Protocol

**Tumor Treatment Fields Therapy for Glioblastoma**

<table>
<thead>
<tr>
<th>Medical Benefit</th>
<th>Effective Date: 07/01/16</th>
<th>Next Review Date: 09/18</th>
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<tbody>
<tr>
<td>Preauthorization</td>
<td>No</td>
<td>Review Dates: 09/15, 05/16, 09/16, 09/17</td>
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This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

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

<table>
<thead>
<tr>
<th>Individuals: • With progressive or recurrent glioblastoma multiforme after initial or repeat surgery, radiotherapy, and/or chemotherapy</th>
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<tbody>
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<td>Interventions of interest are: • Tumor treatment fields therapy as an alternative to standard chemotherapy</td>
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<tr>
<td>Comparators of interest are: • Standard chemotherapy</td>
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<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity</td>
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<th>Individuals: • With glioblastoma multiforme on maintenance therapy after initial treatment with surgery, radiotherapy and/or chemotherapy</th>
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<td>Interventions of interest are: • Tumor treatment fields therapy as an adjunct to standard maintenance therapy</td>
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<td>Comparators of interest are: • Standard maintenance therapy alone</td>
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<td>Relevant outcomes include: • Overall survival • Disease-specific survival • Quality of life • Treatment-related morbidity</td>
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### Description

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. Tumor treatment fields (TTF) therapy is a new, noninvasive technology intended to treat glioblastoma using alternating electric fields.

### Summary of Evidence

For individuals who have progressive or recurrent GBM after initial or repeat surgery, radiotherapy, and/or chemotherapy—who receive TTF therapy as an alternative to standard chemotherapy, the evidence includes a randomized controlled trial (RCT) and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. The published RCT reported no differences in outcomes between patients treated with TTF and with standard chemotherapy. This trial had several methodologic limitations. Comparisons made only included an active control of questionable efficacy, which might not reflect current standard of care. There was high dropout rate (> 20% of patients in each group.
were lost to follow-up) and, for the quality of life outcomes, approximately 25% of enrolled patients had complete data. The two nonrandomized studies were small and had limited validity due to differences in the patient populations treated with TTF and standard care. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have newly diagnosed GBM on maintenance therapy after initial treatment with surgery, radiotherapy, and/or chemotherapy who receive TTF therapy as an adjunct to standard maintenance therapy, the evidence includes an RCT. Relevant outcomes include overall survival, disease-specific survival, symptoms, functional outcomes, quality of life, and treatment-related morbidity. The single RCT reported that patients who received TTF treatment plus temozolomide had longer progression-free survival (3.1 months) and overall survival (4.9 months) than patients who received temozolomide alone. The trial had methodologic limitations, including a lack of a placebo control, differential dropout between groups, and the possibility of adherence bias for outcomes reported with per protocol analysis. Further corroboration of these results is needed in high-quality RCTs. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Tumor treating fields therapy to treat glioblastoma multiforme is considered investigative, including but not limited to the following situations:

- As an alternative to standard chemotherapy for patients with progressive or recurrent glioblastoma multiforme after initial or repeat treatment with surgery, radiotherapy, and/or chemotherapy.
- As an adjunct to standard maintenance therapy in patients with newly diagnosed glioblastoma multiforme following initial treatment with surgery, radiotherapy and/or chemotherapy.

Policy Guidelines

The patient reapplies the transducer arrays at home after the initial instruction.

Medicare Advantage

For Medicare Advantage tumor-treatment fields therapy is considered not medically necessary.

Background

Glioblastome Multiforme

Glioblastomas, also known as GBM, are the most common form of malignant primary brain tumor in adults. They comprise approximately 15% of all brain and central nervous system tumors, and more than 50% of all tumors that arise from glial cells.¹ The peak incidence for GBM occurs between the ages of 45 and 70 years. GBMs are grade IV astrocytomas, the most deadly type of glial cell tumor, and are often resistant to standard chemotherapy.¹ According to the National Comprehensive Cancer Network, GBM is the “deadliest brain tumor with only a third of patients surviving for one year and less than 5% living beyond five years.”²

Treatment

The primary treatment for patients newly diagnosed with GBM is to resect the tumor, confirm a diagnosis while debulking the tumor to relieve symptoms of increased intracranial pressure or compression. At the time of surgery, some patients may undergo implantation of the tumor cavity with a carmustine (bischloroethylnitroso-
urea)–impregnated wafer. The cure rate with local treatment is very low; therefore, postsurgical treatment involves adjuvant radiotherapy, chemotherapy (typically temozolomide), or a combination of the two therapies. After adjuvant therapy, some patients may undergo maintenance therapy with temozolomide. Prognostic factors for success of therapy are age, histology, and performance status or physical condition of the patient.

No standard treatment exists for recurrent GBM. In patients with disease that recurs after initial treatment, additional debulking surgery may be used if recurrence is localized. Other treatment options for recurrent disease include various forms of systemic medications such as bevacizumab, bevacizumab plus chemotherapy (e.g., irinotecan, bischloroethyl nitrosourea/chloroethyl nitrosourea, temozolomide), temozolomide, nitrosourea, procarbazine plus chloroethyl nitrosourea and vincristine), cyclophosphamide, and platinum-based agents.

Fractionated external-beam radiotherapy after surgery is standard adjuvant therapy and may be used to treat recurrent GBM. Response rates in recurrent disease are less than 10%, and progression-free survival rates at six months are less than 20%.

Testing for O6-methylguanine-DNA methyltransferase (MGMT) gene promoter methylation has been proposed as a method to predict which patients with malignant gliomas may benefit from alkylating agent chemotherapy (e.g., temozolomide). Data from randomized controlled trials have shown that MGMT promoter methylation is a predictor to responding to alkylating chemotherapeutic agents. The response and overall survival rates with temozolomide are higher in patients who have MGMT promoter methylation.

**Tumor Treatment Fields Therapy**

TTF therapy is a noninvasive technology intended to treat GBM on an outpatient basis using electrical fields. TTF therapy exposes cancer cells to alternating electric fields of low intensity and intermediate frequency, which are purported to both selectively 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.

Optune, formerly NovoTTF-100A System, is the only legally marketed TTF delivery system available in the United States. Optune is a portable battery or power supply operated device that produces alternating electrical fields within the human body. These fields are called tumor treatment fields and are applied to the patient’s shaved head using electrically insulated surface transducer arrays, such that resistively coupled electric currents are not delivered to the patient. The device is used at home on a continuous basis (20-24 hours a day for the duration of treatment). Patients can carry the device in a backpack or shoulder pack while carrying out activities of daily living.

**Regulatory Status**

In April 2011, the NovoTTF-100A™ System (Novocure, Haifa, Israel; 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 (glioblastoma multiforme), 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.”

On September 28, 2014, FDA approved Novocure’s request to change its products name 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 mar-
keted alternative device currently available for the treatment of newly diagnosed GBM that represents a life-threatening condition.

The FDA-approved label 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.”

Based on the 2011 approval Optune® is also approved for the treatment of recurrent GBM in the supratentorial region of the brain after receiving chemotherapy. The device is intended for use as a monotherapy, and as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

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 Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment 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.