MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Tumor-Treatment Fields Therapy**
Policy Number	**6.01.45**
Category	**Technology Assessment**
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Committee Approval Date	**08/18/16, 08/17/17, 04/19/18, 03/21/19, 03/19/20, 03/18/21, 03/24/22, 03/23/23, 03/21/24**
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Product Disclaimer	• *Services are contract dependent; 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 or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) 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.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, alternating electrical field therapy (tumor-treatment field (TTF) therapy) using Optune (Novocure, Portsmouth, New Hampshire) for treatment of recurrent glioblastoma multiforme (GBM) has been medically proven to be effective and, therefore, is considered **medically appropriate**, when **ALL** of the following criteria have been met:
   A. The patient has had a first or second recurrence of GBM;
   B. The patient has a Karnofsky Performance Status (KPS) of 60 or greater;
   C. The patient has not received prior treatment with Bevacizumab;
   D. The device is to be used as monotherapy after failure of standard medical therapy (e.g., chemotherapy, surgery, and/or radiation therapy);
   E. There is documented evidence that the patient is compliant with the TTF device during a (1) month trial period. Compliance is defined as use of the device for 18 hours or more per day during the one (1) month trial period.

II. Based upon our criteria and assessment of the peer-reviewed literature, TTF therapy using Optune for treatment of newly diagnosed GBM has been medically proven to be effective and, therefore, 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.

III. Based upon our criteria and the lack of peer-reviewed literature, TTF therapy is considered **investigational** for all other indications, including, but not limited to, mesothelioma.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

POLICY GUIDELINES

I. The Optune (Novocure) will be initially allowed for up to six (6) months if the patient is compliant with the regimen. Continued use after six (6) months will require additional documentation that there has been no progression in the patient's condition.

II. The Optune is intended as a treatment for adult patients (aged 22 years or older) with histologically-confirmed GBM.

III. The Optune was approved by the United States Food and Drug Administration (FDA) in April 2011, to deliver TTF therapy to adult patients (aged 22 years or older) with confirmed GBM, 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, as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted.

IV. The Optune was approved by the FDA in October 2015 to deliver TTF therapy to adult patients (aged 22 years or older) with newly-diagnosed GBM. The device is intended to be 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% of patients surviving one year and less than 5% surviving more than five (5) 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 (4) disposable electrode arrays (replaced one (1) to two (2) times per week) that are non-invasively attached to the patient's shaved scalp, placed in such a way as 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-to-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 conducting activities of daily living.

RATIONALE

The United States Food and Drug Administration (FDA) approval of the Optune NovoTTF-100A system, was based on a phase three (3), multi-national, prospective, randomized, controlled trial (RCT) (Stupp et al., 2012). Participating in the study were 237 patients with relapsed or progressive 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 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 the 120 participants in the TTF group started treatment, and 93 participants (78%) completed one (1) cycle (four weeks) of therapy. Discontinuation of TTF therapy occurred in 27 participants (22%), due to noncompliance or the inability to manage 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. Progression Free Survival (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) were noted in 14 participants in the TTF group and seven (7) 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 was available for 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 of 120, versus seven (7) of 117 in the chemotherapy arm). Median response time was longer for those in the TTF arm than the chemotherapy arm (7.3 months versus 5.6 months, p<0.001), and there was a strong correlation (Pearson's *r*) between response and overall survival in the TTF arm (p<0.001), but not in the 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 data set 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 Phase 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 with the device, treatment with TTF at first recurrence, no prior treatment with bevacizumab, and Karnofsky Performance Score (KPS) 90 or greater. The authors suggested that 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 (formerly called the NovoTTF-100A system) for newly diagnosed GBM was based on the results from a clinical trial involving 695 patients who were 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 (7) months with no disease progression, compared to four (4) 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 National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Central Nervous System Cancers V.1.2023 states that due to lack of clear efficacy data, the panel is divided about recommending alternating electric field therapy for the treatment and re-irradiation of recurrent glioblastoma.

In 2019, through the humanitarian device exemption (HDE) process, the FDA approved the Optune Lua system (formerly called the NovoTTF-100L) for treatment of adult patients with unresectable, locally advanced or malignant pleural mesothelioma (MPM), to be used concurrently with pemetrexed and platinum-based chemotherapy (the current gold-standard of treatment). The decision was based on the results of the industry-designed and sponsored STELLAR trial (NCT02397928), which was summarized by Ceresoli et al. This was a prospective, single-arm, multi-center study of 80 participants treated between 2015 and 2018, who had inoperable, previously untreated MPM. The primary endpoint of the trial was overall survival, which was measured from time of diagnosis until date of death. Fifty patients (63%) were treated with a carboplatin and pemetrexed combination with TTF, and 30 patients (37%) received cisplatin and pemetrexed with TTF. Median overall survival was 18.2 months (95% CI 12.1-25.8) and comparable to other recent study results for median overall survival of chemotherapies for treatment of MPM. Even though the median overall survival, objective responses, and progression-free survival results did not appear to be impacted with TTF therapy, the similar outcomes reported in this study were achieved without an increase in systemic toxicity. Thirty-two patients did have severe adverse events during the trial period, which is also consistent with other trials of pemetrexed (anemia, neutropenia, and skin reaction being the most common). The majority of patients did have mild medical device reactions at the site of array adherence on the skin. This study's small sample size, lack of a control group, and lack of quality of life assessment did not provide enough information to draw conclusions on the efficacy of this therapy versus standard medical treatment. Further randomized clinical trials are needed.

The NCCN Clinical Practice Guidelines for Malignant Pleural Mesothelioma V.1.2024 do not reference TTF therapy as a treatment for this indication. In addition to malignant pleural mesothelioma, TTF is being investigated in non-small cell lung cancer, brain metastases from non-small cell lung cancer, pancreatic cancer, ovarian cancer, hepatocellular carcinoma and gastric adenocarcinoma. Future studies are warranted to determine the impact of TTF on the net health outcome.

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.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/appropriate = (NMN).*

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

Code	Description
E0766	Electrical stimulation device used for cancer treatment, includes all accessories, any type

ICD10 Codes

Code	Description
C45.0-C45.9	Mesothelioma (code range)
C71.0-C71.9	Malignant neoplasm of brain (code range)

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*Key Article

KEY WORDS

Electric field therapy, NovoTTF-100A, glioblastoma, Optune, Optune Lua

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD)(L34823) 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& accessed 02/02/2024.