

02-61000-10

Original Effective Date: 10/15/15

Reviewed: 10/27/22

Revised: 05/25/23

Subject: Tumor Treating Fields Therapy

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions	Related Guidelines
Other	References	Updates			

DESCRIPTION:

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults. GBMs are grade IV astrocytomas, and are often resistant to standard chemotherapy.

The primary treatment for GBM is debulking surgery to remove as much of the tumor as possible. At that time, some individuals may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitrosourea [BCNU])–impregnated wafer. Depending on the individual’s physical condition, adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of the 2 are sometimes given. After adjuvant therapy, some may undergo maintenance therapy with temozolomide.

TTF therapy is a noninvasive technology that is intended to treat GBM on an outpatient basis using electrical fields. TTF therapy exposes rapidly dividing cancer cells to electric fields of low intensity and intermediate frequency that alternate in perpendicular orientation. TTF is proposed to inhibit rapidly dividing tumor cells by 2 mechanisms, arrest of cell proliferation and destruction of cells while undergoing division.

Treatment planning software (eg, NovoTAL) is available and designed to be utilized prior to starting TTF treatment. NovoTAL is optional software that a physician can purchase and use to create individualized treatment maps. It is purported to allow the physician to individualize treatment by determining optimal placement of the transducer arrays, based on the individual’s most recent magnetic resonance imaging (MRI) scan, head size and tumor location

REGULATORY STATUS

The Optune™ (formerly NovoTTF-100A System) System was approved by the FDA in April 2011, as a stand-alone treatment for adults age 22 years or older with confirmed GBM that recurs or progresses after surgical and radiation options have been exhausted. In October 2015, the FDA granted approval for use of Optune™ in combination with temozolomide to treat adults age 22 years or older with newly diagnosed GBM. In July 2016, a smaller, lighter version of the Optune® device, called the Optune® System, received FDA approval.

The Food and Drug Administration label includes the following notices:

- “Patients should use Optune for at least 18 hours a day to get the best response to treatment”
- “Patients 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)”

POSITION STATEMENT:

The use of tumor treating fields therapy (TTF) to treat newly diagnosed glioblastoma multiforme (GBM) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

- The device is FDA approved
- Age 22 or older
- There is histologically-confirmed supratentorial glioblastoma (also known as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma)
- Initial treatment with debulking surgery or biopsy followed by chemoradiation with concomitant temozolomide and radiotherapy has been completed, with no documented tumor progression*
- TTF is used in combination with temozolomide
- Karnofsky Performance Status score of 70% or higher, OR Eastern Cooperative Oncology Group (ECOG) performance status 0-1

* Progression is defined as tumor growth greater than 25% compared to smallest measured tumor area, or the appearance of one or more new GBM lesions in the brain.

The use of tumor treating fields therapy (TTF) to treat glioblastoma multiforme recurrence **meets the definition of medical necessity** when **ALL** of the following criteria are met:

- The device is FDA approved
- Age 22 or older
- There is histologically-confirmed recurrence of supratentorial glioblastoma (also known as glioblastoma multiforme [GBM] or World Health Organization [WHO] grade IV astrocytoma) following treatment with chemotherapy and/or radiation
- TTF is used as monotherapy

The use of tumor treating fields therapy (TTF) for all other indications is considered **experimental or investigational**. There is insufficient clinical evidence in the peer-reviewed literature on this technology to support its safety, effectiveness, and long term effects on net health outcomes for other types of cancer.

The use of treatment planning software (eg, NovoTAL) for use with tumor treatment fields for any indication is considered **experimental or investigational**. Data in published medical literature are inadequate to permit scientific conclusions on long-term and net health outcomes.

BILLING/CODING INFORMATION:

HCPCS Coding

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

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following Local Coverage Determination (LCD) was reviewed on the last guideline reviewed date: Tumor Treatment Field Therapy (TTFT) (L34823), located at [cms.gov](https://www.cms.gov).

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at [Coverage Protocol Exemption Request](#)

DEFINITIONS:

Eastern Cooperative Oncology Group (ECOG) Performance Status

A scale used to determine an individual's level of functioning.

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Karnofsky Performance Status Score

A scale used by healthcare providers to quickly evaluate how an individual is feeling on any given day.

100	Normal, no complaints
90	Able to carry on normal activities. Minor signs or symptoms of disease
80	Normal activity with effort
70	Care for self. Unable to carry on normal activity or to do active work
60	Requires occasional assistance, but able to care for most of his needs
50	Requires considerable assistance and frequent medical care
40	Disabled. Requires special care and assistance
30	Severely disabled. Hospitalisation indicated though death nonimminent
20	Very sick. Hospitalisation necessary. Active supportive treatment necessary
10	Moribund
0	Dead

RELATED GUIDELINES:

None.

OTHER:

None.

REFERENCES:

1. AHRQ National Guideline Clearinghouse. NGC:010366, Care of the adult patient with a brain tumor. American Association of Neuroscience Nurses (2014).
2. AHRQ National Guideline Clearinghouse. NGC:010488, The role of targeted therapies in the management of progressive glioblastoma: a systematic review and evidence-based clinical practice guideline. American Association of Neurological Surgeons - Medical Specialty Society; Congress of Neurological Surgeons. July 2014.
3. Ansstas G, Tran DD. Treatment with Tumor-Treating Fields Therapy and Pulse Dose Bevacizumab in Patients with Bevacizumab-Refractory Recurrent Glioblastoma: A Case Series. *Case Rep Neurol.* 2016 Jan 8;8(1):1-9.
4. Benson, L. Tumor Treating Fields Technology: Alternating Electric Field Therapy for the Treatment of Solid Tumors. *Semin Oncol Nurs.* 2018 May;34(2):137-150. doi: 10.1016/j.soncn.2018.03.005. Epub 2018 Apr.
5. Blue Cross Blue Shield Association Evidence Positioning System®. 1.01.29 Tumor-Treatment Fields Therapy, 08/22.
6. Branter J, Basu S, Smith S. Tumour treating fields in a combinational therapeutic approach. *Oncotarget.* 2018 Nov 27;9(93):36631-36644. doi: 10.18632/oncotarget.26344. eCollection 2018 Nov 27.
7. Burri SH, et al. The Evolving Role of Tumor Treating Fields in Managing Glioblastoma: Guide for Oncologists. *Am J Clin Oncol.* 2018 Feb;41(2):191-196.
8. Carrieri FA, Smack C, Siddiqui I, Kleinberg LR, Tran PT. Tumor Treating Fields: At the Crossroads Between Physics and Biology for Cancer Treatment. *Front Oncol.* 2020 Oct 30;10:575992. doi: 10.3389/fonc.2020.575992.
9. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination Tumor Treatment Field Therapy (TTFT) L34823 (Retired 09/30/15).

10. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determination Tumor Treatment Field Therapy (TTFT) L34823 (10/01/15) (Revised 01/01/20).
11. Chen D, Le SB, Hutchinson TE, et al. Tumor Treating Fields dually activate STING and AIM2 inflammasomes to induce adjuvant immunity in glioblastoma. *J Clin Invest*. 2022 Apr 15;132(8):e149258. doi: 10.1172/JCI149258.
12. ClinicalTrials.gov. NCT00916409. A Prospective, Multi-center Trial of NovoTTF-100A Together with Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM. Accessed 09/10/15.
13. ClinicalTrials.gov. NCT01894061. A Prospective Phase II Trial of NovoTTF-100A With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma. Accessed 09/10/15.
14. ClinicalTrials.gov. NCT01755624. A Phase II Randomized Study of TTField Therapy Versus Supportive Care in Non-small Cell Lung Cancer Patients With 1-5 Brain Metastases Following Optimal Standard Local Treatment. Accessed 09/10/15.
15. ClinicalTrials.gov. NCT01756729. A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A in Recurrent GBM Patient. Accessed 09/10/15.
16. ClinicalTrials.gov. NCT01954576. A Phase II Study of the NovoTTF-100A system, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme. Accessed 09/10/15.
17. Connelly J, et al. Planning TTFields treatment using the NovoTAL system-clinical case series beyond the use of MRI contrast enhancement. *BMC Cancer* (2016) 16:842.
18. Davis ME. Glioblastoma: Overview of Disease and Treatment. *Clin J Oncol Nurs*. 2016 Oct 1;20(5):S2-8.
19. Fabian D, et al. Treatment of Glioblastoma (GBM) with the Addition of Tumor-Treating Fields (TTF): A Review. *Cancers (Basel)*. 2019 Feb 2;11(2). pii: E174. doi: 10.3390/cancers11020174.
20. Ghiaseddin AP, Shin D, Melnick K, Tran DD. Tumor Treating Fields in the Management of Patients with Malignant Gliomas. *Curr Treat Options Oncol*. 2020 Jul 30;21(9):76. doi: 10.1007/s11864-020-00773-5.
21. Giladi M, et al. Tumor treating fields (TTFields) delay DNA damage repair following radiation treatment of glioma cells. *Radiat Oncol*. 2017 Dec 29;12(1):206.
22. Hottinger AF, Pacheco P, Stupp R. Tumor treating fields: a novel treatment modality and its use in brain tumors. *Neuro Oncol*. 2016 Oct;18(10):1338-49.
23. Kanner AA, Wong ET, Villano JL, Ram Z; EF-11 Investigators. Post Hoc Analyses of Intention-to-Treat Population in Phase III Comparison of NovoTTF-100A™ System Versus Best Physician's Choice Chemotherapy. *Semin Oncol*. 2014 Oct;41 Suppl 6:S25-34.
24. Kesari S, et al. Tumor-treating fields plus chemotherapy versus chemotherapy alone for glioblastoma at first recurrence: a post hoc analysis of the EF-14 trial. *CNS Oncol*. 2017 Jul;6(3):185-193.
25. Kim EH, Song HS, Yoo SH, Yoon M. Tumor treating fields inhibit glioblastoma cell migration, invasion and angiogenesis. *Oncotarget*. 2016 Aug 18.
26. Kinzel A, et al. Tumor Treating Fields for Glioblastoma Treatment: Patient Satisfaction and Compliance With the Second-Generation Optune® System. *Clin Med Insights Oncol*. 2019 Jan 29;13:1179554918825449. doi: 10.1177/1179554918825449. eCollection 2019.
27. Li T, et al. Dosimetric Impact of a Tumor Treating Fields Device for Glioblastoma Patients Undergoing Simultaneous Radiation Therapy. *Front Oncol*. 2018 Mar 13;8:51.
28. Li X, Jia Z, Yan Y. Efficacy and safety of tumor-treating fields in recurrent glioblastoma: a systematic review and meta-analysis. *Acta Neurochir (Wien)*. 2022 Aug;164(8):1985-1993. doi: 10.1007/s00701-022-05192-z. Epub 2022 Apr 9. PMID: 35397674.

29. Lok E, et al. Analysis of physical characteristics of Tumor Treating Fields for human glioblastoma. *Cancer Med.* 2017 Jun;6(6):1286-1300.
30. Luo C, Xu S, et al. Tumor treating fields for high-grade gliomas. *Biomed Pharmacother.* 2020 Jul;127:110193. doi: 10.1016/j.biopha.2020.110193. Epub 2020 May 11.
31. 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.
32. National Cancer Institute (NCI). Adult Central Nervous System Tumors Treatment (PDQ®). Treatment of Primary Central Nervous System Tumors by Tumor Type (January 2016).
33. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers V1.2015.
34. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers V1.2016.
35. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers V1.2019.
36. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers V1.2020.
37. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers V1.2022.
38. National Institute for Health and Care Excellence. NICE interventional procedures list: TTF for glioblastoma multiforme (851 / 1). Accessed at <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-interventional-procedures-guidance/ip-list>.
39. National Institute for Health and Care Excellence (NICE). NICE Guideline: Brain tumours (primary) and brain metastases in adults. January 2021. Accessed at <https://www.nice.org.uk/guidance/ng99>.
40. Onken J, et al. Acceptance and compliance of TTF treatment among high grade glioma patients. *J Neurooncol.* 2018 Aug;139(1):177-184. doi: 10.1007/s11060-018-2858-9. Epub 2018 Apr 11. PMID: 29644485 DOI: 10.1007/s11060-018-2858-9.
41. Palmer JD, Chavez G, Furnback W, Chuang PY, Wang B, Proescholdt C, Tang CH. Health-Related Quality of Life for Patients Receiving Tumor Treating Fields for Glioblastoma. *Front Oncol.* 2021 Dec 2;11:772261. doi: 10.3389/fonc.2021.772261.
42. Riley MM, San P, Lok E, Swanson KD, Wong ET. The Clinical Application of Tumor Treating Fields Therapy in Glioblastoma. *J Vis Exp.* 2019;(146):10.3791/58937. Published 2019 Apr 16. doi:10.3791/58937.
43. Saria MG, Kesari S. Efficacy and Safety of Treating Glioblastoma With Tumor-Treating Fields Therapy. *Clin J Oncol Nurs.* 2016 Oct 1;20(5):S9-S13.
44. Schwartz MA, Onuselogu L. Rationale and Background on Tumor-Treating Fields for Glioblastoma. *Clin J Oncol Nurs.* 2016 Oct 1;20(5):S20-4.
45. Shah PP, White T, Khalafallah AM, Romo CG, Price C, Mukherjee D. A systematic review of tumor treating fields therapy for high-grade gliomas. *J Neurooncol.* 2020 Jul;148(3):433-443. doi: 10.1007/s11060-020-03563-z. Epub 2020 Jun 23. PMID: 32578135.
46. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomized phase III trial of a novel treatment modality. *Eur J Cancer.* 2012;48:2192-2202.
47. Swanson KD, Lok E, Wong ET. An Overview of Alternating Electric Fields Therapy (NovoTTF Therapy) for the Treatment of Malignant Glioma. *Curr Neurol Neurosci Rep.* 2016 Jan;16(1):8.

48. Thomas AA, Rauschkolb PK. Tumor treating fields for glioblastoma: should it or will it ever be adopted? *Curr Opin Neurol*. 2019;32(6):857–863. doi:10.1097/WCO.0000000000000762.
49. Trusheim J, Dunbar E, Battiste J, Iwamoto F, Mohile N, Damek D, Bota DA, Connelly J. A state-of-the-art review and guidelines for tumor treating fields treatment planning and patient follow-up in glioblastoma. *CNS Oncol*. 2016 Sep 15.
50. Turner SG, Gergel T, Wu H, Lacroix M, Toms SA. The effect of field strength on glioblastoma multiforme response in patients treated with the NovoTTF™-100A system. *World J Surg Oncol*. 2014.
51. Tuszynski JA, et al. An Overview of Sub-Cellular Mechanisms Involved in the Action of TTFIELDS. *Int J Environ Res Public Health*. 2016 Nov 12;13(11).
52. UpToDate. Initial treatment and prognosis of IDH-wildtype glioblastoma in adults. 2022. Accessed at [uptodate.com](https://www.uptodate.com).
53. UpToDate. Initial treatment and prognosis of newly diagnosed glioblastoma in adults. 2021. Accessed at [uptodate.com](https://www.uptodate.com).
54. UpToDate. Management of recurrent high-grade gliomas. 2022. Accessed at [uptodate.com](https://www.uptodate.com).
55. 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.
56. U.S. Food and Drug Administration (FDA). Optune™ (Formerly the NovoTTF-100A System) Approval Order P100034/S013 (10/05/15).
57. Wenger C, Salvador R, Bassier PJ, Miranda PC. Improving Tumor Treating Fields Treatment Efficacy in Patients With Glioblastoma Using Personalized Array Layouts. *Int J Radiat Oncol Biol Phys*. 2016 Apr 1;94(5):1137-43.
58. Wenger C, Salvador R, Bassier PJ, Miranda PC. The electric field distribution in the brain during TTFIELDS therapy and its dependence on tissue dielectric properties and anatomy: a computational study. *Phys Med Biol*. 2015 Sep 21;60(18):7339-57.
59. Wong ET, Lok E, Swanson KD. Clinical benefit in recurrent glioblastoma from adjuvant NovoTTF-100A and TCCC after temozolomide and bevacizumab failure: a preliminary observation. *Cancer Med*. 2015 Mar;4(3):383-91.
60. Wong ET, Lok E, Swanson KD, Gautam S, Engelhard HH, Lieberman F, Taillibert S, Ram Z, Villano JL. Response assessment of NovoTTF-100A versus best physician's choice chemotherapy in recurrent glioblastoma. *Cancer Med*. 2014 Jun;3(3):592-602.
61. Zhu P, Zhu JJ. Tumor treating fields: a novel and effective therapy for glioblastoma: mechanism, efficacy, safety and future perspectives. *Chin Clin Oncol*. 2017 Aug;6(4):41.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 10/27/22.

GUIDELINE UPDATE INFORMATION:

10/15/15	New Medical Coverage Guideline.
04/15/17	Scheduled review. Revised Description section. Added coverage criteria for TTF therapy. Revised Program Exceptions section and Definitions section. Updated references.
05/15/18	Scheduled review. Added coverage statement (E/I) for treatment planning software (eg, NovoTAL). Updated references.

05/15/19	Scheduled review. Revised MCG title and description. Maintained position statement and updated references.
05/15/20	Scheduled review. Maintained position statement and updated references.
07/15/21	Scheduled review. Maintained position statement and updated references.
11/15/22	Scheduled review. Revised description, maintained position statement and updated references.
05/25/23	Update to Program Exceptions section.