BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 1.01.29 Tumor Treating Fields Therapy

Annual Effective Policy Date: October 1, 2025

Original Policy Date: September 2013

Related Policies:

6.01.10 - Stereotactic Radiosurgery and Stereotactic Body Radiotherapy
8.01.08 - Intraoperative Radiotherapy
8.01.59 - Intensity-Modulated Radiotherapy: Central Nervous System Tumors

Tumor Treating Fields Therapy

Description

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Tumor treating fields (TTF) therapy is a noninvasive technology intended to treat glioblastoma, malignant pleural mesothelioma, and non small cell lung cancer on an outpatient basis and at home using electrical fields. Glioblastoma multiforme (GBM) is the most common and deadly malignant brain tumor. It has a very poor prognosis and is associated with low quality of life during treatment. Malignant pleural mesothelioma is an aggressive tumor with few treatment options that is associated with significant morbidity and mortality. Non small cell cancer is the most common type of lung cancer (85%) encompassing 3 subtypes (adenocarcinoma, squamous cell, and large cell carcinoma) and prognosis depends on various factors, including the stage of the cancer, the type of treatment received, and the patient's overall health.

OBJECTIVE

The objective of this evidence review is to determine whether the use of tumor treating fields therapy improves the net health outcome for individuals with solid tumors including glioblastoma multiforme, malignant pleural mesothelioma, and non-small cell lung cancer (NSCLC).

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POLICY STATEMENT

Tumor treating fields therapy to treat glioblastoma multiforme (GBM) is considered **medically necessary** as an adjunct to standard maintenance therapy with temozolomide in individuals with newly diagnosed GBM following initial treatment with surgery, radiotherapy, and/or chemotherapy under the following conditions:

- Individuals ≥18 years of age,
- Supratentorial tumor,
- Karnofsky Performance Status score ≥70%,
- Individual understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the U.S. Food and Drug Administration label (see Policy Guidelines).

Tumor treating fields therapy is considered **not medically necessary** in all other conditions, including but not limited to the following situations:

- As an adjunct to standard medical therapy (eg, bevacizumab, chemotherapy) for individuals with progressive or recurrent GBM,
- As an alternative to standard medical therapy for individuals with progressive or recurrent GBM,
- For brain metastases,
- For cancer in areas other than the brain,
- As an adjunct to standard medical therapy (pemetrexed and platinum-based chemotherapy) for individuals with malignant pleural mesothelioma,
- As an adjunct to standard medical therapy for individuals with non-small cell lung cancer (NSCLC).

POLICY GUIDELINES

Progression was defined in the EF-14 trial (Stupp et al [2015, 2017]) according to the MacDonald criteria (tumor growth >25% compared with the smallest tumor area measured in the individual during the trial or appearance of 1 or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

Per the pivotal trial, individuals ≥18 years of age were eligible for enrollment. The median age was about 56 years with a range of 19 to 83 years; subgroup analyses for younger age groups were not provided.

The recommended Karnofsky Performance Status (KPS) varies from the NCCN guideline (score ≥60). In the pivotal trial the median KPS score at baseline was 90.0, with a range from 60 to 100. Subgroup analyses for individuals with score 60 to 70 were not provided.

The U.S. Food and Drug Administration label includes the following notices:

- Individuals should use Optune for at least 18 hours a day to get the best response to treatment.
- Individuals should finish at least 4 full weeks of therapy to get the best response to treatment. Stopping treatment before 4 weeks lowers the chances of a response to treatment.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

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FDA 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.[7,] 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.[8,]

In October 2015, FDA expanded the indication for Optune in combination with temozolomide to include newly diagnosed GBM.[9,] 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." [10,] 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.[11,]

In October 2024, Optune Lua was approved for "metastatic non-small cell lung cancer along with concurrent drug treatments in adults who have progressed on or after a platinum-based chemotherapy." [6,]

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).[12,] Optune was renamed Optune Gio™ in 2023. [13,]

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RATIONALE

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.

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.

For individuals who have metastatic non-small cell lung cancer (NSCLC) who receive TTF with concurrent standard care including an immune checkpoint inhibitor or docetaxel and who have progressed on or after platinum-based therapy, the evidence includes an open-label RCT conducted in 276 patients. Relevant outcomes include OS, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The LUNAR trial found a significant increase of 3.3 months in OS with TTF in combination with an immune checkpoint inhibitor or docetaxel, but there was no significant improvement in PFS or overall response rate. The trial is limited by the lack of a sham comparator, a lack of baseline molecular testing, and changes in standard of care. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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National Comprehensive Cancer Network

National Comprehensive Cancer Network guidelines on central nervous system cancers (v.5.2024) include recommendations for the treatment of glioblastoma (see Table 1). [3,]For the initial treatment of patients with glioblastoma with good performance status and either methylated or unmethylated or indeterminate O^6-methylguanine-DNA methyltransferase promoter status, treatment with standard brain radiotherapy plus concurrent temozolomide and adjuvant temozolomide plus alternating electric field therapy is a category 1 recommendation. Alternating electric currents therapy (i.e., tumor treating fields [TTF]) is only an option for patients with supratentorial disease. Consideration of alternating electric field therapy for recurrent glioblastoma is a category 2B recommendation.

Table 1. Guidelines for Adjuvant Treatment of Glioblastoma, by Age and Performance Status

Age, y	KPS Score,%	Treatment Options	Category
≤70	≥60	• Standard RT plus concurrent and adjuvant temozolomide plus TTF (preferred) • Standard RT plus concurrent and adjuvant temozolomide	1
≤70	≥60	• Standard RT alone (for unmethylated MGMT promoter status only)	2A
≤70	≥60	• Standard RT plus concurrent and adjuvant lomustine and temozolomide (for methylated or indeterminate MGMT promoter status only)	2B
≤70	<60	• Hypofractionated RT with/without concurrent or adjuvant temozolomide • Temozolomide alone • Palliative/best supportive care	2A
>70	≥60	• Hypofractionated RT plus concurrent and adjuvant temozolomide (for methylated or indeterminate MGMT promoter status only) • Standard RT plus concurrent and adjuvant temozolomide plus TTF	1
>70	≥60	• Standard RT plus concurrent and adjuvant temozolomide • Temozolomide alone (for methylated or indeterminate MGMT promoter status only) • Hypofractionated RT alone (for unmethylated MGMT promoter status only) • Hypofractionated RT plus concurrent and adjuvant temozolomide (for unmethylated MGMT promoter status only)	2A
>70	≥60	• Hypofractionated RT alone (for methylated or indeterminate MGMT promoter status only)	2B

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>70	<60	• Hypofractionated brain RT alone • Temozolomide alone • Palliative/best supportive care	2A

KPS: Karnofsky Performance Status; MGMT: O^6-methylguanine-DNA-methyltransferase; RT: radiotherapy; TTF: tumor treating fields.

The National Comprehensive Cancer Network guidelines on malignant pleural mesothelioma (v.2.2025) do not address TTF as a treatment option for malignant pleural mesothelioma.[27,]

The National Comprehensive Cancer Network guidelines on non-small cell lung cancer (NSCLC)(v.3.2025) do not address TTF as a treatment option for NSCLC.[5,]

Congress of Neurological Surgeons

In 2022, the Congress of Neurological Surgeons released guidelines on role of cytotoxic chemotherapy and other cytotoxic therapies in the management of progressive glioblastoma.[28,] In regard to TTF use in adult patients with progressive glioblastoma, the Congress states that "the use of TTF with other chemotherapy may be considered when treating adult patients with progressive glioblastoma [pGBM]. There is insufficient evidence to recommend TTF to increase overall survival in adult patients with pGBM".

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2013	New policy	Not medically necessary for all indications.
December 2014	Replace policy	Policy updated with literature review, references 8, 16, and 17 added. Editorial revisions made to rationale section. Policy statement unchanged
December 2015	Replace policy	Policy updated with literature review through July 8, 2015; references 10- 11 removed and 10-12 added. Policy statement unchanged.
March 2017	Replace policy	Policy updated with literature review through July 18, 2016, reference 13 added. Policy statements rewritten for clarity but tumor treating fields remains not medically necessary for all indications.

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Date	Action	Description
September 2018	Replace policy	Policy updated with literature review through April 5, 2018; references 10, and 12-13 added. Title changed from "Tumor Treatment Fields Therapy for Glioblastoma, to "Tumor Treating Fields Therapy,. May be considered medically necessary in conjunction with maintenance temozolomide for patients with newly diagnosed glioblastoma multiforme. Investigational for all other non-FDA approved indications.
September 2019	Replace policy	Policy updated with literature review through May 29, 2019; reference 17 added. Regulatory Status section updated to include new FDA indication for malignant pleural mesothelioma. Due to FDA PMA status: "investigational" statement changed to "not medically necessary" and malignant pleural mesothelioma added to list of conditions for which the therapy is considered not medically necessary.
September 2020	Replace policy	Policy updated with literature review through June 1, 2020; references added. Regulatory Status section updated to include information differentiating between Optune and Optune Lua products. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through May 28, 2021; no references added. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through May 23, 2022; references added. Minor editorial refinements to policy statements; intentunchanged.
September 2023	Replace policy	Policy updated with literature review through May 31, 2023; references added. Policy statements unchanged.
September 2024	Replace policy	Policy updated with literature review through May 15, 2024; no references added. Minor editorial refinements to Policy Guidelines section; intent unchanged.
September 2025	Replace policy	Policy updated with literature review through May 16, 2025; references added. Regulatory Status section updated to include new FDA indication for non-small sell lung cancer. Non-small cell lung cancer added to list of conditions for which the therapy is considered investigational.

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