Clinical Policy: Electric Tumor Treating Fields

Reference Number: WNC.CP.129 Coding Implications
Last Review Date: Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Note: When state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Description

Electric tumor treating fields (TTF), also known as alternating electric field therapy, are used for the treatment of glioblastoma, and are delivered by Optune Gio™ (NovoCure®), a portable medical device that generates low-intensity electric fields termed Tumor Treating Fields. TTF are believed to disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through electrodes placed on the scalp. The device is worn throughout the day and attached to the head by electrodes which creates a low intensity, alternating electric field within the tumor that exerts physical forces on electrically charged cellular components, preventing the normal mitotic process and causing cancer cell death prior to division.

Policy/Criteria

I. It is the policy of WellCare of North Carolina® that that TTF therapy is medically necessary for adults > 22 years when meeting one of the following:

- **A.** Request is for an initial 90 days of TTF therapy and **BOTH** of the following:
  1. One of the following indications:
     - a. New diagnosis of glioblastoma, histologically confirmed, and **ALL** of the following:
       - i. Glioblastoma is in the supratentorial region;
       - ii. Member has good performance status, as defined by a Karnofsky Performance Status rating of ≥ 70;
       - iii. Alternating electric field therapy will be delivered in conjunction with temozolomide after standard surgical and/or radiation therapies, have been completed;
     - b. Recurrent glioblastoma, histologically- or radiologically- confirmed and **BOTH** of the following:
       - i. Glioblastoma is in the supratentorial region;
       - ii. Member has good performance status, as defined by a Karnofsky Performance status rating of ≥ 70.

iii. Alternating electric field therapy will be used as a monotherapy, after standard treatment with chemotherapy, surgery, and/or radiation

2. None of the following contraindications:
   a. Implanted medical device such as deep brain stimulator, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, or programmable shunts;
   b. Skull defect such as a missing bone with no replacement, or bullet fragment;
   c. Pregnancy;
   d. Known sensitivity to conductive hydrogels (e.g., gels used on electrocardiogram [ECG] stickers or transcutaneous electrical nerve stimulation [TENS] electrodes);
3. The member agrees to wear the TTF device for 18 hours per day.

B. Request is for an additional 90 days of therapy and both of the following:
1. There has been no disease progression in the last 90 days of TTF therapy.
2. The member agrees to wear the TTF device for 18 hours per day, and was compliant with doing so in the prior authorization period.

II. It is the policy of WellCare of North Carolina® that there is insufficient evidence to support the use of TTF therapy for all other indications.

III. It is the policy of WellCare of North Carolina® that there is insufficient evidence to establish the efficacy of computer mapping software (NovoTalTM) for planning TTF therapy.

Background

Optune Product Description

Optune, formerly NovoTTF-100A produces alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through transducer arrays placed on the scalp. Electric tumor treating fields (TTF) alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for glioblastoma (GBM)). In contrast, the TTF have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little affected by the TTF. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells, nor do they stimulate nerves and muscles. It is noted that, because TTF are only applied to the brain, they have no effect on rapidly proliferating cells in the rest of the body. The

intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature. Thus, TTF application has the advantage of being highly selective and is not expected to be associated with significant toxicity.[1]

Optune Gio™, the second-generation NovoTTF-200A system, is smaller and lighter and allows for increased convenience and manageability. The transducer arrays did not change but post-marketing survey data in patients with GBM indicate that improved handling and portability helped patients comply with daily treatment duration goals for therapeutic efficiency. [19]

Position Statement

Guidelines from the National Comprehensive Cancer Network (NCCN) on central nervous system cancers, recommend alternating electrical fields therapy as a treatment option for newly diagnosed glioblastoma.[11] For patients with good performance status and either methylated or unmethylated/indeterminate O6-methylguanine-DNA methyltransferase (MGMT) promoter status," in conjunction with standard brain radiation therapy plus concurrent temozolomide and adjuvant temozolomide.(category 1 recommendation- based on high- level evidence.)[2] For recurrent glioblastoma, NCCN gives alternating electrical field therapy a 2B rating (consensus based upon lower-level evidence.)[2]

Evidence for Optune

Initial United Stated Food and Drug Administration (FDA) approval for recurrent glioblastoma was based on Stupp et al.'s 2012 phase III clinical trial that randomized 237 patients to chemotherapy-free treatment of NovoTTF (20 to 24hours per day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma[5]. Primary endpoint was improvement of overall survival. Patients were randomized to TTF alone or active chemotherapy control. Responses were more common in the TTF arm (14% versus 9.6%, p=0.19) and TTF-related adverse events were mild. Quality of life analyses favored TTF therapy in most domains. The investigators concluded that no improvement in overall survival was demonstrated. However, efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma. Toxicity and quality of life measures favored TTF.[11]

The FDA based its approval of the newly diagnosed glioblastoma indication of the Optune device on results from a 2015 clinical trial by Stupp et al.[4,5.] The EF-14 trial included 695 patients newly diagnosed with glioblastoma (GBM), and compared those who used Optune with temozolomide to those receiving temozolomide alone. Patients who used the device along with temozolomide lived, on average, about seven months with no disease progression compared to four months for those who had the drug alone. The Optune plus temozolomide group survived for an average of 19.4 months after starting treatment compared to 16.6 months for those who were treated with only temozolomide[5]. One critique of this study is that the study was terminated at the pre- planned intermediate analysis due to success of the TTF treatment. With the newly diagnosed glioblastoma indication, Optune can be used for GBM before the disease progresses. For newly diagnosed GBM, Optune is not intended to be used as a substitute for standard treatments, but rather as an adjunct therapy, and should not be used without a physician's supervision.

Hayes conducted a review of the available literature on TTF, noting that overall the body of evidence was of fair to very poor quality, although it was consistently positive.[6] Hayes found

the evidence to be stronger for the use of TTF for recurrent disease as opposed to newly diagnosed disease, as there were more supportive studies for recurrent disease at the time of publication (2 vs. 6). Out of the 10 studies they reviewed, pertaining to the use of TTF in patients with GBM and select other cancers, two were of fair quality, and the other eight ranged from poor quality to very poor quality. The two fair quality trials were those conducted by Stupp et al. in 2012 and 2015, although these were noted to have limitations such as lack of a sham intervention and significant loss to follow up (22% and 20%, respectively)[6].

A post-hoc analysis of Stupp et al.'s E-14 trial of TTF plus temozolomide versus temozolomide alone in newly diagnosed glioblastoma compared the efficacy of TTF plus physician's choice of chemotherapy versus chemotherapy alone after first recurrence[7]. Median overall survival in the TTF plus chemotherapy was 11.8 months versus 9.2 months for the chemotherapy only group ($p=.049$)[7]. TTF demonstrated low toxicity, consistent with previous studies. Limitations of this analysis are its post-hoc nature, as well as the crossover of 13 patients from the temozolomide only group to the TTF plus chemo group after approval and commercial availability of TTF for recurrent GBM[7].

Vymazal et al. analyzed the response patterns in individuals who exhibited an objective response to TTF in two previous studies in order to evaluate the baseline characteristics of those individuals who responded and to evaluate the relationship between compliance with use and efficacy outcomes.[8] The analysis was completed on one pilot study (n=10) and a phase III trial (n=237) in which TTF was compared to standard chemotherapy. Between both studies, TTF was administered as monotherapy in 130 individuals. Across both trials, there was a 15% response rate (16/110 with a 4% complete response rate)[8]. There were no significant differences in baseline characteristics between the responder and nonresponder groups. In those in which a response was noted, there was frequently a delayed response; the tumor would initially continue to grow before responding to treatment. Analysis supported that an increase in compliance was associated with better treatment response and longer overall survival. The extent of treatment response in those who exhibited a response was dependent on compliance ($p<0.001$)[8].

NovoTal

The NovoTal system (Novocure) is a computer software planning tool that helps direct placement of transducer arrays for TTF therapy.[12] Few studies have evaluated outcomes of TTF planned by physicians with and without the use of NovoTal, and these are limited to a case series, physician use study, and two review articles. Additionally, many of the authors reported ties to Novocure.

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2024, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS ®* 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

Reviews, Revisions, and Approvals	Reviewed Date	Approval Date
Original approval date	03/21	05/21
Reviewed HCPCS and ICD-10-CM codes. References reviewed and updated.	01/22	02/22
Annual review. Replaced I/E language in II & III "with insufficient evidence to support…" References reviewed, updated and reformatted.	09/22	11/22
Added Criteria I.A.3. and Criteria I.B.2. to include that the member/enrollee agrees to wear the device 18 hours per day, and for continuation of therapy, has also been compliant with the wearing the device in the prior authorization period. Background updated with no impact on criteria. Removed ICD-10 codes.	02/23	02/23
NCHC verbiage removed from NC Guidance Verbiage.	04/23	04/23
Annual Review.	11/23	11/23
Updated wording in description with no impact to criteria. In I.A.1.a.iii. added "and/or;" in I.A.b.ii. changed wording to "chemotherapy, surgery, and/or radiation." References reviewed and updated.	02/24	02/24
Annual Review. Changed I.A.1.a.ii. From ≥ 60 to Karnofsky Performance Status of ≥ 70. Added I.A.1.b.ii. "Member has good performance status, as defined by a Karnofsky Performance status rating of ≥ 70. Updated description and background with no clinical significance. Word "Enrollee" removed in I.A.3. HCPCS reviewed, References reviewed and updated.		

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North Carolina Guidance

Eligibility Requirements

1. An eligible beneficiary shall be enrolled in the NC Medicaid Program (Medicaid is NC Medicaid program, unless context clearly indicates otherwise);
2. Provider(s) shall verify each Medicaid beneficiary's eligibility each time a service is rendered.
3. The Medicaid beneficiary may have service restrictions due to their eligibility category that would make them ineligible for this service.

EPSDT Special Provision: Exception to Policy Limitations for a Medicaid Beneficiary under 21 Years of Age

- 42 U.S.C. § 1396d(r) [1905(r) of the Social Security Act]

Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) is a federal Medicaid requirement that requires the state Medicaid agency to cover services, products, or procedures for Medicaid beneficiary under 21 years of age if the service is medically necessary health care to correct or ameliorate a defect, physical or mental illness, or a condition [health problem] identified through a screening examination (includes any evaluation by a physician or other licensed practitioner).

This means EPSDT covers most of the medical or remedial care a child needs to improve or maintain his or her health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

Medically necessary services will be provided in the most economic mode, as long as the treatment made available is similarly efficacious to the service requested by the beneficiary's physician, therapist, or other licensed practitioner; the determination process does not delay the delivery of the needed service; and the determination does not limit the beneficiary's right to a free choice of providers.

EPSDT does not require the state Medicaid agency to provide any service, product or procedure:

I. that is unsafe, ineffective, or experimental or investigational.
II. that is not medical in nature or not generally recognized as an accepted method of medical practice or treatment.

Service limitations on scope, amount, duration, frequency, location of service, and other specific criteria described in clinical coverage policies may be exceeded or may not apply as

long as the provider's documentation shows that the requested service is medically necessary "to correct or ameliorate a defect, physical or mental illness, or a condition" [health problem]; that is, provider documentation shows how the service, product, or procedure meets all EPSDT criteria, including to correct or improve or maintain the beneficiary's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

EPSDT and Prior Approval Requirements

- If the service, product, or procedure requires prior approval, the fact that the beneficiary is under 21 years of age does NOT eliminate the requirement for prior approval.
- **IMPORTANT ADDITIONAL INFORMATION** about EPSDT and prior approval is found in the *NCTracks Provider Claims and Billing Assistance Guide*, and on the EPSDT provider page. The Web addresses are specified below:

NCTracks Provider Claims and Billing Assistance Guide:
https://www.nctracks.nc.gov/content/public/providers/provider-manuals.html
EPSDT provider page: https://medicaid.ncdhhs.gov/

Provider(s) Eligible to Bill for the Procedure, Product, or Service
To be eligible to bill for the procedure, product, or service related to this policy, the provider(s) shall:

i. meet Medicaid qualifications for participation;
ii. have a current and signed Department of Health and Human Services (DHHS) Provider Administrative Participation Agreement; and
iii. bill only for procedures, products, and services that are within the scope of their clinical practice, as defined by the appropriate licensing entity.

Compliance
Provider(s) shall comply with the following in effect at the time the service is rendered:

A. All applicable agreements, federal, state and local laws and regulations including the Health Insurance Portability and Accountability Act (HIPAA) and record retention requirements; and
B. All NC Medicaid's clinical (medical) coverage policies, guidelines, policies, provider manuals, implementation updates, and bulletins published by the Centers for Medicare and Medicaid Services (CMS), DHHS, DHHS division(s) or fiscal contractor(s).

Claims-Related Information
Provider(s) shall comply with the NC Tracks Provider Claims and Billing Assistance Guide, Medicaid bulletins, fee schedules, NC Medicaid's clinical coverage policies and any other relevant documents for specific coverage and reimbursement for Medicaid:

- Claim Type - as applicable to the service provided:
  Professional (CMS-1500/837P transaction)

Institutional (UB-04/837I transaction)
Unless directed otherwise, Institutional Claims must be billed according to the National Uniform Billing Guidelines. All claims must comply with National Coding Guidelines.

- International Classification of Diseases and Related Health Problems, Tenth Revisions, Clinical Modification (ICD-10-CM) and Procedural Coding System (PCS) - Provider(s) shall report the ICD-10-CM and Procedural Coding System (PCS) to the highest level of specificity that supports medical necessity. Provider(s) shall use the current ICD-10 edition and any subsequent editions in effect at the time of service. Provider(s) shall refer to the applicable edition for code description, as it is no longer documented in the policy.
- Code(s) - Provider(s) shall report the most specific billing code that accurately and completely describes the procedure, product or service provided. Provider(s) shall use the Current Procedural Terminology (CPT), Health Care Procedure Coding System (HCPCS), and UB-04 Data Specifications Manual (for a complete listing of valid revenue codes) and any subsequent editions in effect at the time of service. Provider(s) shall refer to the applicable edition for the code description, as it is no longer documented in the policy. If no such specific CPT or HCPCS code exists, then the provider(s) shall report the procedure, product or service using the appropriate unlisted procedure or service code.
  Unlisted Procedure or Service
  CPT: The provider(s) shall refer to and comply with the Instructions for Use of the CPT Codebook, Unlisted Procedure or Service, and Special Report as documented in the current CPT in effect at the time of service.
  HCPCS: The provider(s) shall refer to and comply with the Instructions For Use of HCPCS National Level II codes, Unlisted Procedure or Service and Special Report as documented in the current HCPCS edition in effect at the time of service
- Modifiers - Providers shall follow applicable modifier guidelines.
- Billing Units - Provider(s) shall report the appropriate code(s) used which determines the billing unit(s).
- Co-payments -
  For Medicaid refer to Medicaid State Plan:
  https://medicaid.ncdhhs.gov/get-involved/nc-health-choice-state-plan

- Reimbursement - Provider(s) shall bill their usual and customary charges. For a schedule of rates, refer to: https://medicaid.ncdhhs.gov/.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and

accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.