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Medical Benefit		Effective Date: 04/01/20	Next Review Date: 01/21
Preauthorization	Yes	Review Dates: 09/15, 05/16, 09/16, 09/17, 07/18, 01/19, 07/19, 09/19, 01/20	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With newly diagnosed glioblastoma multiforme on maintenance therapy after initial treatment 	Interventions of interest are: <ul style="list-style-type: none"> Tumor treating fields therapy as an adjunct to standard maintenance therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard maintenance therapy alone 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Quality of life Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With progressive or recurrent glioblastoma multiforme 	Interventions of interest are: <ul style="list-style-type: none"> Tumor treating fields therapy as an adjunct or alternative to standard medical therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard medical therapy 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Quality of life Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With unresectable, locally advanced or metastatic, malignant pleural mesothelioma 	Interventions of interest are: <ul style="list-style-type: none"> Tumor treating fields therapy as an adjunct or alternative to standard medical therapy 	Comparators of interest are: <ul style="list-style-type: none"> Standard medical therapy 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Quality of life Treatment-related morbidity

DESCRIPTION

Tumor treating fields (TTF) therapy is a noninvasive technology intended to treat glioblastoma and malignant pleural mesothelioma 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 of treatment. Malignant pleural mesothelioma is an aggressive tumor with few treatment options that is associated with significant morbidity and mortality.

SUMMARY OF EVIDENCE

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes a randomized controlled trial

(RCT). Relevant outcomes include overall survival, 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 and an increase of 4.9 months in overall survival with the addition of TTF therapy to standard maintenance therapy (i.e., temozolomide) in patients with newly diagnosed GBM. Although patients were not blinded to treatment assignment, progression-free survival was assessed by blinded evaluators, and the placebo effects on the objective measure of overall survival are expected to be minimal. 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 a meaningful 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 and nonrandomized comparative studies. Relevant outcomes are overall survival, 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 (overall survival) 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. A high-quality, prospective RCT is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have unresectable, locally advanced or metastatic, malignant pleural mesothelioma who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes one single-arm observational study conducted in 80 patients. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The study has not been published but is described in the FDA Summary associated with its Humanitarian Device Exemption designation. In patients who received TTF therapy in combination with pemetrexed and cisplatin or carboplatin, median overall survival was 18.2 months (95% CI 12.3 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 evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

POLICY

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

- Adult patients ≥ 22 years of age
- Supratentorial tumor
- Karnofsky Performance Status score $\geq 70\%$
- Patient understands device use, including the requirement for a shaved head, and is willing to comply with use criteria according to the Food and Drug Administration label (see Policy Guidelines).

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

- As an adjunct to standard medical therapy (e.g., bevacizumab, chemotherapy) for patients with progressive or recurrent glioblastoma multiforme
- As an alternative to standard medical therapy for patients with progressive or recurrent glioblastoma multiforme
- For brain metastases
- For cancer in areas other than the brain
- As an adjunct to standard medical therapy (pemetrexed and platinum-based chemotherapy) for patients with malignant pleural mesothelioma.

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 patient during the trial or appearance of one or more new tumors in the brain that are diagnosed radiologically as glioblastoma multiforme).

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 four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances of a response to treatment.

MEDICARE ADVANTAGE

TREATMENT FOR NEWLY DIAGNOSED GLIOBLASTOMA MULTIFORME

Tumor treatment field therapy (TTFT) may be considered **medically necessary** for the treatment of newly diagnosed Glioblastoma Multiforme (GBM) only when all of the following criteria are met:

- The patient has histologically confirmed (World Health Organization (WHO) grade IV astrocytoma), newly diagnosed, supratentorial GBM; AND,
- The patient has received initial treatment with maximal debulking surgery (when feasible), followed by chemotherapy and radiotherapy; AND,
- Tumor treatment field therapy is initiated within seven weeks from the last dose of concomitant chemotherapy or radiotherapy, whichever is later; AND,
- The patient has no evidence of progression by Response Assessment in Neuro-Oncology (RANO) criteria; AND,
- The patient has a Karnofsky Performance Score (KPS) of at least 70; AND,
- The patient will use TTFT for an average of 18 hours per day.

TTFT is considered **not medically necessary** for the treatment of newly diagnosed Glioblastoma Multiforme (GBM) if all of the above criteria above are not met.

TREATMENT FOR NEWLY DIAGNOSED GBM BEYOND THE FIRST THREE MONTHS OF THERAPY

TTFT beyond the first three months of therapy may be considered **medically necessary** and requires that no sooner than the 60th day but no later than the 91st day after initiating therapy, the treating practitioner must conduct a clinical re-evaluation and document that the patient is continuing to use and is benefiting from TTFT.

Documentation of clinical benefit is demonstrated by:

1. Face-to-face clinical re-evaluation by the treating practitioner; AND,
2. Objective evidence of adherence to therapy, reviewed by the treating practitioner.

Adherence to therapy is defined as the use of TTFT for an average of 18 hours per day (excluding days the treating practitioner has documented a medical need to limit or interrupt treatment).

TTFT beyond the first three months of therapy will be considered as **not medically necessary** if the above criteria are not met.

If the practitioner re-evaluation does not occur until after the 91st day but the evaluation demonstrates that the patient is benefiting from TTFT as defined in criteria one and two above, TTFT may be considered **medically necessary** with the date of that re-evaluation.

RECURRENT GBM

TTFT is considered **not medically necessary** for the treatment of recurrent GBM.

OTHER USES

The use of TTFT for any indications other than newly diagnosed GBM is considered **not medically necessary**.

BACKGROUND

GLIOBLASTOMA MULTIFORME

Glioblastomas, also known as glioblastoma multiforme (GBM), are the most common form of malignant primary brain tumor in adults.¹ GBMs are grade IV astrocytomas, a rapidly progressing and deadly type of glial cell tumor that is often resistant to standard medical therapy (e.g., bevacizumab, chemotherapy). Together, anaplastic astrocytomas and glioblastomas comprise approximately 38% of all brain and central nervous system tumors.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years, with a median age at diagnosis of 64 years. Glioblastomas have the lowest survival rate of any central nervous system tumor; in one report, about a third of patients survived to one year, and the five-year survival rate was around 5%.²

Treatment of Newly Diagnosed GBM

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, chemotherapy (typically temozolomide), or a combination of these two therapies is recommended. After adjuvant therapy, patients may undergo maintenance therapy with temozolomide. Maintenance temozolomide is given for five days of every 28-day cycle for six 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.³ For

patients with good performance status, the most aggressive treatment (standard radiotherapy [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 essentially all patients.

Treatment of Recurrent GBM

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 radiotherapy 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 (e.g., 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 six months is less than 20%.⁴ 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.

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.⁵ 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®.⁶

In October 2015, FDA expanded the indication for Optune® in combination with temozolomide to include newly diagnosed GBM.⁷ 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, FDA expanded the indication for the NovoTTFTM-100L System to include “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.”⁸

FDA product code: NZK.

RELATED PROTOCOLS

Intensity-Modulated Radiotherapy: Central Nervous System Tumors

Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas

Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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