KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Tumor Treatment Field Therapy

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Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	Tumor Treatment Field Therapy (TTFT) (L34823)
Local Coverage Article	Tumor Treatment Field Therapy (TTFT) (A52711)

For Non-Medicare Members

I. Tumor-treating fields (TTF) to treat primary (not recurrent) supratentorial glioblastoma multiforme (GBM) may be considered medically necessary when **ALL of the following** are met:
   A. Patient is 18 years of age or older; and
   B. Karnofsky Performance Status* is 70% or higher; and
   C. Documentation of histologically confirmed primary glioblastoma multiforme; and
   D. Patient has completed standard concomitant chemoradiation with temozolomide(TMZ); and
   E. Disease did not progress through chemo radiation (possible “pseudo progression” does not exclude patients from receiving TTF) and
   F. TTF will be administered concurrently with TMZ, unless TMZ has been ineffective, not tolerated, or is contraindicated and
   G. TTF must be started no later than 60 days from the end of chemo radiation

II. Continued treatment of TTF can be covered until the second radiological progression (meaning 2 consecutive images showing tumor progression) or clinical deterioration

All authorizations are for 90 days. Re-authorizations require updated clinical notes and imaging.

*Karnofsky Performance Status Scale

Condition	Value (%)	level of Functional Capacity
Able to carry on normal activity and to work; no special care needed	100%	No complaints; no evidence of disease
	90%	Able to carry on normal activity; minor signs or symptoms of disease
	80%	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed	70%	Cares for self; unable to carry on normal activity or to do active work
	60%	Requires occasional assistance but is able to care for most personal needs

Back to Top

	50%	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; diseases may be progressing rapidly	40%	Disabled; requires special care and assistance
	30%	Severely disabled; hospital admission indicated although death not imminent
	20%	Very sick; hospital admission necessary; active supportive treatment necessary
	10%	Moribund; fatal processes progressing rapidly

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Glioblastoma (GBM), an incurable disease, has the highest incidence rate (3.19/100,000 population) amongst the central nervous system (CNS) tumors with an average survival of 15 months (Thakkar et al., 2014). Numerous genetic and environmental risk factors have been investigated but none is associated with a large population of GBM (Wrensch, Minn, Chew, Bondy, & Berger, 2002). The median age of diagnosis is 64 years and GBM is frequently found in the supratentorial region (Adams et al., 2013). GBM is an aggressive malignancy with poor prognosis and low survival. The first year relative survival rate is 35% and this estimate decreases over time (Ostrom et al., 2013) making the long term survival very harsh. Standard treatment consists of resection with combination of radiation and chemotherapy. These therapies, whether combined or utilized alone, do not significantly decrease mortality and do not lack adverse effects. Because GBM infiltrates the brain, it is prone to recurrence. Management of recurrence became challenging and therefore indispensable for better clinical outcomes. Different therapeutic options have been investigated but tumor treating fields (TTFields), a novel treatment, seems comparable to standard chemotherapy including Temozolomide and is less toxic (Roger Stupp et al., 2012).

TTFields, developed by NovoCure Ltd, is a medical device for the treatment of recurrent GBM. It is a portable, non-invasive, battery-operated and wearable device that disrupts the division of cancer cells and proliferation in the supratentorial region by delivering low-intensity and intermediate frequency (200 kHz) alternating electric fields via transducer arrays applied to the scalp by means of hypoallergenic ceramic disks, which are placed on the scalp using Hydrogel (Axelgaard Manufacturing Co, Ltd, Fallbrook, CA) as a conductor; It is believed that TTFields inhibits cytokinesis and microtubule assemble, and therefore inhibiting growth and causing death of cancer cells (Butowski, Wong, Mehta, & Wilson, 2013). The NovoTTF-100A received premarket approval from the Food and Drug Administration (FDA) on April 10, 2011 for treatment in adult patients with confirmed GBM, following confirmed recurrence in an upper region of the brain after receiving chemotherapy. The device is intended to be used independently and as an alternative to standard medical therapy after surgical and radiation options have been exhausted (FDA 2011).

The review of the safety and effectiveness of TTFields Therapy for the treatment of recurrent GBM in adults has been reviewed previously. However, it is being reviewed based on a request from the Clinical Review Unit with a focus on the combination of TTFields plus Temozolomide as maintenance therapy on newly diagnosed GBM. It is also being reviewed for coverage decision support.

Medical Technology Assessment Committee (MTAC)

Tumor Treatment Fields Therapy

08/19/2013: MTAC REVIEW

Evidence Conclusion: The randomized phase III trial sought to compare the overall survival of subjects treated with the NovoTTF-100A alone to subjects treated with the best standard of care (BSC) chemotherapy available for recurrent GBM (Stupp, Wong et al. 2012). In the clinical study, 237 subjects with previously diagnosed GBM who experienced recurrence of their tumor or their condition worsened despite conventional therapy (surgery and

 Back to Top

chemo-radiotherapy followed by chemotherapy) were randomly assigned to receive either NovoTTF-100A stand-alone treatment or the BSC chemotherapy (as determined by the local physician). The primary endpoint for the study was overall survival, as assessed by the log-rank test in the intent-to-treat population. In addition, the study examined the safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and toxicities. Secondary endpoints measured in the study included the progression free survival rate at 6 months, time to progression, one-year survival rate, quality of life and radiological response rate. The ITT population includes all subjects who were randomized to the trial. At a median follow up of 39 months 93% of patients had died. The analysis was performed by the treatment group to which the subject was randomized. The study results showed that overall survival with the NovoTTF-100A System was no superior to that seen with active best standard of care chemotherapy. There was a slightly higher incidence of neurological adverse events in the NovoTFF-100A treated group (43.1%) compared to the best standard of care control group (36.3%). Mild to moderate skin irritation beneath the device electrodes was seen in 16% of NovoTFF-100A-treated subjects. NovoTFF-100A treated subjects experienced a lower frequency of the classic adverse events as seen with chemotherapy (such as gastrointestinal, hematological and infectious adverse events) with the best standard of care. Quality of life surveys indicated an improved quality of life in the NovoTFF-100A recurrent GBM subjects compared to the best standard of care recurrent GBM subjects. The trial was generally well designed and conducted with recruitment from 28 different clinics, randomization and minimal loss to follow up. Limitations identified by the authors include the somewhat heterogenous patient population with patients included after progression of one or several lines of prior chemotherapy. The authors also observed that the study could have benefited from a placebo or treatment-free control arm. Some limitations that are not highlighted by the authors include the decreasing number of subjects remaining after 12 months which may limit the ability to reliably estimate the long-term survival outcomes. Furthermore, it is important to note that the primary investigator, as well as a number of other authors had financial and professional ties with the manufacturer of the device Novocure Ltd., Rye Beach, New Hampshire. Although the study failed to show that the NovoTTF-100A treatment is superior to chemotherapy with respect to overall survival the NovoTTF-100A treatment exhibits minimal toxicity, has clinically comparable primary and secondary effectiveness and better quality of life compared to the chemotherapies used in the control arm of the study.

Articles: A literature search was conducted revealing a small pilot trial and one larger pivotal study. The pilot study was an open-label prospective single arm study to assess the safety and effectiveness of TTFields for the treatment of GBM. The pivotal study was prospective, open label, best standard of care randomized control trial to compare the overall survival of subjects treated with NovoTTF-100A alone to subjects treated with the best standard of care chemotherapy available for recurrent GBM. In addition, the search revealed a case study illustrating one patient's success with TTFields therapy and one expert opinion article discussing the concept, evidence and future of TTFields. The clinical study that formed the FDA's basis for determining that the NovoTTF-100A System is safe and effective for its intended use was selected for review: Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, et al. NovoTFF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomized phase III trial of a novel treatment modality. *European Journal of Cancer*. 2012;48, 2192-2202. See Evidence Table.

The use of TT Fields Therapy does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Tumor Treating Fields plus Temozolomide as maintenance therapy for Glioblastoma Multiforme (GBM)

03/21/2016: MTAC REVIEW

Evidence Conclusion: The previous review on TTFields, completed in 2013, aimed to determine the safety and efficacy of TTFields therapy compared to standard medical therapy, for the treatment of recurrent GBM for adult patients. The study evaluating NovoTTF-100A versus Physician Choice Chemotherapy in recurrent glioblastoma (Roger Stupp et al., 2012) was reviewed and no improvement in overall survival was identified. The author of the review concluded that there was insufficient evidence to determine the safety and effectiveness of TTFields Therapy. Stupp, R., S. Taillibert, et al. (2015). "Maintenance Therapy With Tumor-treating Fields plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial." See Evidence Table 1. This randomized phase 3 trial, open label, parallel design, multicenter, (R. Stupp et al., 2015) intended to assess the efficacy and safety of TTFields in combination with temozolomide for treatment of patients with GBM after initial treatment with chemoradiation. After patients were diagnosed, they were initially treated with chemoradiation comprised of Temozolomide and concomitant radiation. Brain MRI was required 2 weeks prior to starting the maintenance treatment (to exclude progression cases). After completion of the initial treatment, patients were randomized at a ratio of 2 to 1 to receive TTFields + Temozolomide (n=466) or Temozolomide alone (n=229).TTFields was initiated within 4-7 weeks from the last dose of concomitant chemoradiotherapy. While Temozolomide was given on a basis of 150-200 mg/m2/d for 5 days every 28 days for 6-12 cycles, TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. The primary outcome was progression-free survival (PFS) in the intent-

 Back to Top

to-treat population (significance level of 0.01) and the secondary outcome was the overall survival (OS) in the per-protocol population (significance level of 0.006). Safety and tolerability were also evaluated. A total of 695 patients were recruited but the trial was terminated after the interim analysis showed a benefit in Progression Free Survival. This interim analysis was conducted after the first 315 randomized patients reached a minimum of 18-month follow-up. Thus, data from 315 patients with 210 patients in the intervention group and 105 patients in the control group were analyzed. Baseline characteristics were nearly similar across the groups with median age of 57 years. The findings were based on the interim analysis. Patients who were treated with TTFields plus Temozolomide had longer PFS [7.1 months (CI, 5.9 – 8.2)] than those who were treated with Temozolomide alone [4 months (95%CI, 3.3 – 5.2)]. Likewise, patients who were treated with TTFields plus Temozolomide had longer OS [20.5 months (16.7 - 25)] than those who were treated with Temozolomide alone [15.6 months (CI, 13.3 – 19.1)]. In addition, no major increases in toxic effects were associated with the intervention. The most common adverse events were thrombocytopenia, mild to moderate skin irritation, and general disorders. In conclusion, the combination of TTFields plus Temozolomide prolonged PFS as well as OS compared to Temozolomide alone for the maintenance treatment of patients with GBM. However, this is an interim analysis with less than 50% of participation with exclusion of patients with early progression decreasing the quality of the evidence. MTAC will re-review the technology once full data are analyzed. Conclusion: The interim analysis with less than 50% participation suggests that TTF plus Temozolomide may prolong progression-free survival and overall survival versus Temozolomide alone. Nevertheless, the study failed to include patients with severe prognosis, therefore results should be interpreted with cautious. Other pitfalls remain in the open-label nature of the RCT leading to placebo effects and variation in the delivery of chemotherapy and radiochemotherapy.
Articles: A literature search was conducted revealing 13 articles (Please refer to appendix B) of which one meets inclusion criteria (studies involving histologically confirmed GBM, standard concomitant chemoradiation with Temozolomide, age >18 years with ≥ 70% on Karnofsky Performance Status (KPS) score and good renal and bone marrow function, received TTFields plus Temozolomide as maintenance therapy). The study on "Maintenance Therapy with tumor-treating fields plus temozolomide vs Temozolomide alone for Glioblastoma: A randomized clinical trial" will be critically appraised.

The use of Tumor Treating Fields (TTFields) plus Temozolomide as maintenance therapy for Glioblastoma multiforme (GBM) does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	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

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

Date Created	Date Reviewed	Date Last Revised
10/01/2013	10/01/2013[MPC], 10/07/2014[MPC], 08/04/2015[MPC], 05/03/2016[MPC], 04/04/2017[MPC], 02/06/2018[MPC], 02/05/2019[MPC], 02/04/2020[MPC], 02/02/2021[MPC], 02/01/2022[MPC], 02/07/2023[MPC]	09/06/2016

[MPC] Medical Policy Committee

Revision History	Description
03/21/2016	Added MTAC Review for of Tumor Treating Fields (TTFields) plus Temozolomide as maintenance therapy for Glioblastoma multiforme (GBM)
05/03/2016	MPC approved GH developed criteria for Tumor Treating Fields (TTFields)

Back to Top

09/06/2016	Criteria added for continued treatment of TTF
06/28/2017	Added Medical Directors Comments
03/06/2018	MPC approved revised criteria for continued treatment of TTF

Back to Top