MEDICAL POLICY

POLICY TITLE	**TUMOR TREATING FIELDS THERAPY (FORMERLY TUMOR-TREATMENT FIELDS THERAPY FOR GLIOBLASTOMA)**
POLICY NUMBER	**MP 6.054**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**3/1/2024**

I. POLICY

For newly diagnosed Glioblastoma when used in adjuvant treatment:
Tumor Treating Fields Therapy (TTF) may be considered **medically necessary** for adult individuals (22 years of age or older) with newly diagnosed glioblastoma, when the ALL of the following criteria are met:

- Histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma)
- Tumor located in the supra-tentorial region of the brain
- Karnofsky Performance Status score 60 or higher
- Completed standard therapeutic options, such as maximum safe debulking surgery, concomitant temozolomide, or radiotherapy
- TTF is prescribed with adjuvant temozolomide (maintenance)
- Willingness to use the TTF device daily for at least 18 hours

For recurrent Glioblastoma when used as a monotherapy:
Tumor Treating Fields Therapy (TTF) may be considered **medically necessary** when used as a monotherapy for adult individuals (22 years of age or older) with recurrent glioblastoma, when ALL of the following criteria are met:

- Histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma)
- Tumor located in the supra-tentorial region of the brain
- Karnofsky Performance Status score 60 or higher
- Completed standard therapeutic options, such as maximum safe debulking surgery or systemic chemotherapy or irradiation
- Willingness to use the TTF device daily for at least 18 hours
- No contraindications for TTF use

TTF is considered **not medically necessary** for individuals with glioblastoma who have any of the following: an implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted devices in the brain, documented clinically significant arrhythmias, or

evidence of increased intracranial pressure.

All other uses of TTF are considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

Policy Guidelines

Karnofsky Performance Scale

Value	Level of Functional Capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work; no special care needed
90	Able to carry on normal activity; minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do active work	Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed
60	Requires occasional assistance but is able to care for most needs	
50	Requires considerable assistance and frequent medical care.	
40	Disabled, requires special care and assistance	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly
30	Severely disabled, hospitalization is indicated although death is no imminent	
20	Hospitalization is necessary, very sick, active support treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

TOP

Glioblastome Multiforme

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. Glioblastomas are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (eg, bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 49.1% of all primary malignant brain tumors. Mean age at GBM diagnosis is 65 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; the 5-year survival rate and average length of survival is estimated at 6.9% and 8 months, respectively.

Treatment of Newly Diagnosed Glioblastoma Multiform

The primary treatment for patients newly diagnosed with GBM is to resect the tumor to confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. If total resection is not feasible, subtotal resection and open biopsy are options. During surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bis-chloroethylnitrosourea) impregnated wafer. Due to the poor efficacy of local treatment, postsurgical treatment with adjuvant radiotherapy (RT), chemotherapy (typically temozolomide), or a combination of these 2 therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for 5 days of every 28-day cycle for 6 cycles. Response and overall survival rates with temozolomide are higher in patients who have O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation.

Prognostic factors for therapy success are age, histology, performance status or physical condition of the patient, and extent of resection. National Comprehensive Cancer Network recommendations include patient age and Karnofsky Performance Status score as important determinants of postsurgical treatment choice (see the Supplemental Information section). For patients with good performance status, the most aggressive treatment (standard RT plus temozolomide) is recommended. For patients with poor performance status, only single treatment cycles or even palliative or supportive care are recommended. Hypofractionated RT is indicated for patients with poor performance status because it is better tolerated, and more patients are able to complete RT.

Treatment of GBM is rarely curative, and tumors will recur in essentially all patients.

Treatment of Recurrent Glioblastoma Multiforme

When disease recurs, additional debulking surgery may be used if the recurrence is localized. Due to radiation tolerances, re-radiation options for patients with recurrent GBM who have previously received initial external-beam RT are limited. There is no standard adjunctive treatment for recurrent GBM. Treatment options for recurrent disease include various forms of systemic medications such as the antivascular endothelial growth factor drug bevacizumab, alkylating agents such as nitrosoureas (eg, lomustine, carmustine), or retreatment with temozolomide. Medical therapy is associated with side effects that include hematologic toxicity, headache, loss of appetite, nausea, vomiting, and fatigue. Response rates in recurrent disease are less than 10%, and the progression-free survival rate at 6 months is less than 20%. There is a need for new treatments that can improve survival in patients with recurrent GBM or reduce the side effects of treatment while retaining survival benefits.

Malignant Pleural Mesothelioma

Malignant pleural mesothelioma (MPM) is an aggressive tumor that is associated with significant morbidity and mortality. It is associated with asbestos exposure and has a latency period of about 40 years after asbestos exposure. Recommendations for treatment are mainly chemotherapy as first line with pemetrexed plus platinum. Surgical cytoreduction is also recommended in selected patients with early-stage disease. Adjuvant radiation can be offered for patients who have resection of intervention tracts found to be histologically positive or for palliation of symptomatic patients.

Tumor Treating Fields Therapy

Tumor treating fields therapy (TTF), also known as alternating electric fields, is a noninvasive technology intended to treat GBM and malignant pleural mesothelioma on an outpatient basis using electrical fields. TTF exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported selectively both to inhibit tumor growth and reduce tumor angiogenesis. TTF are proposed to inhibit rapidly dividing tumor cells by two mechanisms: arrest of cell proliferation and destruction of cells while undergoing division. TTF are delivered by transducer arrays placed on the skin close to the tumor and act regionally and noninvasively to inhibit tumor growth.

Regulatory Status

In April 2011, the NovoTTF-100A™ System (Novocure; assigned the generic name of TTF) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The FDA approved label reads as follows: "The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age 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 and is intended as an alternative to standard medical therapy for recurrent GBM after surgical and radiation options have been exhausted."

In September 2014, FDA approved Novocure's request for a product name change from NovoTTF-110A System to Optune®.

In October 2015, FDA expanded the indication for Optune in combination with temozolomide to include newly diagnosed GBM. The device was granted priority review status in May 2015 because there was no legally marketed alternative device available for the treatment of newly diagnosed GBM, a life-threatening condition. In July 2016, a smaller, lighter version of the Optune device, called the Optune System (NovoTTF-200A System), received FDA approval.

The FDA-approved label for newly diagnosed GBM reads as follows: "This device is indicated as treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM). Optune with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."

In May 2019, the FDA approved a modified version of the Optune System (NovoTTF-100A System), which is now called the Optune Lua™ System (NovoTTF™-100L System), for "treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy. The indication was modified from that granted for the Humanitarian Device Exemption designation to more clearly identify the patient population the device is intended to treat and in which the safety and probable benefit of the device is supported by the available clinical data."

In September 2021, the FDA granted breakthrough designation to the NovoTTF-200T System for use together with atezolizumab and bevacizumab for the first-line treatment of patients with unresectable or metastatic liver cancer.

To date, all of the existing tumor treating fields products fall under the brand name Optune. In March 2020, the manufacturer of Optune products announced a plan to include a suffix after the brand name for newly approved indications to further delineate specific indications for individual products (eg, Optune Lua).

IV. RATIONALE

TOP

Summary of Evidence

For individuals who have newly diagnosed glioblastoma multiforme (GBM) on maintenance therapy after initial treatment who receive tumor treating fields (TTF) therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial (RCT) and a systematic review. Relevant outcomes include overall survival (OS), disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The EF-14 trial found a significant increase of 2.7 months in progression-free survival (PFS) and an increase of

4.9 months in OS with the addition of TTF therapy to standard maintenance therapy (ie, temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, PFS was assessed by blinded evaluators, and the placebo effects on the objective measure of OS are expected to be minimal. In a systematic review that included the EF-14 trial along with other observational studies, the pooled median OS and PFS in newly diagnosed patients who received TTF therapy was 21.7 months and 7.2 months, respectively. This technology represents a clinically significant option in the treatment of patients with GBM, for whom options are limited. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have progressive or recurrent GBM who receive TTF therapy as an adjunct or alternative to standard medical therapy, the evidence includes an RCT, nonrandomized comparative studies, and a systematic review of these data. Relevant outcomes are OS, disease-specific survival, quality of life, and treatment-related morbidity. The single RCT evaluating TTF therapy for recurrent GBM did not show superiority of TTF therapy for the primary outcome (OS) compared with physicians' choice chemotherapy. Because no serious adverse effects have been identified with TTF therapy, this raises the possibility that treatment with TTF might reduce the toxicity associated with treatment for recurrent GBM. A reduction in chemotherapy-associated toxicity without loss of efficacy would be considered a net health benefit. However, this RCT is not sufficient to permit conclusions on the efficacy of the device. Because the trial was not designed as a noninferiority trial, no inferences of noninferiority compared with chemotherapy can be made. Also, quality of life assessment was measured in an insufficient number of patients to reach firm conclusions on differences in quality of life between TTF therapy and medical treatment. The highest quality study of TTF combined with medical treatment for recurrent GBM is a post hoc analysis of the EF-14 trial. Two registry studies also evaluated real-world outcomes in patients enrolled in the PRiDe registry compared to patients in the EF-11 study. In a systematic review that included the RCT and post hoc analysis of the EF-14 trial, along with other observational studies, the pooled median OS and PFS in patients with recurrent GBM who received TTF therapy was 10.3 months and 5.7 months, respectively. A high-quality, prospective RCT is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

National Comprehensive Cancer Network guidelines on central nervous system cancers includes a recommendation for alternating electric field therapy as an initial treatment option for glioblastoma. They also give consideration of alternating electric field therapy for recurrent glioblastoma. Therefore, the evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a single-arm prospective study conducted in 80 patients and a retrospective study of 5 US patients. Relevant outcomes include OS, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. In patients who received TTF therapy in combination with pemetrexed and cisplatin or carboplatin, median OS was 18.2 months (95% confidence interval [CI], 12.1 to 25.8 months). Because there was no comparison group, it is not possible to make conclusions about the effectiveness of the

intervention compared to medical therapy alone. The retrospective study is the first publication of real-world implementation of TTF for MPM. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

TOP

Karnofsky Performance Status is a standard way of measuring the ability of individuals to perform ordinary tasks. The Karnofsky Performance Status scores range from 0-100. A higher score means the patient is better able to carry out daily activities. Karnofsky Performance Status 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. Also called KPS.

VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

TOP

Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

POLICY TITLE	TUMOR TREATING FIELDS THERAPY (FORMERLY TUMOR-TREATMENT FIELDS THERAPY FOR GLIOBLASTOMA)
POLICY NUMBER	MP 6.054

May Be Considered Medically Necessary: When used for Tumor Treating Fields Therapy for Glioblastoma

Procedure Codes					
E0766	A4555				

ICD-10-CM Diagnosis Codes	Description
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified

IX. REFERENCES

TOP

1. *National Cancer Institute (NCI). Adult Central Nervous System Tumors Treatment (PDQ)Health Professional Version. Updated January 18, 2022.*
2. *National Brain Tumor Society. Glioblastoma Facts & Figures.*
3. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 1.2023.*
4. *Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer. Sep 2012; 48(14): 2192-202. PMID 22608262*
5. *U.S. Food and Drug Administration (FDA). Tumor treatment fields. NovoTTF-10A System. Summary of safety and effectiveness data (SSED). Premarket Approval Application (PMA) No. P100034. 2011.*
6. *U.S. Food and Drug Administration (FDA). Supplemental application for device name change. 2014.*
7. *U.S. Food and Drug Administration (FDA). Summary of Safety and Effectiveness Data (SSED): OptuneTM (formerly NovoTTF-100ATM System) 2015.*
8. *U.S. Food and Drug Administration (FDA). NovoTTF 100L System: Summary of Safety and Probable Benefit. May 23, 2019.*
9. *FDA Grants Breakthrough Device Designation to the NovoTTF-200T System for Advanced Liver Cancer. September 9, 2021.*

10. *Novocure. Novocure announces Optune Lua as the brand name for the NovoTTF-100L system. March 19, 2020.*
11. *Davies AM, Weinberg U, Palti Y. Tumor treating fields: a new frontier in cancer therapy. Ann N Y Acad Sci. Jul 2013; 1291: 86-95. PMID 23659608*
12. *Pless M, Weinberg U. Tumor treating fields: concept, evidence and future. Expert Opin Investig Drugs. Aug 2011; 20(8): 1099-106. PMID 21548832*
13. *Regev O, Merkin V, Blumenthal DT, et al. Tumor-Treating Fields for the treatment of glioblastoma: a systematic review and meta-analysis. Neurooncol Pract. Aug 2021; 8(4): 426-440. PMID 34277021*
14. *Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. JAMA. Dec 19 2017; 318(23): 2306-2316. PMID 29260225*
15. *Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. JAMA. Dec 15 2015; 314(23): 2535-43. PMID 26670971*
16. *Zhu JJ, Goldlust SA, Kleinberg LR, et al. Tumor Treating Fields (TTFields) therapy vs physicians' choice standard-of-care treatment in patients with recurrent glioblastoma: a post-approval registry study (EF-19). Discov Oncol. Oct 14 2022; 13(1): 105. PMID 36239858*
17. *Kesari S, Ram Z. Tumor-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial. CNS Oncol. Jul 2017; 6(3): 185-193. PMID 28399638*
18. *Mrugala MM, Engelhard HH, Dinh Tran D, et al. Clinical practice experience with NovoTTF-100A™ system for glioblastoma: The Patient Registry Dataset (PRiDe). Semin Oncol. Oct 2014; 41 Suppl 6: S4-S13. PMID 25213869*
19. *Wong ET, Lok E, Swanson KD, et al. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. Cancer Med. Jun 2014; 3(3): 592-602. PMID 24574359*
20. *Kanner AA, Wong ET, Villano JL, et al. Post Hoc analyses of intention-to-treat population in phase III comparison of NovoTTF-100A™ system versus best physician's choice chemotherapy. Semin Oncol. Oct 2014; 41 Suppl 6: S25-34. PMID 25213871*
21. *Ceresoli GL, Aerts JG, Dziadziuszko R, et al. Tumour Treating Fields in combination with pemetrexed and cisplatin or carboplatin as first-line treatment for unresectable malignant pleural mesothelioma (STELLAR): a multicentre, single-arm phase 2 trial. Lancet Oncol. Dec 2019; 20(12): 1702-1709. PMID 31628016*
22. *Kutuk T, Appel H, Avendano MC, et al. Feasibility of Tumor Treating Fields with Pemetrexed and Platinum-Based Chemotherapy for Unresectable Malignant Pleural Mesothelioma: Single-Center, Real-World Data. Cancers (Basel). Apr 16 2022; 14(8). PMID 35454925*
23. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Mesothelioma: Pleural. Version 1.2023.*
24. *Germano IM, Ziu M, Wen P, et al. Congress of Neurological Surgeons systematic review and evidence-based guidelines update on the role of cytotoxic chemotherapy and other*

cytotoxic therapies in the management of progressive glioblastoma in adults. J Neurooncol. Jun 2022; 158(2): 225-253. PMID 35195819

25. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 1.01.29 Tumor Treating Fields Therapy. August 2023*

X. POLICY HISTORY

TOP

MP 6.054	**11/3/2021 Minor Review.** Karnofsky Performance Status changed from 70 to 60. Adult patient age changed from 18 to 22. References added. Regulatory status updated. NCCN statement added. Karnofsky Performance Status Definition added.
	11/16/2022 Consensus review. Added policy guidelines to include Karnofsky Performance Status table. Background and ref updated. No coding changes.
	8/25/2023 Consensus review. Minor editorial refinements to policy statements; intent unchanged. Title change; formerly Tumor-Treatment Fields Therapy for Glioblastoma. Updated background, rationale, and references. No changes to coding.
	1/19/2024 Administrative update. Clinical benefit added.

TOP