National Medical Policy

Subject: Electric Tumor Treatment Fields (e.g. Optune Device, formerly NovoTTF-100A)

Policy Number: NMP523

Effective Date*: September 2013

Updated: May 2016

This National Medical Policy is subject to the terms in the IMPORTANT NOTICE at the end of this document.

For Medicaid Plans: Please refer to the appropriate State’s Medicaid manual(s), publication(s), citation(s), and documented guidance for coverage criteria and benefit guidelines prior to applying Health Net Medical Policies.

The Centers for Medicare & Medicaid Services (CMS)
For Medicare Advantage members please refer to the following for coverage guidelines first:

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Instructions
- Medicare NCDs and National Coverage Manuals apply to ALL Medicare members in ALL regions.
- Medicare LCDs and Articles apply to members in specific regions. To access your specific region, select the link provided under “Reference/Website” and follow the search instructions. Enter the topic and your specific state to find the coverage determinations for your region. *Note: Health Net must follow local coverage determinations (LCDs) of Medicare Administration Contractors (MACs) located outside their service area when those MACs have exclusive coverage of an item or service. (CMS Manual Chapter 4 Section 90.2)
• If more than one source is checked, you need to access all sources as, on occasion; an LCD or article contains additional coverage information than contained in the NCD or National Coverage Manual.

• If there is no NCD, National Coverage Manual or region specific LCD/Article, follow the Health Net Hierarchy of Medical Resources for guidance.

Current Policy Statement
Health Net, Inc. may consider the Optun device, formerly known as the NovoTTF-100A System, medically necessary for treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme, following histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy on a case by case basis. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

Health Net, Inc. considers the Optune device, formerly known as the NovoTTF-100A System, (i.e., electronic tumor treatment field, ETTF*) with temozolomide as investigational for the treatment of adult patients (≥22 years old), newly diagnosed with histologically-confirmed supratentorial glioblastoma multiforme (GBM), following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotheraphy. At this time, there is a paucity of peer reviewed literature to support this.

*NOTE: Treatment with TTFields is delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m2/d) was given for 5 days of each 28-day cycle.

Definitions
GBM       Glioblastoma multiforme
PS        Performance status
TTF       Tumor treatment fields

Codes Related To This Policy
NOTE:
The codes listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit documents and medical necessity criteria. This list of codes may not be all inclusive.

On October 1, 2015, the ICD-9 code sets used to report medical diagnoses and inpatient procedures have been replaced by ICD-10 code sets.

ICD-9 Codes
191.0-191.9    Malignant neoplasm of brain

ICD-10 Codes
C71.0-C71.9    Malignant Neoplasm of brain

CPT Codes
N/A
**Scientific Rationale – Update May 2016**

On September 24, 2014, Novocure received a supplemental approval (P100034-S010) to their original premarket approval (PMA) for the NovoTTF-100A (P100034) permitting a name change of the Novo TTF 100A system to Optune.

Per the FDA (October 8, 2015) an expanded indication for the Optune device was approved, to treat patients with newly-diagnosed glioblastoma multiforme (GBM). It is given along with the chemotherapy drug temozolomide (TMZ) following standard treatments that include surgery, and radiation therapy and chemotherapy used together. The FDA based its approval of the expanded indication of the Optune device on results from a clinical trial by Stupp et al. (2015, noted in the paragraph below) involving 695 patients newly diagnosed with GBM that compared those who used Optune with TMZ to those receiving TMZ alone. Patients who used the device along with TMZ lived, on average, about seven months with no disease progression compared to four months for those who had the drug alone. The Optune plus TMZ group survived for an average of 19.4 months after starting treatment compared to 16.6 months for those who were treated with only TMZ. Optune was initially approved in 2011 to treat patients with GBM that recurred or progressed after chemotherapy. With this expanded indication, Optune can be used as part of a standard treatment 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.

Stupp et al. (2015) evaluated the safety and efficacy of TTF in individuals with newly diagnosed glioblastoma following chemoradiation therapy. This multi-center clinical trial with the identification # NCT00916409 enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis. The patients were randomized (2:1) to either TTF with temozolomide or temozolomide alone. The primary endpoint was identified as progression-free survival (PFS) in the intent-to-treat (ITT) population (significant threshold, p≤0.01). An interim analysis was designed into the study to be conducted on the first 315 participants who had completed at least 18 months of follow-up. At interim analysis, the median PFS in the TTF plus temozolomide group was 7.1 months (95% confidence interval [CI], 5.9-8.2 months) compared to 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide group (Hazard Ratio [HR] 0.62; 98.7% CI, 0.43-0.89; stratified log-rank, p=0.001). The secondary end point, the overall survival (OS) in the per-protocol population also showed significant improvement in the treatment group versus control. Median overall survival in the per-protocol population in the TTF plus temozolomide group versus the temozolomide alone group was 20.5 months (95% CI, 16.7-25.0 months) and 15.6 months (95% CI, 13.3-19.1 months) respectively (HR, 0.64; 99.4% CI, 0.42-0.98; p=0.004). Based on the interim analysis results, the study was terminated and individuals in the control group were offered TTF in addition to temozolomide. A total of 11 individuals crossed over and began using TTF. With the exception of a higher incidence of localized skin reactions in the TTF plus temozolomide group, the incidence, distribution, and severity of adverse events were similar across both treatment groups. This trial does contain a few limitations. As enrollment was not initiated until following radiochemotherapy, this initial phase of treatment is subject to variability. Participants were excluded from participation for progression during early radiotherapy; therefore, those with a very poor prognosis were not included in
the sample population. In addition, as TTF was continued beyond tumor progression, there was additional data on this group, increasing the potential for reporting bias. In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTF fields to maintenance temozolomide chemotherapy, significantly prolonged progression-free and overall survival. Final analysis of the data will be completed when data collection is completed on the entire study population, tentatively expected at the end of 2016. (FDA approval of combination of Optune together with temozolomide for newly diagnosed GBM, with specific criteria, is based on this study).

Vymazal et al. (2015) analyzed the response patterns in individuals who exhibited an objective response 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. 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% CR rate). 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 OS. The extent of treatment response in those who exhibited a response was dependent on compliance (p<0.001). Although the analysis did note potential characteristics which predict response to TTF, further studies are needed.

There is a Clinical Trial on 'A Phase II Study of Optune (NovoTTF) in Combination With Bevacizumab (BEV) and Temozolomide (TMZ) in Patients With Newly Diagnosed Unresectable Glioblastoma (GBM)' which is currently recruiting participants. The Clinicaltrials.gov identifier number is NCT02343549, and it was last updated January 27, 2016. All patients will complete best standard of care radiation, temozolomide and bevacizumab (6 weeks). Within two weeks of completion of this initial treatment period, study patients will be fitted with the NovoTTF-100A System (i.e., Optune device) and treated continuously. They will be treated with TTF fields for 12 months for an average of 18 hours per day. The patient may elect to take a treatment break for a total of 3 days per month, for each month and still be in compliance. This will consist of wearing four electrically insulated electrode arrays on the head. The patients will also continue with maintenance temozolomide/bevacizumab. The estimated study completion date is June 2017.

**Position Statements**

Per NCCN, (V1. 2015 on CNS Cancer), it notes under Treatment for Recurrence: "For the diffuse or multiple" and "local" pathways the option 'Consider alternating electric field therapy for glioblastoma' changed from category 3 to category 2B.

The same NCCN guidelines mention that "Temozolomide is recommended if tumor is methylguanine methyl-transferase (MGMT) promoter methylated". These guidelines also state that with glioblastoma "Temozolomide can be used as an adjuvant RX, concurrent with RT, post-radiation therapy, and with recurrence therapy". NCCN does mention that Temozolomide is now standard of care in conjunction with post-op RT for younger good performance patients with glioblastoma. There is no mention in the NCCN guidelines of the Optune device to be used along with Temozolomide.

The World Health Organization (WHO, 2015) classifies astrocytomas into four grades depending on how fast they are growing and the likelihood that they will infiltrate to nearby brain tissue:
1. Grade I astrocytoma is usually a non-infiltrating tumor.
2. Grade II astrocytoma is also called low-grade astrocytoma or diffuse astrocytoma and is usually an infiltrating tumor.
3. Grade III astrocytoma is also called anaplastic (malignant) astrocytoma because this tumor grows more quickly than a grade II astrocytoma.
4. Grade IV astrocytoma is also called glioblastoma or GBM and is the most aggressive type of nervous system tumor. It is also referred to as glioblastoma multiforme because of its wide variety of appearances under the microscope.

GBM occurs most often in adults between the ages of 50 and 80, is more common in men, and accounts for 23% of all primary brain tumors.

Per WHO, (2015), Grade IV astrocytoma: The three main forms of treatment for GBM are surgery and radiation or chemotherapy. These treatments may be used alone or in combination with one another. The initial treatment in most cases is surgical excision and removal of as much as the tumor as possible (resection). Often, only a portion of the tumor can be safely removed because malignant cells may have spread to surrounding brain tissue. Because surgery cannot completely remove a tumor, radiation therapy and chemotherapy are used following surgery to continue treatment. This was the most current information on the WHO site, since the combination of the Optune device and temozolomide, for newly diagnosed adults with GBM with specific criteria as noted above, was not FDA approved until October 2015.

**Scientific Rationale – Update September 2015**

Kanner et al. (2014) et al. performed a treatment-based analysis of data from the pivotal phase III trial of the NovoTTF-100A System versus best physician's choice (BPC) chemotherapy in patients with recurrent glioblastoma multiforme (GBM), with particular focus on efficacy in patients using NovoTTF Therapy. Median overall survival (OS) was compared for recurrent GBM patients receiving at least one full cycle of treatment with NovoTTF-100A System or BPC chemotherapy (modified intention-to-treat [mITT] population) in the recently reported phase III trial. The relationship between NovoTTF-100A System compliance and OS was evaluated in the ITT population. Kaplan-Meier analyses examined treatment-related differences in OS for various patient subgroups. Median OS was significantly higher in patients receiving >1 course of NovoTTF Therapy versus BPC (7.7 v 5.9 months; hazard ratio, 0.69; 95% confidence interval [CI], 0.52-0.91; P =.0093). Median OS was also significantly higher in patients receiving NovoTTF Therapy with a maximal monthly compliance rate >75% ( >18 hours daily) versus those with a <75% compliance rate (7.7 v 4.5 months; P =.042), and Kaplan-Meier analysis demonstrated a significant trend for improved median OS with higher compliance (P =.039). Additional post hoc analysis showed significantly higher median OS with NovoTTF Therapy than with BPC for patients with prior low-grade glioma, tumor size >18 cm2, Karnofsky performance status >80, and those who had previously failed bevacizumab therapy. When used as intended in mITT patients with recurrent GBM, NovoTTF Therapy provides an OS benefit compared with chemotherapy in patients with recurrent GBM. This contrasts with the equivalent efficacy reported previously based on analysis of all randomized ITT subjects, including many who did not receive a full cycle of treatment. Higher NovoTTF Therapy compliance corresponds with greater survival benefit in the present study.

Mrugala et al. (2014) completed the NovoTTF-100A System, a novel antimitotic cancer therapy recently approved for the treatment of recurrent GBM, based on phase III (EF-11) trial results. The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received NovoTTF Therapy in a
Data were collected from all adult patients with recurrent GBM who began commercial NovoTTF Therapy in the United States between October 2011 and November 2013. Overall survival (OS) curves were constructed for PRiDe using the Kaplan-Meier method. Median OS in PRiDe was compared for patients stratified by average daily compliance (>75% vs <75% per day) and other prognostic variables. Adverse events were also evaluated. Data from 457 recurrent GBM patients who received NovoTTF Therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received NovoTTF Therapy for first recurrence (33% vs 9%) and had received prior bevacizumab therapy (55.1% vs 19%). Median OS was significantly longer with NovoTTF Therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 vs 6.6 months; HR, 0.66; 95% CI, 0.05 to 0.86, P = .0003). One- and 2-year OS rates were more than double for NovoTTF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% vs 20%; 2-year: 30% vs 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse events were detected in PRiDe. As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the NovoTTF Therapy transducer arrays. Results from PRiDe, together with those previously reported in the EF-11 trial, indicate that NovoTTF Therapy offers clinical benefit to patients with recurrent GBM. NovoTTF Therapy has high patient tolerability and favorable safety profile in the real-world, clinical practice setting.

Scientific Rationale – Update September 2014

In 2011, the U.S. Food and Drug Administration (FDA) approved the NovoTTF-100A System (NovoCure, LTD), a portable medical device that generates low-intensity electric fields termed Tumor Treating Fields (TTF) for the treatment of recurrent glioblastoma. Approval was based on results of a clinical trial that randomized 237 patients to TTF or chemotherapy. Similar survival was noted in the two arms, and TTF therapy was associated with lower toxicity and improved quality of life.

In 2013, NCCN included in their guidelines on Central Nervous System Cancers, alternating electric field therapy for recurrent disease in individuals with glioblastoma as a treatment option. NCCN noted the recommendation was a category 2B recommendation (i.e., based on lower-level evidence, there is NCCN consensus that the intervention is appropriate).

NCCN guidelines on Central Nervous System Cancers were recently updated (Version 1.2014). Regarding treatment of glioblastoma, the guidelines now note that treatment options for recurrent disease include palliative/best supportive care if poor performance status, systemic chemotherapy, or surgery for symptomatic, large lesion. These recommendations are all category 2A recommendations from NCCN (i.e., there is uniform NCCN consensus that the intervention is appropriate.) The most recent updated guidelines have been revised and now state that alternating electric field therapy for recurrent disease in individuals with glioblastoma as a treatment option is a category 3 recommendation, (i.e, there is major disagreement that the intervention is appropriate) and no longer a 2B recommendation.

Turner et al (2014) presented three patients with GBM in whom the fields were adjusted at recurrence and the effects of each adjustment. The authors believed there may be a higher risk of treatment failure on the edges of the field where the field strength may be lower. The first patient underwent subtotal resection, radiotherapy with temozolomide (TMZ), and then began NovoTTF Therapy with metronomic TMZ. She had good control for nine months; however, new bifrontal lesions developed, and her fields were adjusted with a subsequent radiographic
response. Over the next five months, her tumor burden increased and death was preceded by a right insular recurrence. A second patient underwent two resections followed by radiotherapy/TMZ and NovoTTF Therapy/TMZ. Six months later, two new distal lesions were noted, and he underwent further resection with adjustment of his fields. He remained stable over the subsequent year on NovoTTF Therapy and bevacizumab. A third patient on NovoTTF Therapy/TMZ remained stable for two years but developed a small, slow growing enhancing lesion, which was resected, and his fields were adjusted accordingly. Interestingly, the pathology showed giant cell GBM with multiple syncitial-type cells. The authors concluded, based on these observations, they believe that field strength may play a role in 'out of field' recurrences and that either the presence of a certain field strength may select for cells that are of a different size or that tumor cells may change size to avoid the effects of the TTFields.

Elzinga and Wong (2014) reported although bevacizumab has been in use for recurrent glioblastoma, patients who experience incomplete or no response to bevacizumab may be predisposed to early bevacizumab treatment failure. However, the addition of TTFields therapy may augment the efficacy from bevacizumab. The authors reported on a patient with recurrent cystic glioblastoma who received add-on TTFields therapy due to an incomplete response to single-agent bevacizumab. After 6 cycles of therapy, a resolution of cystic enhancement was noted, together with reduction of the tumor cyst and resolution of most of the cerebral edema in the surrounding brain. However, the patient also suffered from relapsed disease at locations distant from the original glioblastoma and the corresponding radiation fields received at initial diagnosis. The authors concluded that combination TTFields and bevacizumab therapy is safe and may be efficacious for patients with recurrent glioblastoma. A further study would be needed to determine the relapse pattern and the distribution of the electric fields in the brain.

Lacouture et al (2014) reported the occurrence of dermatologic adverse events (dAEs) from NovoTTF's is primarily due to the continuous contact between the array-related components and the scalp for periods of 3-4 days (together with other risk factors). These dAEs may include allergic and irritant dermatitis, mechanical lesions, ulcers, and skin infection. The incidence of dAEs in the phase III trial (n = 116) was 16% (2% grade 2, 0% grade 3/4); the post-marketing surveillance program (n = 570) revealed 156 (21.8%) dAEs with some patients reporting more than one event. Prophylactic strategies for dAEs include proper shaving and cleansing of the scalp and array relocation. Treatment-based strategies are AE-specific and include topical or oral antibiotics, topical corticosteroids, and isolation of affected skin areas from adhesives and pressure. The addition of skin care strategies to the NovoTTF-100A System use will maximize adherence to therapy while maintaining quality of life, all of which contribute to the therapeutic benefit of NovoTTF Therapy in recurrent glioblastoma.

Numerous clinical trials are recruiting participants:

- A phase II trial evaluating how well Novocure's Tumor Treating Electric Fields (NovoTTF) therapy works in treating patients with recurrent glioblastoma multiforme. (NCT01954576)

- A phase II trial that seeks to determine the efficacy of the combination of Bevacizumab and NovoTTF-100A in Bevacizumab naive patients with recurrent GBM as measured by 6-month progression free survival (NCT01894061)
• A phase III prospective, randomly controlled pivotal trial, designed to test the efficacy and safety of NovoTTF-100A, as an adjuvant to the best standard of care in the treatment of newly diagnosed GBM patients (NCT00916409)

• A Proposed Pilot Study of Combined NOVOTTF-100A+ Bevacizumab, and Hypofractionated Stereotactic Irradiation for Bevacizumab-Naive Recurrent Glioblastoma (NCT01925573)

Scientific Rationale – Initial
Glioblastoma, also called glioblastoma multiforme (GBM) is the most common and most lethal brain tumor, with only a third of the patients surviving for one year and < 5% living beyond 5 years. Treatment options for GBM include surgical resection with or without Gliadel Wafer (BCNU), radiation therapy, and chemotherapy. Decisions regarding aggressiveness of surgery for primary brain lesions are complex and depend on the age and performance status (PS); proximity to "eloquent" areas of the brain; feasibility of decreasing the mass effect with aggressive surgery; respectability of the tumor (including the number and location of lesions) and time since last surgery in patients with recurrent disease.

Per NCCN guidelines, “Management of recurrent tumors depends on the extent of disease and patient condition. For local recurrence, repeat resection, with or without wafer placement in the surgical bed, can be performed if possible. Following re-resection, or if the local recurrence is unresectable, poor performance patients should undergo palliative/best supportive care without further active treatment. If PS is favorable, systemic chemotherapy may be administered (especially for anaplastic oligodendrogliomas); re-irradiation is a category 2B option (i.e. Based on lower level of evidence, there is NCCN consensus that the intervention is appropriate) to consider if prior radiation achieved a good/durable response. Patients with recurring glioblastoma may also consider alternating electric field therapy (category 2B). In the case of diffuse or multiple recurring lesions, the options are: palliative/best supportive care for poor performance patients; systemic chemotherapy; surgery to relieve mass effect; or consider alternating electric field therapy for glioblastomas (category 2B).”

The NovoTTF-100A System (NovoCure, LTD) was approved by the Food and Drug Administration (FDA) in April 2011 and is indicated for treatment of adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme, following histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

The FDA approval was based on results of a phase III clinical trial that randomized 237 patients to chemotherapy-free treatment of NovoTTF (20-24h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma (Stupp et al 2012). Primary end-point was improvement of overall survival. Patients (median age 54 years (range 23-80), Karnofsky performance status 80% (range 50-100) were randomised to Tumor Treatment Fields (TTF) alone (n=120) or active chemotherapy control (n=117). Number of prior treatments was two (range 1-6). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66-1.12]; p=0.27), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% (p=0.13), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, p=0.19). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% (p=0.022) of
patients treated with TTF and chemotherapy, respectively. 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 clearly favored TTF.

The FDA approval concluded the following:

“Recurrent GBM is a fatal, end-stage, disease with a 1-year survival of less than 20% and a negligible 5-year survival. The outcome of patients with this disease has not improved significantly in the past decade despite the introduction of temozolomide, Bevacizumab and the use of Gliadel wafers. Quality of life of recurrent GBM patients is compromised due to the neurological deficits caused by the tumor itself together with the considerable side effects of the various standard chemotherapies and experimental treatments. Treatment options for recurrent GBM are very limited, and all have limitations, including severe potential side effects. These options include tumor resection in a minority of cases (with or without Gliadel Wafer implantation), additional radiotherapy boost in selected cases and chemotherapy using bevacizumab.

Compared to previous chemotherapy approvals for recurrent GBM, the current pivotal trial was generally well designed and conducted (e.g., randomized superiority study, multi-center, half of the subjects from the US, data poolable between countries, and minimal loss to follow-up). Although the pivotal study failed to show that NovoTTF-100A is superior to best standard of care (BSC) in overall survival and secondary effectiveness endpoints, NovoTTF-100A treatment exhibits minimal toxicity, clinically comparable primary and secondary effectiveness, and better quality of life compared to the chemotherapies used in the control arm of the study.”

NovoTTF-100A is a portable battery or power supply operated device that generates low-intensity electric fields, called Tumor Treatment Fields (TTFs). TTFs 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 by the patient 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. The device has been shown in both in vitro and in vivo studies to slow and reverse tumor growth by inhibiting mitosis, the process by which cells divide and replicate.

TTFs harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTF technology takes advantage of the special characteristics, geometrical shape, and rate of dividing cancer cells, which make them susceptible to the effects of the alternating electric TTFs. These special fields 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 GBM). TTFs have been shown to disrupt mitotic spindle microtubule assembly and to lead to dielectrophoretic dislocation of intracellular macromolecules and organelles during cytokinesis. These processes lead to physical disruption of the cell membrane and to programmed cell death (apoptosis). The TTFs have not been shown to affect cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be minimally affected by the TTFs.
Treatment parameters are preset by NovoCure such that there are no electrical output adjustments available to the patient. Based on detailed training provided by the physician, the patient will learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the electrodes need to be replaced once to twice a week and the scalp re-shaved in order to maintain optimal contact. Patients carry the device in an over-the-shoulder bag or backpack and receive continuous treatment without changing their daily routine.

The device is contraindicated in individuals with an active implanted medical device, a skull defect (i.e., missing bone with no replacement), shunt(s) or bullet fragment(s) as this may lead to malfunctioning of the implanted device, tissue damage or render the device ineffective. It is also contraindicated in individuals with a sensitivity to conductive hydrogels (e.g., gel used on electrocardiogram stickers or transcutaneous electrical nerve stimulation electrodes).

Continued approval of the FDA approval is contingent upon the submission of periodic reports, at intervals of one year (unless otherwise specified) from the date of approval. In addition, the company must conduct a post-approval study (PAS), “The New Enrollment Study for NovoTTF-100A in Recurrent GBM Patients” and will address whether the overall survival of patients treated with NovoTTF-100A is non-inferior to the survival of patients treated with the best standard of care (chemotherapy). The study will be conducted in at least 30 sites, at least half of them in the United States, and may include centers with previous experience with the device. Patients 22 years old and older will be included in the PAS. A total of 486 subjects will be enrolled, with 243 subjects per study arm. All study participants will be followed until death. Post approval study (PAS) Progress Reports every six months during the first two years and annually are also required.

Kirson et al (2009) explored the efficacy and toxicity of combining TTFs, with chemotherapeutic treatment in-vitro, in-vivo and in a pilot clinical trial. Cell proliferation in culture was studied in human breast carcinoma (MDA-MB-231) and human glioma (U-118) cell lines, exposed to TTFs, paclitaxel, doxorubicin, cyclophosphamide and dacarbazine (DTIC) separately and in combinations. In addition, we studied the effects of combining chemotherapy with TTFs in an animal tumor model and in a pilot clinical trial in recurrent and newly diagnosed GBM patients. The efficacy of TTFs-chemotherapy combination in-vitro was found to be additive with a tendency towards synergism for all drugs and cell lines tested (combination index $<or= 1$). The sensitivity to chemotherapeutic treatment was increased by 1-3 orders of magnitude by adjuvant TTFs therapy (dose reduction indexes 23 - 1316). Similar findings were seen in an animal tumor model. Finally, 20 GBM patients were treated with TTFs for a median duration of 1 year. No TTFs related systemic toxicity was observed in any of these patients, nor was an increase in Temozolomide toxicity seen in patients receiving combined treatment. In newly diagnosed GBM patients, combining TTFs with Temozolomide treatment led to a progression free survival of 155 weeks and overall survival of 39+ months. Investigators concluded the results indicate that combining chemotherapeutic cancer treatment with TTFs may increase chemotherapeutic efficacy and sensitivity without increasing treatment related toxicity.

Salzberg et al (2008) evaluated the safety, tolerability, and efficacy profile of TTFields treatment in patients with locally advanced and/or metastatic solid tumors using the NovoTTF100A device in an open, prospective pilot study. All 6 patients were heavily pre-treated with several lines of therapy; no additional standard treatment option was available to them. TTFs treatment using continuous NovoTTF-100A lasted a minimum of 14 days and was very well tolerated. No related serious
adverse events occurred. Outcomes showed 1 partial response of a treated skin metastasis from a primary breast cancer, 3 cases where tumor growth was arrested during treatment, and 1 case of disease progression. One mesothelioma patient experienced lesion regression near TTFs with simultaneous tumor stability or progression in distal areas. Investigators concluded although the number of patients in this study is small, the lack of therapy toxicity and the efficacy observed in data gathered to date indicate the potential of TTFs as a new treatment modality for solid tumors, definitely warranting further investigation.

Electric tumor treating fields technology is also being studied as a treatment for other solid tumors (e.g., non-small cell lung cancer, breast cancer). However, there is a paucity of published evidence from randomized controlled trials examining the long-term safety and effectiveness of TTF as a treatment of tumors. Clinical trials are ongoing.

**Review History**

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<td>September 2013</td>
<td>Medical Advisory Council, initial approval</td>
</tr>
<tr>
<td>September 2014</td>
<td>Update – Revised policy statement to consider the NovoTTF-100A System medically necessary on a case by case basis.</td>
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<tr>
<td>May 2016</td>
<td>Update – Added FDA approval (10/5/15) of Optune with temozolomide for the treatment of adult patients (&gt;22 years old) with newly diagnosed and histologically-confirmed, supratentorial glioblastoma multiform (GBM) following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy. This was added as investigational, since there is a paucity of peer-reviewed literature to support it. Revised title of policy to: 'Electric Tumor Treatment Fields (e.g. Optune Device, formerly NovoTTF-100A).’ Codes updated.</td>
</tr>
</tbody>
</table>

**This policy is based on the following evidence-based guidelines:**

3. Hayes. Optune (NovoTTF 100 A System; Novocure) for the Treatment of Recurrent Glioblastoma. February 26, 2015

**References – Update May 2016**


References – Update September 2015

References – Update September 2014

References - Initial

Important Notice

General Purpose.
Health Net's National Medical Policies (the "Policies") are developed to assist Health Net in administering plan benefits and determining whether a particular procedure, drug, service or supply is medically necessary. The Policies are based upon a review of the available clinical information including clinical outcome studies in the peer-reviewed published medical literature, regulatory status of the drug or device, evidence-based guidelines of governmental bodies, and evidence-based guidelines and positions of select national health professional organizations. Coverage determinations are made on a case-by-case basis and are subject to all of the terms, conditions, limitations, and exclusions of the member's contract, including medical necessity requirements. Health Net may use the Policies to determine whether under the facts and circumstances of a particular case, the proposed procedure, drug, service or supply is medically necessary. The conclusion that a procedure, drug, service or supply is medically necessary does not constitute coverage. The member's contract defines which procedure, drug, service or supply is covered, excluded, limited, or subject to dollar caps. The policy provides for clearly written, reasonable and current criteria that have been approved by Health Net's National Medical Advisory Council (MAC). The clinical criteria and medical policies provide guidelines for determining the medical necessity criteria for specific procedures, equipment, and services. In order to be eligible, all services must be medically necessary and otherwise defined in the member's benefits contract as described this "Important Notice" disclaimer. In all cases, final benefit determinations are based on the applicable contract language. To the extent there are any conflicts between medical policy guidelines and applicable contract language, the contract language prevails. Medical policy is not intended to override the policy that defines the member's benefits, nor is it intended to dictate to providers how to practice medicine.

Policy Effective Date and Defined Terms.
The date of posting is not the effective date of the Policy. The Policy is effective as of the date determined by Health Net. All policies are subject to applicable legal and regulatory mandates and requirements for prior notification. If there is a discrepancy between the policy effective date and legal mandates and regulatory requirements, the requirements of law and regulation shall govern. * In some states, prior notice or posting on the website is required before a policy is deemed effective. For information regarding the effective dates of Policies, contact your provider representative. The Policies do not include definitions. All terms are defined by Health Net. For information regarding the definitions of terms used in the Policies, contact your provider representative.

Policy Amendment without Notice.
Health Net reserves the right to amend the Policies without notice to providers or Members. In some states, prior notice or website posting is required before an amendment is deemed effective.

No Medical Advice.
The Policies do not constitute medical advice. Health Net does not provide or recommend treatment to members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

No Authorization or Guarantee of Coverage.
The Policies do not constitute authorization or guarantee of coverage of particular procedure, drug, service or supply. Members and providers should refer to the Member contract to determine if exclusions, limitations, and dollar caps apply to a particular procedure, drug, service or supply.
Policy Limitation: Member’s Contract Controls Coverage Determinations.
Statutory Notice to Members: The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illnesses or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. The determination of coverage for a particular procedure, drug, service or supply is not based upon the Policies, but rather is subject to the facts of the individual clinical case, terms and conditions of the member’s contract, and requirements of applicable laws and regulations. The contract language contains specific terms and conditions, including pre-existing conditions, limitations, exclusions, benefit maximums, eligibility, and other relevant terms and conditions of coverage. In the event the Member’s contract (also known as the benefit contract, coverage document, or evidence of coverage) conflicts with the Policies, the Member’s contract shall govern. The Policies do not replace or amend the Member’s contract.

Policy Limitation: Legal and Regulatory Mandates and Requirements
The determinations of coverage for a particular procedure, drug, service or supply is subject to applicable legal and regulatory mandates and requirements. If there is a discrepancy between the Policies and legal mandates and regulatory requirements, the requirements of law and regulation shall govern.

Reconstructive Surgery
CA Health and Safety Code 1367.63 requires health care service plans to cover reconstructive surgery. “Reconstructive surgery” means surgery performed to correct or repair abnormal structures of the body caused by congenital defects, developmental abnormalities, trauma, infection, tumors, or disease to do either of the following:

1. To improve function or
2. To create a normal appearance, to the extent possible.

Reconstructive surgery does not mean “cosmetic surgery,” which is surgery performed to alter or reshape normal structures of the body in order to improve appearance.

Requests for reconstructive surgery may be denied, if the proposed procedure offers only a minimal improvement in the appearance of the enrollee, in accordance with the standard of care as practiced by physicians specializing in reconstructive surgery.

Reconstructive Surgery after Mastectomy
California Health and Safety Code 1367.6 requires treatment for breast cancer to cover prosthetic devices or reconstructive surgery to restore and achieve symmetry for the patient incident to a mastectomy. Coverage for prosthetic devices and reconstructive surgery shall be subject to the co-payment, or deductible and coinsurance conditions, that are applicable to the mastectomy and all other terms and conditions applicable to other benefits. "Mastectomy" means the removal of all or part of the breast for medically necessary reasons, as determined by a licensed physician and surgeon.

Policy Limitations: Medicare and Medicaid
Policies specifically developed to assist Health Net in administering Medicare or Medicaid plan benefits and determining coverage for a particular procedure, drug, service or supply for Medicare or Medicaid members shall not be construed to apply to any other Health Net plans and members. The Policies shall not be interpreted to limit the benefits afforded Medicare and Medicaid members by law and regulation.