4% in the TTF group, compared with 15.1% in the active control group (p=0.13). Objective radiologic responses (partial and complete response) were noted in 14 participants in the TTF group and seven in the active control group, with a calculated response

rate of 14.0% (95% CI, 7.9% to 22.4%) versus 9.6% (95% CI, 3.9% to 18.8%), respectively. Sixteen percent of the TTF participants had grade 1 and 2 contact dermatitis on the scalp, which resolved with

topical corticosteroids. Active control group participants experienced grade 2 to 4 events by organ system related to the pharmacologic activity of chemotherapy agents used; severe (grades 3 and 4) toxicity was observed in 3% of participants. Longitudinal quality of life (QOL) data were available in 63 participants (27%). There were no meaningful differences observed between the groups in the domains of global health and social functioning. However, cognitive, emotional, and role functioning favored TTF therapy, whereas physical functioning favored chemotherapy. Symptom scale analysis was in accordance with treatment-associated toxicity; appetite loss, diarrhea, constipation, nausea, and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue were reported in the chemotherapy-treated patients and not in the TTF group. In summary, this RCT failed to demonstrate the primary end point of improved survival with TTF therapy in comparison to chemotherapy. Limitations of the trial included a somewhat heterogeneous patient population, with participants included after progression of one or several lines of chemotherapy, as well as the use of different chemotherapy regimens in the control group. Another limitation was the absence of a placebo/supportive care arm. In the setting of advanced disease, the supportive care arm would have been useful to gauge the safety and efficacy of treatment for both groups of patients. Treatments used in the active control arm (best standard of care chemotherapy) in the recurrent disease setting have previously demonstrated limited efficacy, thus limiting the ability to determine the true treatment effect of TTF. Data from a trial of TTF versus placebo, or TTF plus standard chemotherapy versus standard chemotherapy alone, would, therefore, provide a better assessment of treatment efficacy.

A subgroup analysis of patient data of this phase 3 trial (Wong et al, 2014) evaluated the different characteristics of responders and nonresponders in the TTF group compared to the active control group. More patients in the TTF arm were considered responders (14/120 vs 7/117 in the chemotherapy arm.) Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months vs 5.6 months, $p<0.001$), and there was a strong correlation (Pearson's *r*) between response and OS in the TTF arm ($p<0.001$) but not in chemotherapy arm ($p=0.29$). Compared with the chemotherapy arm, a higher proportion of responders in the TTF arm had a prior low-grade histology (36% vs 0%). These differences in treatment responder groups suggest that TTF therapy may differentially benefit certain types of GBM; however, the small numbers of responders in both groups limits generalizations that can be drawn from this analysis.

An analysis of the NovoTTF-100A™ Patient Registry Dataset (PRiDe) of 457 patients with recurrent GBM who were treated with NovoTTF therapy in the United States between October 2011 and November 2013 and a comparison to patient data in the Phase 3 trial were performed (Mrugula et al 2014) to provide a larger dataset of patients with recurrent GBM treated with TTF therapy. No new adverse events in the PRiDe group of patients were reported compared to the Phase 3 trial group. However median overall survival was longer in the TTF group in the PriDe group (9.6 months) compared to the TTF group in the Phase 3 trial (6.6 months) or to the active chemotherapy group in the Phawe 3 trial (6.0 months). Median treatment time was almost double for the TTF PriDe group compared to either the TTF or chemotherapy group in the Phase 3 trial. Favorable prognostic factors in the PriDe group included 75% or more daily compliance of the device, treatment with TTF at first recurrence, no prior treatment with bevacizumab, and Karnofsky Performance Score (KPS) 90 or greater. The authors suggested there are subsets of patients who derive significant benefit from TTF therapy and that TTF therapy using the NovoTTF-100A™ device is safe and efficacious to treat recurrent GBM.

The FDA approval of the Optune® device, formally, the NovoTTF-100A system for newly diagnosed glioblastoma multiforme (GBM) was based on the results from a clinical trial involving 695 patients newly diagnosed with GBM. The study compared those who used the device with temozolomide (TMZ) to those receiving TMZ alone (Stupp, 2015). Patients who used the device along with TMZ lived, on average, about seven months with no disease progression compared to four months for those who had the drug alone. The device plus TMZ group survived for an average of 19.4 months after starting treatment compared to 16.6 months for those who were treated with TMZ alone.

The use of TTF therapy has been described in a number of case series. However, without evidence from additional high quality comparative studies, these studies provide limited additional evidence about whether TTF therapy improves outcomes compared with currently available therapy for GBM.

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Central Nervous System (v 1.2016) states that alternating electrical field therapy for glioblastoma may be considered as a treatment option for recurrent disease (Category 2A).

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*

CPT Codes

Code	Description
There are no specific CPT codes for tumor treatment field therapy	

HCPCS Codes

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

ICD10 Codes

Code	Description
C71.0-C71.9	Malignant neoplasm of brain (code range)

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*Key Article

KEY WORDS

Electric field therapy, NovoTTF-100A, glioblastoma.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Tumor Treatment Field Therapy. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34823&ver=27&CntrctrSelected=389*1&Cntrctr=38you+do+finger9&s=41&DocType=Active&bc=AggAAAIAgAAA&