VHA Office of Integrated Veteran Care
Clinical Determination and Indication
Tumor Treating Fields (TTFs)Therapy

CDI Number: 00002

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I. Disclaimer

This document is currently in draft and is intended to be used as a reference for non-VA providers and not intended to replace clinical judgment when determining care pathways. These guidelines do not guarantee benefits or constitute medical advice.

II. Clinical Determinations and Indications

a. Indications for Tumor Treating Fields (TTFs)Therapy

i. Optune

Tumor Treating Fields (TTFs) therapy with the Optune device is indicated for the treatment of newly diagnosed glioblastoma (GBM) and/or grade 4 astrocytoma and will be considered **medically necessary** when **ALL** the following criteria are met: (1 in Indented bullets)

- Veteran is 22 years or older
- Histologically confirmed GBM/grade 4 astrocytoma
- Initial treatment completed with maximal safe resection or biopsy, followed by concurrent chemotherapy and radiotherapy
- Administered with adjuvant temozolomide (Temodar), as tolerated
- Recurrence of glioblastoma after primary treatment of maximal safe resection or biopsy, followed by concurrent chemotherapy and radiotherapy
- TTFs therapy is initiated within 7 weeks from the last dose of concomitant chemotherapy or radiotherapy, whichever is the latter
- No evidence of progression by Response Assessment in Neuro-Oncology (RANO) criteria
- Karnofsky Performance Score (KPS) of at least 70 and/or Eastern Cooperative Oncology Group (ECOG) of 0 or 1

- Upon completion of required device training, the ability to apply/remove device, operate device (or caregiver) and use TTFs therapy for at least 18 hours per day

Note: Veteran will be monitored for three months for side effects and treatment tolerance. On the 60th day of treatment with Optune, but no later than the 91st day of TTFs treatment, providers will be required to evaluate effectiveness of treatment and determine the need for continued use.

ii. Optune Lua

Tumor Treating Fields (TTFs) therapy with the Optune Lua device is considered investigational and experimental for the following indications:

- Unresectable, or locally advanced, malignant pleural mesothelioma

There is insufficient evidence from peer-reviewed medical literature to support the safety and efficacy of this treatment. Therefore, Optune Lua is considered not medically necessary for the treatment of unresectable, or locally advanced, malignant pleural mesothelioma.

b. Limitations/Exclusions & Contraindications

i. Optune

Conditions/indications for which TTFs therapy with the Optune device is **not medically necessary** include, but are not limited to the following:

- Use for indications other than newly diagnosed or recurrent GBM/grade 4 astrocytoma

TTFs therapy with the Optune device is **not indicated** if any of the following are applicable:

- Cardiac pacemaker or implantable defibrillator
- Deep brain, spinal cord, or vagus nerve stimulator
- Major skull defect (e.g., missing bone)
- Metal within the brain (e.g., aneurysm clip, bullet fragment)
- Programmable ventriculoperitoneal shunt
- Pregnant, or trying to get pregnant

For all conditions not listed in section II.a. of this document, TTFs therapy with Optune is considered **not medically necessary** due to insufficient evidence of efficacy and safety.

c. Request for Durable Medical Equipment

Community providers will utilize the Request for Service Form 10-10172 to submit DME and/or Prosthetic requests to their local VA Facility Community Care office.

All fields in the DME sections of the Request for Service Form 10-10172 must be filled out with accurate information to ensure proper processing and facilitation of the DME request. To facilitate timely review of the DME request, the most recent office notes and plan of care must accompany the request. Incomplete forms with missing information and/or supplementary documents will result in processing delays and prevent the local VA Facility Community Care office from fulfilling the DME request, delaying care for the Veteran.

d. Description of Treatment

Optune

The Optune device is an FDA-approved glioblastoma treatment that works by creating TTFs, which are delivered by insulated surface transducer arrays applied directly to the scalp, providing continuous low-intensity, alternating electric fields within the tumor. This action disrupts rapidly dividing cells, causing cancer cell death and halting tumor growth. The treatment is individualized by transducer array configuration for scalp placement in relation to the tumor site using magnetic resonance imaging (MRI) guidance.

A trained individual places four adhesive transducer array patches on the surface of the shaved scalp to deliver the TTFs. The transducer arrays are then connected to the portable Optune device and battery pack. The transducer arrays require a shaved scalp and patch replacement at least twice a week. The device should be in place, at a minimum, 18 hours a day. The transducer arrays and the device should never get wet. Bathing requires the transducer arrays to be covered with a shower cap and disconnection of the device.

III. Background and Supporting Information

The following information is for reference purposes only in accordance with the medical benefits package outlined in 38 C.F.R. § 17.38 (b). Each subsection supports VA's determinations for medical necessity and alignment with generally accepted standards of medical practice.

a. Background of Information

All existing tumor treating fields (TTFs) products fall under the brand name Optune. In March 2020, the manufacturer of Optune announced a plan to include a suffix after the brand name for any newly approved indications to

further identify specific indications for individual products. To date there are two TTFs, Optune and Optune Lua.

Optune & Glioblastoma

Glioblastoma (GBM) is the most common type of malignant brain tumor among adults. These cancerous tumors develop from glial cells, which normally nourish nerve cells of the brain (neurons) and form scar tissue that help repair brain damage when injury occurs. Glioblastoma is fast-growing, aggressive, and recurs even after treatment. It invades brain tissue but does not spread outside of the central nervous system. If untreated, GBM/Grade 4 Astrocytoma can result in death in six months or less. When treated, the median overall survival is approximately 15 months.

A patient's presenting symptoms may vary, depending upon the location and size of the tumor. Many of the symptoms are related to brain swelling and increased pressure within the brain. Symptoms may present as:

- Headaches
- Seizures
- Nausea and vomiting
- Drowsiness
- Changes in personality
- Weakness on one side of the body
- Memory loss
- Speech difficulty or changes in vision

The exact cause of glioblastoma is unknown. Surgical removal of the tumor, or a biopsy, can confirm the diagnosis and provide additional information for planning therapy. Physical exam and imaging findings may be used to support the diagnosis. Imaging studies used may be computed tomography (CT) and magnetic resonance imaging (MRI). Magnetic resonance imaging (MRI) is the gold standard for imaging of glioblastoma. A neurosurgeon may also use advanced imaging to further define fiber tracts, blood volume, and metabolic function of the tumor.

Standard treatment modalities for GBM include maximal-safe surgical resection, followed by radiotherapy with concurrent temozolomide and 6-12 months of adjuvant chemotherapy. Tumor treating fields/Optune is considered as an additional treatment modality after surgery, radiotherapy, and temozolomide.

Optune is a wearable, portable device indicated to treat GBM. Once applied to the scalp, Optune delivers TTFs, which are alternating electric fields, directly into the area the cancer is located. These TTFs slow down or stop

GBM cancer cell division. To get the best response from treatment, Optune should be worn for at least 18 hours per day and should not be stopped before four full weeks of therapy is completed.

Optune Lua & Pleural Mesothelioma

Optune Lua is the newest TTFs therapy device and is proposed for the treatment of unresectable, or locally advanced, malignant pleural mesothelioma. However, research is limited and there is insufficient evidence to recommend Optune Lua for the treatment of pleural mesothelioma.

There are four types of mesothelioma cancers: pleural, peritoneal. pericardial and testicular. Each year approximately 3,300 people in the United States are diagnosed with a mesothelioma cancer and pleural mesothelioma accounts for 80% of the 3,300 diagnoses.

Pleural mesothelioma is a cancer of the lining around the lungs and the number one risk factor for mesothelioma is asbestos exposure. Once inhaled, asbestos fibers embed in the pleura, or lining around the lungs, and causes inflammation and scarring. Over time, the inflammation and scarring can lead to the development of mesothelioma. On a rare occasion it has been suggested that radiation exposure and a genetic mutation missing a BAP1 gene may be potential causes of pleural mesothelioma.

Mesothelioma is classified into three histologies:

- Epithelioid mesothelioma is the most common histology of malignant mesothelioma (60% to 80% of cases) and has the best prognosis
- Sarcomatoid mesothelioma is the rarest form of malignant mesothelioma (10% to 15% of cases). It grows faster, is more aggressive, and harder to treat than epithelioid mesothelioma
- Biphasic mesothelioma is a rare form of malignant mesothelioma (10% to 15% of cases). Biphasic mesothelioma is a mix of both epithelioid and sarcomatoid cell types

Pleural mesothelioma may not cause any symptoms until it is well advanced, and the tumor(s) has grown large enough to affect the tissues and/or organs around it. The most common symptoms associated with pleural mesothelioma are:

- Dry and persistent cough
- Shortness of breath
- Pain in the side of the chest or lower back
- Swelling in face and/or arms
- Unexplained weight loss
- Night sweats

- Fatigue
- Fever

Pleural mesothelioma is generally suspected through a physical exam, medical history, and diagnostic imaging such as chest x-rays, CT, and positron emission tomography (PET) scan. A biopsy or fluid aspiration is needed to confirm the diagnosis. Fluid aspiration includes obtaining a fluid sample from around the lungs through a thoracentesis. In some patients a biopsy of the lining of the lung is needed to detect cancer cells and is obtained through a thoracoscopy or bronchoscopy.

Standard treatment for pleural mesothelioma includes surgery, radiation therapy, chemotherapy, and immunotherapy. Some patients have achieved long-term survival after aggressive treatment, but currently pleural mesothelioma is not considered to be a curable cancer for the majority of patients.

The Optune Lua device is similar to the Optune device. It is a portable and wearable device applied to the patient's chest and/or back. The device delivers TTFs directly to the targeted cancer area. The limited data available for Optune Lua device states that Optune Lua device must be worn for at least 18 hours per day and for four full weeks of therapy. Treatment of pleural mesothelioma with Optune Lua has not been proven and is classified as experimental and investigational at this time.

b. Research, Clinical Trials, and Evidence Summaries

i. Optune

Studies support the use of TTFs for the treatment of newly diagnosed glioblastoma (GBM) and/or grade IV astrocytoma to increase median overall survival time.

Regev et al. (2021) conducted a systematic review and meta-analysis of PubMed, Scopus, and Cochrane databases to evaluate the effect, safety, efficacy, and cost of using TTFs for patients with either newly diagnosed or recurrent GBM. A total of twenty studies, including 1,636 patients (542 new GBM and 1,094 recurrent GBM) were analyzed for clinical outcomes and 11,558 patients (6,403 new GBM and 5,155 recurrent GBM) were analyzed for safety endpoints. The results showed improved clinical efficacy in patients receiving TTFs with a median overall survival of 20.9 months versus 16 months in patients not receiving TTFs. A median progression free survival of 6.7 months in patients receiving TTFs versus 4 months in patients not receiving TTFs. The overall safety profile was also positive, with no known system toxicities. Results show concerns about cost-effectiveness as

the estimated cost for receiving TTFs was $21,000 per month. In conclusion, this study supports the use of TTFs for GBM in adjunct with the standard of care treatments.

Stupp et al. (2017) evaluated whether TTFs improves progression-free and overall survival of newly diagnosed GBM with the addition of TTFs therapy plus temozolomide maintenance treatment compared with temozolomide alone, often referred to as the EF-14 study. The trial included 695 participants who had tumor resection and completed chemoradiation therapy. Of the 695 randomized patients, 637 (92%) completed the trial. The median progression-free survival from randomization was 6.7 months in the TTFs plus temozolomide group and 4.0 months in the temozolomide alone group. Conclusion showed median overall survival was 20.9 months in the TTFs plus temozolomide group compared to 16.0 months in the temozolomide alone group.

ii. Optune Lua

There are studies evaluating the role of Optune Lua in malignant plural mesothelioma. However, the evidence is not compelling for an improvement in survival or palliation of symptoms in these patients. The patient populations in the studies are heterogeneous, the studies are not randomized or designed to address whether there is compelling evidence that the use of Optune Lua in mesothelioma patients leads to an improvement in overall survival or palliation of cancer symptoms.

Ceresoli et al. (2019) conducted a prospective single-arm phase 2 trial, also known as the STELLAR study. The focus of this study was to assess patient response to a combination of chemotherapy and TTFs directed to the thorax of patients with unresectable, locally advanced, or malignant pleural mesothelioma. The study included 80 patients who met the following criteria: minimum age of 18, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, and at least one measurable lesion according to modified Response Evaluation Criteria in Solid Tumors for mesothelioma. Patients received continuous TTFs at a frequency of 150 kHz to the thorax and chemotherapy with intravenous pemetrexed (500 mg/m2) plus intravenous platinum (either cisplatin 75 mg/m2 or carboplatin) every 21 days for up to six cycles. The primary endpoint of the trial was overall survival. Results showed a median overall survival rate of 18.2 months. The most common grade 3 or worse adverse events were anemia (11%), neutropenia (9%), and thrombocytopenia (5%). The only adverse side effect reported was skin reaction and was

reported as grade 1-2 in 53 (66%) patients, and as grade 3 in 4 (5%) patients. Authors concluded the trial showed encouraging overall survival results and the combined treatment modality was safe. However, the lack of a comparison group limits the conclusions. Authors indicate further investigation in a randomized trial is needed which has not been performed.

Kutuk et al. (2022) completed a retrospective review of five patients diagnosed with malignant pleural mesothelioma. The objectives of this review were to evaluate the implementation, device usage rates, clinical outcomes, and treatment-related toxicities associated with TTFs and pemetrexed plus platinum-based chemotherapy in patients with unresectable MPM, outside the initial trial results. Patients were enrolled onto an FDA-required HDE protocol from 2019 to 2021. All patients were treated with continuous TTFs (150 kHz) and pemetrexed plus platinum-based chemotherapy. TTFs usage was recorded electronically by the device as average daily use in hours per day. Treatment response was evaluated using Modified Response Evaluation Criteria in Solid Tumors (RECIST) for malignant pleural mesothelioma. Treatment related toxicities was defined as any event within 90 days of treatment and was evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events. Resulted showed, the median number of 4-week TTFs cycles was 5 (range: 2-7 cycles). Median TTFs device use in the first 3 months was 12.5 h per day (range: 5-16.8 h), resulting in 52% (21-70%) of the potential daily duration. The median follow-up was 5.4 months (range: 1.1-20.9 months). Treatment-related dermatitis was the only side effect associated with TTFs and was reported as grade 1-2 in all patients. Authors concluded that this study was the first real-world implementation of TTFs for malignant pleural mesothelioma and further studies are needed to increase patient use and optimize management of adverse skin reactions.

c. U.S. Food & Drug Administration (FDA) Information

Optune

VA generally only approves use of medical devices that have received at least FDA clearance for 510(k) Premarket Notification. The FDA has determined these Class II devices are substantially equivalent (SE) to legally marketed predicate devices and may be marketed in the U.S.

To search for devices that have received FDA 510(k) clearance or Premarket Approval (PMA), please visit the FDA Devices database.

Information	Description
Product Name	Optune (formerly the NovottF-100A System)
PMA Applicant	Novocure Ltd.
Address	555 Thirteenth Street, NW Washington, DC 20004
Approval Date	October 05, 2015
Approval Letter	P100034-S013 Letter (fda.gov)

d. Medicare Coverage Determinations

Available Medicare coverage determinations are listed below as a resource. VA and Medicare are governed by separate laws and regulations; thus, VA coverage determinations may be different.

NCD Number	Name	Effective Date
None	N/A	N/A

LCD Number	Contractor	Original/Revision Effective Date
L34823	CGS Administrations, LLC	01/01/2020
L34823	Noridian Healthcare Solutions, LLC	01/01/2020

- (NCD: National Coverage Determination
- LCD: Local Coverage Determination

IV. Definitions

Term	Definition
Adjuvant	Auxiliary treatment that is given after primary treatment
Bronchoscopy	A procedure to look at air passages with a small camera that is located at the end of a flexible tube
Central nervous system	The part of the nervous system consisting of neurons, axons, and supporting tissue that constitute the brain and spinal cord
Concomitant	Accompanying or associated
ECOG Performance Status Scale	Performance status scale measures a patient's level of functioning to care for themself, perform daily activity, and individual physical ability
Fiber Tracts	A type of white matter tract that connects the cortex with other areas in the central nervous system

Term	Definition
Glial Cells	A type of cell that provides physical and chemical support to neurons and holds them in place
Glioblastoma (GBM)	A highly malignant, rapidly growing type of brain tumor that arises from glial cells in the brain
Grade 4 Astrocytoma	What was previously called GBM may now fall under a new category of isocitrate dehydrogenase (IDH) mutant, grade 4 astrocytoma
Histology	The microscopic study of the anatomy of biological tissues
Karnofsky Performance Score (KPS)	An assessment tool for functional impairment used to compare effectiveness of different therapies and to assess the prognosis in individual patients
Maximal-safe surgical resection	The removal of all tumors, as gauged by magnetic resonance imaging
Neurons	A specialized cells that transmits nerve impulses
Pleural Mesothelioma	A rare and aggressive form of lung cancer caused by exposure to asbestos
Pleural Space	The cavity between the lungs and the chest wall
Response Assessment in Neuro-Oncology (RANO) criteria	Radiographic criteria to assess response to treatment, divides responses into four types based on MRI and clinical features: complete response, partial response, stable disease, and progression
Supratentorial	The area located above the tentorium cerebelli, comprised of the cerebrum, ventricles, choroid plexus, pineal gland, hypothalamus, pituitary gland, and optic nerve
Temozolomide	Alkylating antineoplastic agent used to treat specific types of brain cancer (e.g., glioblastoma, anaplastic astrocytoma)
Thoracentesis	A procedure to remove fluid within the pleural space
Thoracoscopy	A procedure to visualize the lung surfaces and pleural space through a viewing tube (a thoracoscope)

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VI. CDI History/Revision Information

- Explanation of changes to the CDI

Revision Type	Date of Revision	Update(s) Made to CDI

Content Updates	12/21/23	• Updates to Optune
		  ○ Added clinical trial: Regev et al. (2021)
		• Addition of Optune Lua
		  ○ Included Optune Lua for the treatment of unresectable, locally advanced, or malignant pleural mesothelioma as investigational and experimental