



**INSTRUCTIONS FOR USE
REVISION 1.0**

NOVOTTF-100A System

This manual is intended for physicians prescribing the use of the NovoTTF-100A System.

Additional information is found in the following materials:

- Patient Information and Operation Manual

Caution: Federal law restricts this device to sale by or on the order of a physician

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Indications for Use

The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM), following histologically- or radiologically-confirmed recurrence in the supra-tentorial 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.

Contraindications, Warnings and Precautions

Contraindications

- Do not use the NovoTTF-100A System if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement), a shunt or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts. Use of the NovoTTF-100A System together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of the NovoTTF-100A System together with skull defects, shunts or bullet fragments has not been tested and may possibly lead to tissue damage or render the NovoTTF-100A System ineffective.
- Do not use the NovoTTF-100A System if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with the NovoTTF-100A System may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure

Warnings

- Warning – Use the NovoTTF-100A only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (NovoCure). Ask to see a certificate signed by NovoCure that says they completed a training course. Your training will include a detailed review of this manual and practice in the use of the system. In addition, you will be trained in what to do if there are problems with

treatment. Use of the NovoTTF-100A without receiving this training can result in breaks in treatment and may rarely cause increased scalp rash, open sores on your head, allergic reactions or even an electric shock.

- Warning - Do not use the NovoTTF-100A if you are 21 years old or younger. The system has not been tested in persons 21 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.
- Warning - Do not use the NovoTTF-100A if you are pregnant, you think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. The NovoTTF-100A was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant or if it will be effective.
- Warning - In case of skin irritation, which appears as redness under the electrodes (a mild rash), use over-the-counter topical steroids (0.1% hydrocortisone cream) when replacing electrodes. This will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin break down, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing electrodes. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals. Taking a break from treatment may lower your chance to respond to treatment.
- Warning - All servicing procedures must be performed by qualified and trained personnel. If you attempt to open and service the system alone you may cause damage to the system. You could also get an electric shock by touching the inner parts of the device.

Precautions

- Caution - Keep the NovoTTF-100A out of the reach of children. If children touch the device, they could damage the device. This could cause a break in treatment. Breaks in treatment may lower your chance to respond to treatment.
- Caution - Do not use any parts that do not come with the NovoTTF-100A Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment. Breaks in treatment may lower your chance to respond to treatment.
- Caution – If your doctor used plates or screws to close your skull bone during your surgery, be careful when placing the electrodes. Make sure the round disks that make up the electrodes are not on top of the areas where you can feel the screws or plates under your skin. In other words, make sure the screws or plates under your skin are in between the round

disks that make up the electrodes. If you do not do this, you may have increased skin damage which may lead to a break in treatment. Breaks in treatment may lower the chance of the device being effective.

- Caution – Tell your doctor before using the device if you have an inactive implanted medical device in the brain (for example, stents, plastic drug delivery reservoirs, aneurysm clips or coils, device leads). Use of the NovoTTF-100A device in subjects with inactive implanted medical devices in their brain was not been tested and could lead to tissue damage or lower the chance of the device being effective.
- Caution - Do not use the NovoTTF-100A if any parts look damaged (torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Use of damaged components can damage the device, and cause a break in treatment. Breaks from treatment may lower your chance to respond to treatment.
- Caution - Do not wet the device or electrodes. Getting the device wet may damage it, preventing you from receiving treatment for the right amount of time. Getting the electrodes very wet is likely to cause the electrodes to come loose from your head. If this happens, the device will turn off and you will need to change the electrodes.
- Caution - Before connecting or disconnecting the electrodes, make sure that the NovoTTF power switch is in the OFF position. Disconnecting electrodes with the device power switch in the ON position may cause a device alarm to go off, and could damage the device.

Notice! The NovoTTF-100A System and electrodes will activate metal detectors.

Notice! Do not use the NovoTTF-100A if your tumor is located in the lower parts of the brain close to the spinal cord. Ask your doctor if your tumor is located in this part of your brain. The NovoTTF-100A has not been tested in patients with tumors in these locations. It is unknown whether these tumors will respond to treatment.

Notice! You should use the NovoTTF-100A for at least 18 hours a day to get the best response to treatment. Using the NovoTTF-100A for less than 18 hours a day lowers the chances that you will respond to treatment.

Notice! Do not stop using the NovoTTF-100A before you finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances that you will respond to treatment.

Notice! Do not stop using the NovoTTF-100A even if you have used it less than the recommended 18 hours per day. You should stop using the device only if your doctor tells you to. Stopping treatment could lower the chances that you will respond to treatment.

Notice! If you plan to be away from home for more than 2 hours, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Make sure you have at least 12 extra electrodes at all times. This will last you until the next electrode shipment arrives. Remember to order more electrodes when there are at least 12 extra electrodes left. If you do not order electrodes in time you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1.5 hours from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! You should carry the Troubleshooting Guide (Section 26) at all times. This guide is necessary to ensure the NovoTTF-100A System works properly. If you do not work the system correctly you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Do not block the device vents located on the sides of the NovoTTF-100A device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device.

Notice! Do not block the battery charger vents located on the front of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging.

Notice! Before using an electrode, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the electrode may be damaged. A damaged electrode will not work properly and may cause the device to turn off.

Notice! The electrodes are for single use and should not be taken off your head and put back on again. If you put a used electrode back on your head again, it may not stick well to your skin and the device could turn off.

Description

The NovoTTF-100A System for the treatment of recurrent GBM is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields ("TTFs") within the human body. TTFs are applied to the patient by electrically-insulated surface electrodes. The TTFs are inferred to disrupt the rapid cell division exhibited by cancer cells.¹

The NovoTTF-100A System is comprised of two main components: (1) an Electric Field Generator (the NovoTTF-100A device); and (2) INE Insulated Electrodes (the electrodes). In addition, the following components are also included in the NovoTTF-100A Treatment Kit: power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

Treatment parameters are preset by NovoCure such that there are no electrical output adjustments available to the patient. The patient must 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.

Principles of Operation

The NovoTTF-100A produces alternating electrical fields within the human body that are inferred 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.

TTFs harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTF technology takes advantage of the special characteristics and geometrical shape of dividing 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).

¹ Kirson, E. D., V. Dbaly, et al. (2007). "Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors." Proc Natl Acad Sci U S A **104**(24): 10152-7.

In contrast, the TFields 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 TFields. 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 TFields 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, TField application has the advantage of being highly selective and is not expected to be associated with significant toxicity.

The above mechanisms of action are consistent with the extensive research regarding the effects of TFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature.

Preclinical Data

TFields have been shown both *in vitro* and *in vivo* to effectively inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TFields can be frequency-tuned to effectively inhibit different cancer cell types (*i.e.*, the smaller the cell, the higher the frequency needed), due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase².

Specifically, TFields have been shown to inhibit glioblastoma cells *in vitro* and *in vivo* at a frequency of 200 kHz and an intensity of 0.7 V/cm. Based on realistic finite element mesh simulations and direct measurements of TFields intensity in experimental animals, and in the human brain, NovoCure has concluded that effective TField intensities can be generated in the brains of large animals and humans. Extensive safety studies in healthy animals (mice, rats and rabbits) have shown that TFields are not associated with significant systemic toxicities. Neither acute, nor chronic systemic toxicities were seen when TFields were applied to the torso or head, at different

² Kirson, E. D., Z. Gurvich, et al. (2004). "Disruption of cancer cell replication by alternating electric fields." Cancer Res 64(9): 3288-95.

frequencies (100-200 kHz), different intensities and for different periods of time³.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for the NovoTTF-100A System has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

³ Kirson, E. D., V. Dbaly, et al. (2007).

Clinical Data

Pilot Clinical Study in Recurrent GBM⁴

The NovoTTF-100A has been tested in 10 recurrent GBM subjects in a single center, pilot study in Europe. In this study, NovoTTF-100A monotherapy led to a significant increase in time to progression (from 13 to 26 weeks; $p=0.013$), PFS6 (from 15 to 50%) and overall survival (OS) (from 6.0 to 14.7 months; $p=0.002$) compared to matched concomitant and historical comparator groups. The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device electrodes.

Other Clinical Experience in Recurrent GBM

In late 2009, NovoCure began limited marketing of the device in Europe under its CE mark approval. Fourteen (14) recurrent GBM patients have been treated so far with a median OS of 6.4 months, as of August 2010. No device events have been reported as of March 2011.

Pivotal Clinical Study in Recurrent GBM

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with NovoTTF-100A to those treated with an effective best standard of care (BSC) chemotherapy (including bevacizumab).

The following were the objectives of the study:

- To prospectively compare the median overall survival of recurrent GBM subjects treated with NovoTTF-100A to those treated with best standard of care (BSC)
- To prospectively determine PFS6, TTP, %1-year survival and quality of life of subjects treated with NovoTTF-100A compared to BSC.
- To collect evidence of the safety of TTFields applied to subjects with recurrent GBM using the NovoTTF-100A System.

⁴ Ibid.

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows:

Inclusion Criteria

- a. Pathological evidence of GBM using WHO classification criteria
- b. ≥ 18 years of age
- c. Not a candidate for further radiotherapy or additional resection of residual tumor
- d. Subjects with disease progression (by Macdonald criteria (i.e., $> 25\%$ or new lesion)) documented by CT or MRI within 4 weeks prior to enrollment
- e. Karnofsky scale ≥ 70
- f. Life expectancy at least 3 months
- g. Participants of childbearing age must use effective contraception.
- h. All subjects must sign written informed consent.

Exclusion Criteria

- a. Actively participating in another clinical treatment trial
- b. Within 4 weeks from surgery for recurrence
- c. Within 4 weeks from any prior chemotherapy
- d. Within 4 weeks from radiation therapy
- e. Pregnant
- f. Significant co-morbidities within 4 weeks prior to enrollment:
 - 1) Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
 - 2) Total bilirubin $>$ upper limit of normal
 - 3) Significant renal impairment (serum creatinine > 1.7 mg/dL)
 - 4) Coagulopathy (as evidenced by PT or APTT > 1.5 times control in subjects not undergoing anticoagulation)
 - 5) Thrombocytopenia (platelet count $< 100 \times 10^3/\mu\text{L}$)
 - 6) Neutropenia (absolute neutrophil count $< 1 \times 10^3/\mu\text{L}$)
 - 7) Anemia (Hb < 10 g/L)
 - 8) Severe acute infection
- g. Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias.
- h. Infra-tentorial tumor
- i. Evidence of increased intracranial pressure (midline shift > 5 mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

Study Procedures:

Treatment Arm

At treatment initiation subjects were hospitalized for 24 hours. During this period baseline examinations were performed and NovoTTF-100A treatment

was initiated by the investigator under continuous medical supervision. The subjects were also instructed by the investigator on the operation of the NovoTTF-100A System and battery replacement. Once the subjects were trained in operating the device they were released to continue treatment at home. The subjects received continuous NovoTTF-100A treatment. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Subjects received the best effective standard of care chemotherapy practiced at each of the participating centers. The effective BSC treatments used in the study were comprised mainly of the following chemotherapies: Platinum based chemotherapy (Carboplatin), Nitrosureas (BCNU), Procarbazine, Procarbazine, lomustine and vincristine (PCV), Temozolomide, Bevacizumab, and Imatinib, erlotinib, irinotecan (mainly in Europe). Because these therapies were included in the trial as a group, no comparisons can be made to each individual chemotherapy regimen. Chemotherapeutic treatment protocol was according to standard procedures at each of the participating centers.

Follow Up

During treatment, and until progression for subjects who stopped treatment before progression, all subjects were seen once a month at an outpatient clinic where they underwent medical follow up and routine laboratory exams. An MRI was performed every 2 months until disease progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each subject. Medical follow-up continued for 2 months following disease progression. Subject survival was assessed based on monthly telephone interviews with the subjects' caregivers.

Subject Characteristics: 237 subjects (120 NovoTTF-100A; 117 BSC) with progressive or recurrent GBM were enrolled in the study. Baseline characteristics were as follows: mean age: 53.6 years; Karnofsky score: $81.6 \pm 11\%$; tumor size (cm^2): 16.1 ± 12.4 ; progression number: 1.4 ± 0.9 ; re-operated: 26%; male: 70%; previous low grade: 10%; prior bevacizumab failure: 19%. Baseline characteristics were similar between treatment groups with slightly more men in the NovoTTF-100A group than in the BSC group (77% vs. 62%), a lower incidence of frontal lobe tumors in the NovoTTF-100A group than in the BSC group (32% vs. 50%), and a slightly higher mean KPS in the NovoTTF-100A group than in the BSC group (83% vs. 80%), though the median KPS was 80% in both groups. Adjusted analyses for all pre-specified or all statistically significant baseline covariates for overall survival did not change the outcome of the trial.

Demographics and Baseline Characteristics by Treatment Group		
Intent-to-Treat (ITT) Population		
	NovoTTF-100A	BSC
Characteristics	(N=120)	(N=117)
	n (%)	n (%)
Race		
Caucasian	111 (93)	106 (91)
African American	2 (2)	5 (4)
Asian	0	3 (3)
Hispanic	7 (6)	2 (2)
Other	0	1 (1)
Female Gender	28 (23)	44 (38)
Frontal Tumor Position	38 (32)	58 (50)
Bilateral or Midline Tumor Location	23 (19)	17 (15)
Prior Avastin Use	24 (20)	21 (18)
Re-operation for Recurrence	33 (28)	29 (25)
Prior Low-grade Glioma	12 (10)	11 (9)
Median Age (years) (min, max)	54 (24, 80)	54 (29,74)
Median Weight (kg)	80	80.5
Mean # of Prior GBM Recurrences	1.5	1.3
Median Karnofsky Performance Score (min, max)	80 (50, 100)	80 (50, 100)
Median Tumor Area (mm²)	1440	1391
Median Time from GBM Diagnosis to Randomization (days)	334.5	340
Mean Time from last Radiotherapy Dose to Randomization (Months)	13.71	13.93

Effectiveness Results:

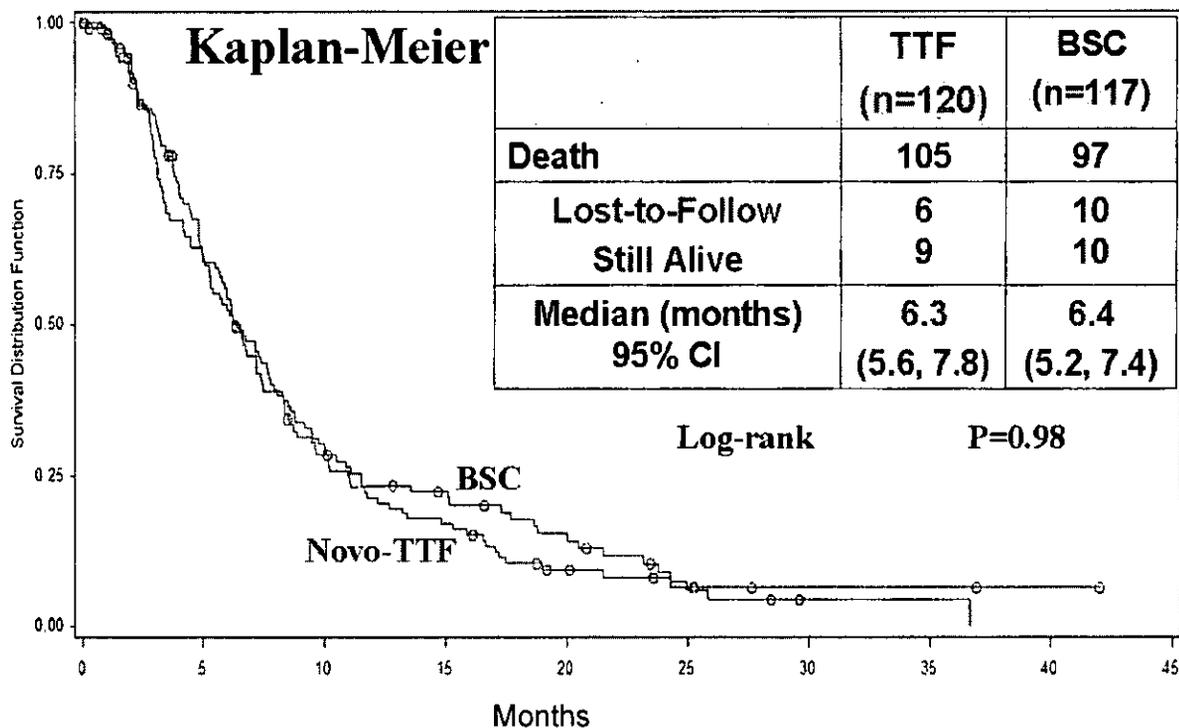
Primary Effectiveness Endpoint: Overall survival (OS)

In the ITT population which included all randomized subjects (Novo-TTF=120, BSC=117), overall survival in subjects treated with NovoTTF-100A was comparable to that observed in subjects treated with BSC (median OS=6.3 vs. 6.4 months; p=0.98). In the US, the median overall survival was 6.1 vs. 5.3 months in the ITT population. The pivotal study data establish that NovoTTF-100A therapy is comparable to BSC therapy in extending OS.

Overall Survival Summary (ITT Population)		
	Treatment Group	
	NovoTTF	BSC
N	120	117
Median OS (months)	6.3	6.4
Log-rank p- Value	0.98	
HR (95% CI)	1.00 (0.76 – 1.32)	

The Kaplan-Meier survival curve for the two treatment groups appeared to be very similar during the first 12 months of follow-up, where 80% of the events occurred in both groups. Between 12 and 24 months, the survival curves separated slightly in favor of the BSC control group. However, after 12 months, the number of subjects remaining may be too small to reliably estimate the long term survival outcome.

Primary Effectiveness Endpoint Analysis: ITT population



Correlation between Treatment Compliance and Overall Survival: The NovoTTF-100A device has an internal log file which allows the calculation of subject compliance with treatment. Higher overall survival was observed in NovoTTF-100A subjects who were treated 75% or more of the time on average (OS=7.7 months) compared to subjects treated less than 75% of the time on average (OS=4.5 months).

Secondary Effectiveness Endpoints: Secondary endpoint results support the findings in the primary endpoint. The one-year survival is similar in the NovoTTF-100A and BSC groups in the ITT population (21.9% vs. 22.1%). Progression free survival at 6 months (PFS6) is the same in the ITT population (21.4% vs. 15.2%). Radiological response rates from the subset of patients evaluated were reported as 14% for the NovoTTF-100A group compared to 9.6% for the BSC group in the ITT population. Median time to progression (TTP) was 9.3 weeks for NovoTTF vs. 9.6 weeks for BSC.

Summary of Secondary Endpoints (ITT Population)		
Secondary Endpoints	Treatment Group	
	NovoTTF	BSC
N	120	117
1-year survival	21.9% 25/114	22.1% 23/104
PFS6 (%)	21.4% 22/103	15.2% 14/92
Radiological Response Rate (%)	14.0% 14/100	9.6% 7/73
Median TTP (weeks)	9.3	9.6

Quality of Life: Quality of life in subjects using the NovoTTF-100A System was better than those on BSC chemotherapy in most subscale domains, including vomiting, nausea, pain, diarrhea, constipation, cognitive and emotional functioning.

Safety Results: The characteristic adverse events of almost all chemotherapies are seen in a significantly higher proportion of BSC control subjects than in NovoTTF-100A subjects: gastrointestinal (30% vs. 8%), hematological (19% vs. 4%) and infectious (12% vs. 4%). Mild to moderate skin reaction beneath the device electrodes was observed in 16% of NovoTTF-100A subjects; none of these cases was assessed as severe by the investigator, all resolved after discontinuing treatment, and all were treated with topical steroids and periodic shifting of electrode positions.

Percentage of Subjects with AEs in the NovoTTF-100A versus BSC Groups (Including Incidence of Severe and Related AEs) ≥ 2%						
	NovoTTF-100A (N=116)			BSC Chemotherapy (N=91)		
System Organ Class	% of subjects			% of subjects		
Preferred Term	All AEs	Severe	Related	All AEs	Severe	Related
Percentage of Subjects with ≥1 AE	55	16	22	59	19	48
Blood and lymphatic system disorders	4	1	0	19	4	16
Anaemia	2	0	0	2	0	2
Leukopenia	1	0	0	7	1	4
Lymphopenia	2	1	0	3	1	2
Neutropenia	1	0	0	2	0	2
Thrombocytopenia	3	0	0	12	2	10
Cardiac disorders	7	1	0	7	0	2
Oedema peripheral	5	1	0	3	0	2
Tachycardia	1	0	0	3	0	0
Ear and labyrinth disorders	1	0	0	3	0	2
Ear pain	0	0	0	2	0	2
Endocrine disorders	2	0	0	2	0	0
Cushingoid	2	0	0	1	0	0
Eye disorders	3	0	0	5	0	1
Dry eye	2	0	0	0	0	0
Vision blurred	1	0	0	2	0	1
Gastrointestinal disorders	8	1	0	30	3	30
Abdominal pain	0	0	0	7	0	3
Aphthous stomatitis	0	0	0	2	0	2
Constipation	2	0	0	4	0	2
Diarrhoea	0	0	0	12	2	11
Nausea	3	0	0	16	0	14
Vomiting	3	0	0	7	0	7
General disorders and administration site conditions	13	1	2	15	1	9
General physical health deterioration	2	0	0	1	0	0
Malaise	9	1	2	11	0	8
Pyrexia	2	0	0	1	0	0

Percentage of Subjects with AEs in the NovoTTF-100A versus BSC Groups (Including Incidence of Severe and Related AEs) ≥ 2%						
System Organ Class	NovoTTF-100A (N=116)			BSC Chemotherapy (N=91)		
	% of subjects			% of subjects		
Preferred Term	All AEs	Severe	Related	All AEs	Severe	Related
Infections and infestations	4	0	0	12	1	0
Candidiasis	3	0	0	3	0	0
Ear infection	0	0	0	2	0	0
Urinary tract infection	0	0	0	3	1	0
Injury, poisoning and procedural complications	18	15	16	1	0	0
Fall	4	0	1	0	0	0
Medical device site reaction (rash under electrodes)	16	0	16	0	0	0
Investigations	7	2	0	5	1	2
Blood lactate dehydrogenase increased	2	0	0	1	0	1
Hepatic enzyme abnormal	1	0	0	2	1	2
Weight increased	1	0	0	2	0	0
Metabolism and nutrition disorders	8	1	0	13	3	3
Anorexia	0	0	0	4	1	3
Diabetes mellitus	2	0	0	0	0	0
Hyperglycaemia	2	0	0	2	1	0
Hypokalaemia	2	0	0	4	1	1
Musculoskeletal and connective tissue disorders	5	0	1	9	0	0
Back pain	2	0	0	3	0	0
Muscular weakness	0	0	0	3	0	0
Pain in extremity	0	0	0	2	0	0
Neoplasms benign, malignant and unspecified	2	2	0	2	1	0
Neoplasm progression	2	2	0	2	1	0
Nervous system disorders	43	7	3	36	5	3
Amnesia	3	0	0	0	0	0
Balance disorder	2	0	0	0	0	0
Brain oedema	1	0	0	2	0	0
Cognitive deterioration	2	1	0	2	0	0
Cognitive disorder	2	0	0	2	0	0
Convulsion	9	3	0	4	2	0
Coordination abnormal	2	0	0	4	0	0
Cranial nerve disorder	3	0	0	1	0	0

Percentage of Subjects with AEs in the NovoTTF-100A versus BSC Groups (Including Incidence of Severe and Related AEs) \geq 2%						
	NovoTTF-100A (N=116)			BSC Chemotherapy (N=91)		
System Organ Class	% of subjects			% of subjects		
Preferred Term	All AEs	Severe	Related	All AEs	Severe	Related
Difficulty in walking	1	0	0	2	0	0
Dizziness	3	0	0	2	0	2
Dysaesthesia	2	0	0	1	0	0
Dysphasia	3	0	0	2	0	0
Headache	16	2	3	10	0	2
Hemianopia	2	0	0	4	1	0
Hemiparesis	9	0	0	4	1	0
Hyperreflexia	3	0	0	2	0	0
Hypoaesthesia	2	0	0	3	0	0
Hyporeflexia	0	0	0	2	0	0
Memory impairment	2	0	0	0	0	0
Nervous system disorder	3	1	0	3	0	0
Neuropathy peripheral	2	1	0	1	0	0
Tremor	2	0	0	2	0	0
Psychiatric disorders	10	0	0	8	0	0
Agitation	2	0	0	0	0	0
Depression	2	0	0	5	0	0
Insomnia	2	0	0	2	0	0
Mental status changes	5	0	0	1	0	0
Renal and urinary disorders	6	1	0	3	0	1
Pollakiuria	2	0	0	0	0	0
Urinary incontinence	3	1	0	2	0	0
Respiratory, thoracic and mediastinal disorders	6	0	0	11	1	0
Cough	3	0	0	4	0	0
Dyspnea	2	0	0	4	1	0
Nasopharyngitis	0	0	0	2	0	0
Skin and subcutaneous tissue disorders	8	0	1	10	0	5
Alopecia	0	0	0	3	0	3
Rash	4	0	0	0	0	0
Swelling face	2	0	0	1	0	0
Vascular disorders	4	2	0	7	2	2
Hypertension	1	0	0	3	0	0
Pulmonary embolism	1	1	0	2	2	1

Treatment Emergent Serious Adverse Events (SAEs) by Body System and Preferred Term				
System Organ Class Preferred Term	NovoTTF-100A [N=116]		BSC Chemotherapy [N=91]	
	# of Events (Frequency)	# of Sub. (Incidence)	# of Events (Frequency)	# of Sub. (Incidence)
Number with ≥1 SAE	16	15 (13)	11	10 (11)
Blood and lymphatic system disorders	0	0 (0)	1	1 (1)
Febrile neutropenia	0	0 (0)	1	1 (1)
Cardiac disorders	2	2 (2)	0	0 (0)
Oedema peripheral	2	2 (2)	0	0 (0)
Gastrointestinal disorders	0	0 (0)	1	1 (1)
Intestinal perforation	0	0 (0)	1	1 (1)
General disorders and administration site conditions	1	1 (1)	0	0 (0)
General physical health deterioration	1	1 (1)	0	0 (0)
Infections and infestations	0	0 (0)	3	2 (2)
Cellulitis	0	0 (0)	1	1 (1)
Pneumonia	0	0 (0)	1	1 (1)
Urinary tract infection	0	0 (0)	1	1 (1)
Injury, poisoning and procedural complications	1	1 (1)	0	0 (0)
Cerebrospinal fluid leakage	1	1 (1)	0	0 (0)
Metabolism and nutrition disorders	1	1 (1)	1	1 (1)
Anorexia	0	0 (0)	1	1 (1)
Dehydration	1	1 (1)	0	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2	2 (2)	2	2 (2)
Neoplasm progression	2	2 (2)	2	2 (2)
Nervous system disorders	5	5 (4)	1	1 (1)
Convulsion	3	3 (3)	0	0 (0)
Headache	2	2 (2)	0	0 (0)
Nervous system disorder	0	0 (0)	1	1 (1)
Psychiatric disorders	1	1 (1)	0	0 (0)
Mental status changes	1	1 (1)	0	0 (0)

Treatment Emergent Serious Adverse Events (SAEs) by Body System and Preferred Term				
System Organ Class Preferred Term	NovoTTF-100A [N=116]		BSC Chemotherapy [N=91]	
	# of Events (Frequency)	# of Sub. (Incidence)	# of Events (Frequency)	# of Sub. (Incidence)
Respiratory, thoracic and mediastinal disorders	1	1 (1)	0	0 (0)
Dyspnoea	1	1 (1)	0	0 (0)
Vascular disorders	2	2 (2)	2	2 (2)
Cerebral hemorrhage	1	1 (1)	0	0 (0)
Pulmonary embolism	1	1 (1)	2	2 (2)

Device-Related AEs

Adverse Event	NovoTTF-100A [N=116]
	# (%)
Medical device site reaction	18 (16)
Headache	4 (3)
Malaise	2 (2)
Muscle twitching	1 (1)
Fall	1 (1)
Skin ulcer	1 (1)

Conclusions: The NovoTTF-100A is a portable, battery operated device which delivers TTFields to patients with recurrent GBM. The results of the pivotal trial showed that NovoTTF-100A subjects had comparable overall survival to subjects receiving the best available chemotherapy in the US today (OS 6.3 vs. 6.4 months; HR 1.0; p=0.98). Similar results showing comparability of NovoTTF-100A to BSC chemotherapy in the ITT population were seen in all secondary endpoints. The NovoTTF-100A subjects experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to BSC controls. The only device-related adverse events seen were a mild to moderate skin irritation beneath the device electrodes, which was easily treated with topical ointments. Finally, certain quality of life measures were better in NovoTTF-100A subjects as a group when compared to subjects receiving effective BSC chemotherapy.

Directions for Use

Detailed directions for use for the NovoTTF-100A System can be found in:

- The NovoTTF-100A Patient Information and Operation Manual

Abbreviations

AE – Adverse event

BSC – Best standard of care (effective chemotherapies)

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor.

ITT – Intent-to-Treat

kHz – kilo hertz; number of cycles per second

NovoTTF-100A (also called **TTFIELD Generator** or **NovoTTF-100A device**) – A portable battery, or power supply, operated device for delivering 200 kHz TTFIELDS to the brain of patients with recurrent GBM.

OS – Overall survival

PFS6 – Proportion of patients alive and progression free at 6 months from randomization

Radiological Response Rate - sum of complete and partial radiological response rates

TTFIELDS – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated electrodes to the region of the body inflicted with a solid tumor. The fields have been shown *in vitro* to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase.

TTP – Time to progression

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

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8 April 2011



NovoTTF-100A

Patient Information
and
Operation Manual

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This manual is for doctors prescribing the NovoTTF-100A System.

This manual is for patients using the NovoTTF-100A System.

2 Glossary of Medical Terms

Cancer - abnormal cell division that spreads without control

Chemotherapy - medication used to destroy cancer cells

Clinical trial - a research study that involves people

Contraindications - situations when a treatment should not be used

Glioblastoma Multiforme (GBM) - a type of brain cancer; other medical names for GBM are "glioblastoma", "grade IV glioma" or "grade IV astrocytoma"

INE Electrodes - Insulated Electrodes

Local - in one part of the body

MRI scan - a procedure that uses a magnet to create pictures of areas inside the body

NovoTTF-100A - (also called **TTFIELD generator** or **NovoTTF-100A device**) - A portable device for delivering TTFIELDS to the brain of patients with recurrent GBM

NovoTTF-100A Treatment Kit - The TTFIELD generator with all other parts (batteries, charger, connection cable, power supply and carrying case)

NovoTTF-100A System - The NovoTTF-100A Treatment Kit with the electrodes

Radiation - a treatment involving x-rays used to kill tumor cells

Recurrence/Recurrent - when cancer comes back after removal

Steroids - when taken by mouth or IV (through the vein), a medication used to lower swelling around a brain tumor and help with symptoms related to the brain. When used on the skin, a medication that can reduce inflammation.

Systemic - throughout the body

Topical - on the surface of the skin

TTFIELDS - Tumor Treating Fields: Alternating electric fields, delivered using electrodes to the part of the body with a solid tumor. The fields have been shown to destroy tumor cells.

Tumor - an abnormal growth of tissue

3 What is NovoTTF-100A Therapy and How Does It Work?

Your doctor has prescribed the NovoTTF-100A System because you are a good candidate for the device.

The NovoTTF-100A System is a treatment for adult patients (22 years of age or older). A doctor may use it to treat a patient with brain cancer (called glioblastoma multiforme, or "GBM") that reappears in the higher parts of the brain after they have had chemotherapy (cancer drugs). The NovoTTF-100A is used alone, instead of standard medical therapy for GBM, after other treatment options such as surgery and radiation have been used. A discussion of brain cancer and treatment options is found at the end of this Patient Manual in Section 29.

The NovoTTF-100A System is a portable device. It produces electric fields, called tumor treatment fields ("TTFs"). Electrodes connected to the device apply TTFs to your head. The TTFs are intended to destroy brain cancer cells. The device and battery are carried in a shoulder bag. You should use them all the time.

In this manual, the term "NovoTTF-100A Treatment Kit" refers to the NovoTTF-100A electric field generator (also called "the device"), connection cable, power supply, battery, battery charger and battery rack. The term "NovoTTF-100A System" (also called "NovoTTF-100A") refers to the Treatment Kit plus the electrodes.

4 Contraindications, Warnings and Precautions

Contraindications

- Do not use the NovoTTF-100A System if you have an active implanted medical device, a skull defect (such as, missing bone with no replacement), a shunt or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts. Use of the NovoTTF-100A System together with implanted electronic devices has not been tested and may lead to malfunctioning of the implanted device. Use of the NovoTTF-100A System together with skull defects, shunts or bullet fragments has not been tested and may possibly lead to tissue damage or render the NovoTTF-100A System ineffective.
- Do not use the NovoTTF-100A System if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (EKG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with the NovoTTF-100A System may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

- Warning - Use the NovoTTF-100A only after receiving training from qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (NovoCure). Ask to see a certificate signed by NovoCure that says they completed a training course. Your training will include a detailed review of this manual and practice in the use of the system. In addition, you will be trained in what to do if there are problems with treatment. Use of the NovoTTF-100A without receiving this training can result in breaks in treatment and may rarely cause increased scalp rash, open sores on your head, allergic reactions or even an electric shock.

- Warning - Do not use the NovoTTF-100A if you are 21 years old or younger. The system has not been tested in persons 21 years old or younger. It is unknown what side effects the device may cause in these cases or if it will be effective.
- Warning - Do not use the NovoTTF-100A if you are pregnant, think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. The NovoTTF-100A was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant or if it will be effective.
- Warning - In case of skin irritation, which appears as redness under the electrodes (a mild rash), use over-the-counter topical steroids (0.1% hydrocortisone cream) when replacing electrodes. This will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin break down, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing electrodes. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals. Taking a break from treatment may lower your chance to respond to treatment.
- Warning - All servicing procedures must be performed by qualified and trained personnel. If you attempt to open and service the system alone you may cause damage to the system. You could also get an electric shock by touching the inner parts of the device.

Precautions

- Caution - Keep the NovoTTF-100A out of the reach of children. If children touch the device, they could damage the device. This could cause a break in treatment. Breaks in treatment may lower your chance to respond to treatment.
- Caution - Do not use any parts that do not come with the NovoTTF-100A Treatment Kit, or that were not sent to you by the device manufacturer or given to you by your doctor. Use of other parts, manufactured by other

companies or for use with other devices, can damage the device. This may lead to a break in treatment. Breaks in treatment may lower your chance to respond to treatment.

- Caution – If your doctor used plates or screws to close your skull bone during your surgery, be careful when placing the electrodes. Make sure the round disks that make up the electrodes are not on top of the areas where you can feel the screws or plates under your skin. In other words, make sure the screws or plates under your skin are in between the round disks that make up the electrodes. If you do not do this, you may have increased skin damage which may lead to a break in treatment. Breaks in treatment may lower the chance of the device being effective.
- Caution – Tell your doctor before using the device if you have an inactive implanted medical device in your brain (such as a stent, plastic drug delivery reservoir, aneurysm clip or coil, or device lead). Use of the NovoTTF-100A device in subjects with inactive implanted medical devices in their brain was not tested and could lead to tissue damage or lower the chance of the device being effective.
- Caution - Do not use the NovoTTF-100A if any parts look damaged (torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Use of damaged components can damage the device, and cause a break in treatment. Breaks from treatment may lower your chance to respond to treatment.
- Caution - Do not wet the device or electrodes. Getting the device wet may damage it, preventing you from receiving treatment for the right amount of time. Getting the electrodes very wet is likely to cause the electrodes to come loose from your head. If this happens, the device will turn off and you will need to change the electrodes.
- Caution - Before connecting or disconnecting the electrodes, make sure that the NovoTTF power switch is in the OFF position. Disconnecting electrodes with the device power switch in the ON position may cause a device alarm to go off, and could damage the device.

Notice! The NovoTTF-100A System and electrodes will activate metal detectors.

Notice! Do not use the NovoTTF-100A if your tumor is located in the lower parts of the brain close to the spinal cord. Ask your doctor if your tumor is located in this part of your brain. The NovoTTF-100A has not been tested in patients with tumors in these locations. It is unknown whether these tumors will respond to treatment.

Notice! You should use the NovoTTF-100A for at least 18 hours a day to get the best response to treatment. Using the NovoTTF-100A for less than 18 hours a day lowers the chances that you will respond to treatment.

Notice! Do not stop using the NovoTTF-100A before you finish at least four full weeks of therapy to get the best response to treatment. Stopping treatment before four weeks lowers the chances that you will respond to treatment.

Notice! Do not stop using the NovoTTF-100A even if you have used it less than the recommended 18 hours per day. You should stop using the device only if your doctor tells you to. Stopping treatment could lower the chances that you will respond to treatment.

Notice! If you plan to be away from home for more than 2 hours, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Make sure you have at least 12 extra electrodes at all times. This will last you until the next electrode shipment arrives. Remember to order more electrodes when there are at least 12 extra electrodes left. If you do not order electrodes in time you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery

begins to shorten. For example, if the low battery indicator light flashes within only 1.5 hours from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! You should carry the Troubleshooting Guide (Section 26) at all times. This guide is necessary to ensure the NovoTTF-100A System works properly. If you do not work the system correctly you may have a break in your treatment. Breaks in treatment may lower your chance to respond to treatment.

Notice! Do not block the device vents located on the sides of the NovoTTF-100A device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device.

Notice! Do not block the battery charger vents located on the front of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging.

Notice! Before using an electrode, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the electrode may be damaged. A damaged electrode will not work properly and may cause the device to turn off.

Notice! The electrodes are for single use and should not be taken off your head and put back on again. If you put a used electrode back on your head again, it may not stick well to your skin and the device could turn off.

5 What are the Risks of Treatment with NovoTTF-100A?

Skin irritation is often seen under the electrodes when using the NovoTTF-100A System. This will look like a red rash, small sores or blisters on your scalp. In general, this will not cause skin damage that cannot be fixed. The irritation can be treated with steroid cream or by moving the electrodes. If you do not use steroid cream, the skin irritation could become more serious. This may lead to open sores, infections, pain and blisters. If this happens, stop using the steroid cream and contact your doctor.

Headaches, weakness, convulsions and thinking changes were seen in the clinical study of the NovoTTF-100A. In the device group, 18 out of 116 patients had headaches, 10 out of 116 patients had weakness, 10 out of 116 patients had convulsions and 6 out of 116 patients had thinking changes. These events are also seen in patients with recurrent GBM who do not use the NovoTTF-100A device. However, there was a higher rate of these problems overall in NovoTTF-100A patients (43.1%) compared to patients on cancer drugs (36.3%). Only skin redness and open sores are related to the NovoTTF-100A treatment itself.

By using the NovoTTF-100A System instead of cancer drugs, patients would avoid many of the side effects due to cancer drugs. These include infections, nausea, vomiting, loss of appetite, and tiredness. Three times as many patients who used cancer drugs had these side effects compared to patients who used the NovoTTF-100A.

The table below shows the occurrence of medical problems in patients using the NovoTTF-100A compared to patients on cancer drugs.

Occurrence Risks of medical problems in patients using the NovoTTF-100A compared to patients on cancer drugs

Medical problem	NovoTTF-100A	Cancer Drugs
Lower white and red blood cell counts	5 out of 116 subjects (4%)	17 out of 91 subjects (19%)
Vomiting, nausea and diarrhea	9 out of 116 subjects (8%)	27 out of 91 subjects (30%)
General disorders	15 out of 116 subjects (13%)	14 out of 91 subjects (15%)
Infections	5 out of 116 subjects (4%)	11 out of 91 subjects (12%)
Rash under device electrodes and other injuries	21 out of 116 subjects (18%)	1 out of 91 subjects (1%)
Nutrition disorders	9 out of 116 subjects (8%)	12 out of 91 subjects (13%)
Brain disorders*	50 out of 116 subjects (43%)	33 out of 91 subjects (36%)
Behavioral disorders*	12 out of 116 subjects (10%)	7 out of 91 subjects (8%)
Breathing disorders	7 out of 116 subjects (6%)	10 out of 91 subjects (11%)

* Brain and behavioral disorders are normal symptoms of recurrent GBM

The table below shows the occurrence of certain events when the NovoTTF-100A System was used correctly and incorrectly in the clinical study.

**Occurrence of Certain Problems with correct and incorrect use of the
NovoTTF-100A System**

Event	Likelihood of Event	Outcome/Harm	Likelihood of Outcome
Correct use			
Skin reaction	18 out of 116 subjects (16%)	Mild scalp redness (rash)	17 out of 18 subjects (95%)
Skin reaction	18 out of 116 subjects (16%)	Moderate scalp redness (rash with little sores and blisters)	6 out of 18 subjects (33%)
Incorrect use			
Skin reaction	1 out of 116 subjects (1%)	Open sore on scalp	1 out of 1 subjects (100%)
Use in a patient with a pacemaker	1 out of 121 subjects (1%)	Heart problems	0 out of 1 subject (0%)
Use in patients 21 years or younger	0 out of 120 subjects (0%)	Unknown	Unknown
Use in pregnant women	0 out of 120 subjects (0%)	Unknown	Unknown
Use in patients with implanted electronic devices, shunts or bullet fragments	0 out of 120 subjects (0%)	Unknown	Unknown
Known allergic reaction to electrode gels	0 out of 120 subjects (0%)	Increased redness and itching, (rarely may even lead to severe allergic reactions such as shock and breathing failure)	Unknown
Opening the device for service by untrained personnel	0 out of 120 subjects (0%)	Damage to the device and risk of electric shock	Unknown
Incorrect uses not predicted	Unknown	Unknown	Unknown

6 What are the Benefits of Treatment with NovoTTF-100A?

Patients using the NovoTTF-100A System lived similar amount of time compared to patients using cancer drugs. In the clinical study, half of the patients in both groups lived for more than 6.4 months. 22 out of each 100 patients lived for one year or longer.

Patients using the NovoTTF-100A had a better quality of life (see Section 7 below).

Below is a table showing the effects on the benefit of the device, when it is used correctly or incorrectly.

Benefit from correct and incorrect use of the NovoTTF-100A System

Event	Likelihood of Event	Outcome	Likelihood of Outcome
Correct use			
Use of the device for at least 18 hours a day	85 out of 98 subjects (87%)	Survival 3 months longer compared to subjects treated less than 18 hours a day	81 out of 85 (95%)
Incorrect use			
Use of the device for less than 18 hours a day	13 out of 98 subjects (13%)	Survival 3 months shorter compared to subjects treated at least 18 hours a day	12 out of 13 (92%)
Wetting the device or soaking the electrodes	Unknown	Treatment break	Unknown
Handling of the device by children	Unknown	Treatment break	Unknown

7 What Studies Have Been Conducted with NovoTTF-100A?

A clinical study tested the NovoTTF-100A System against the best standard of care chemotherapy (cancer drugs). The study included 237 subjects with recurrent GBM (120 NovoTTF-100A subjects and 117 cancer drugs subjects).

Subjects who used the NovoTTF-100A System lived a similar amount of time compared to subjects who were taking cancer drugs. NovoTTF-100A subjects and cancer drugs subjects lived for an average of 6.4 months after treatment was started. In addition, the same portion of subjects who used the NovoTTF-100A or cancer drugs were alive one year after starting treatment. That is, 22 out of every 100 subjects were alive at one year when using NovoTTF-100A or cancer drugs. Finally, when subjects used the NovoTTF-100A, the tumor shrank to at least half of its original size in 14 out of 100 (14%) NovoTTF-100A subjects compared to 7 out of 73 (10%) cancer drugs subjects. The NovoTTF-100A was similar to cancer drugs in other measures of treating GBM. Quality of life was better in NovoTTF-100A subjects compared to cancer drugs subjects.

The number of subjects with digestive problems, blood problems, or infections was three times lower in the NovoTTF-100A group than in the cancer drugs group. That is, 17 out of 91 subjects on cancer drugs had blood problems compared to 5 out of 116 subjects using the NovoTTF-100A System. 27 out of 91 subjects on cancer drugs had digestive problems compared to 9 out of 116 subjects using the NovoTTF-100A System. 11 out of 91 subjects on cancer drugs had infections compared to 5 out of 116 subjects using the NovoTTF-100A System.

18 out of 116 NovoTTF-100A subjects had mild or moderate skin reaction under the electrodes (red rash, small sores or blisters). This was expected. None of these cases of skin irritation caused damage to the skin that could not be fixed. The reaction went away after being treated with steroid cream and moving the electrodes. In all cases, the rash went away after stopping treatment. One subject

had a larger open sore under his electrodes, which healed after moving the electrodes to another place.

The clinical study found that the NovoTTF-100A was similar in effectiveness to cancer drugs in treating GBM. NovoTTF-100A subjects as a group had a better quality of life without many of the side effects of cancer drugs.

Ask your doctor for more details about the clinical studies of the NovoTTF-100A Systems. For more information, visit our website: www.novocure.com

8 About the NovoTTF-100A System

The NovoTTF-100A System is a portable medical device. It delivers electric fields called "TTFields" to the brain using electrodes. TTFields are intended to kill cancer cells.

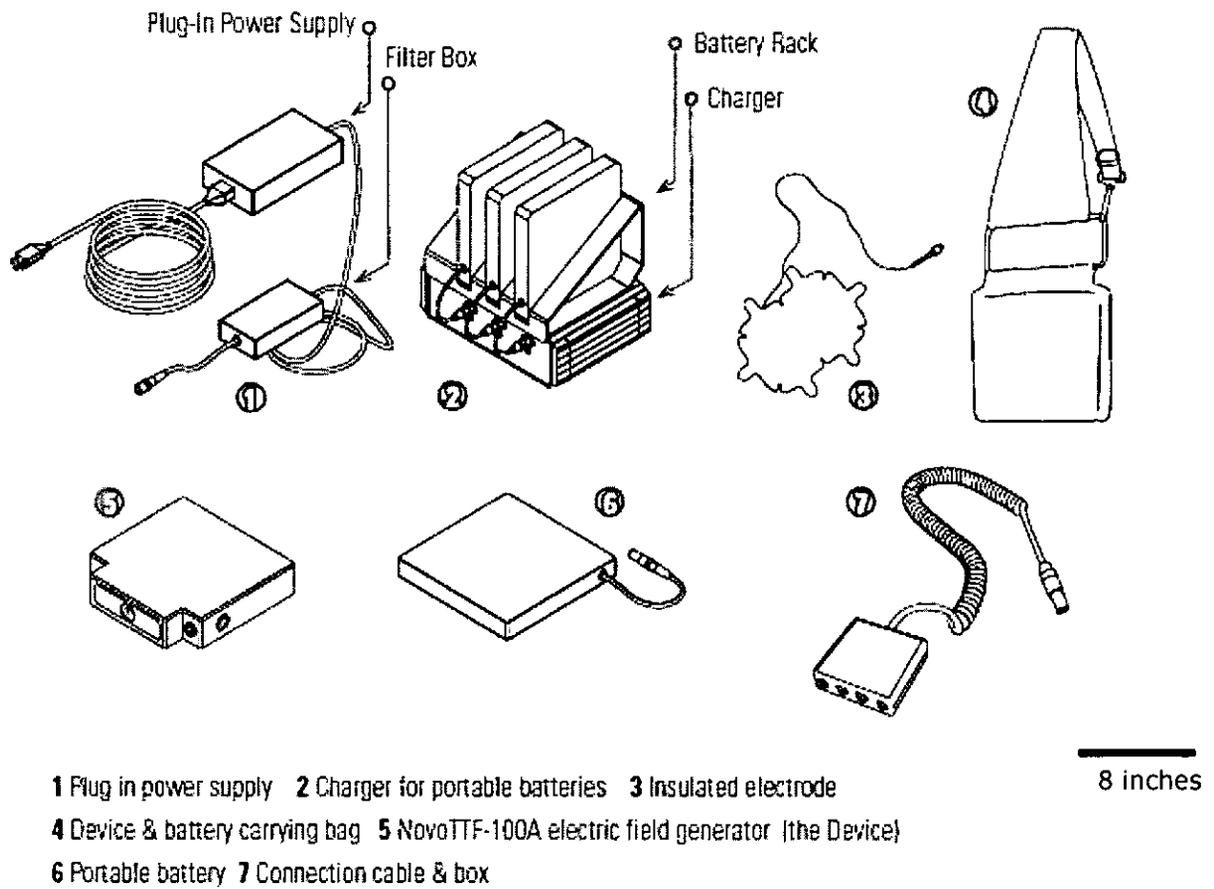
Your doctor has prescribed the NovoTTF-100A for use at home. You may be able to use the NovoTTF-100A System on your own, or you may need help from a doctor, family member, or other caregiver. Use the NovoTTF-100A as many hours per day as possible. Only take short breaks for personal needs. Use the device for at least four weeks. When starting treatment at your doctor's clinic, your doctor will tell you how to use the device, replace electrodes, recharge and replace batteries, and plug in the device. Your doctor will also teach you what to do if an alarm beeps and will give you a telephone number to call for technical support. After this short training at the doctor's office, with the help of a family member or care provider if needed, you will be able to properly work the NovoTTF-100A System. You will also be able to change the batteries, charge the batteries and replace the electrodes as needed.

The NovoTTF-100A can be carried when you are using a battery. You can continue your normal daily life while carrying the device in a shoulder bag or backpack. The Treatment Kit includes four rechargeable batteries. Each battery will last for two to three hours. For sleeping, or other times when you plan to stay in the same place for a while, plug the device into a standard wall outlet.

The NovoTTF-100A does not need regular maintenance. The NovoTTF-100A also does not have any settings for you to change. The only things you need to do are check that the device has a power supply (a charged battery, or is plugged into the wall) and turn it on and off. If the device is not working, an alarm will beep. A simple Troubleshooting Guide is provided in this manual (Section 26). You can also call the 24-hour technical support telephone number (Section 27).

Shave your scalp and change the electrodes every 4 to 7 days. Keep treatment breaks to a minimum. Interrupt treatment only for personal needs such as bathing, exercise, or any time where the device may be a distraction. Stop treatment to replace the electrodes. To take a shower, unplug the electrodes from the device (leave the electrodes on your head) and put a shower cap on your head so it does not get wet. You can take a full shower and wet your head when you are not wearing the electrodes (for example, when you have taken them off but before replacing them with a new pair). You can wear a wig or hat over the electrodes, if you wish.

9 Overview of the NovoTTF-100A System



10 Overview of INE Electrodes

INE Electrodes are electrodes that are used with the NovoTTF-100A Treatment Kit only.

Four electrodes are used at one time. Put the electrodes on a clean, shaven scalp. Put them on your scalp in the place where your doctor told you, based on the location of your tumor. When you put the electrodes on your head, apply the colored rings to the connectors that go with each electrode location. The locations and their colors are: front (blue), back (red), right (yellow), and left (white).

The electrodes are disposable. Change them one to two times per week (every 4 to 7 days). Your hair growth will prevent good contact between the electrodes and your scalp. Shave the scalp again before you apply a new set of electrodes.

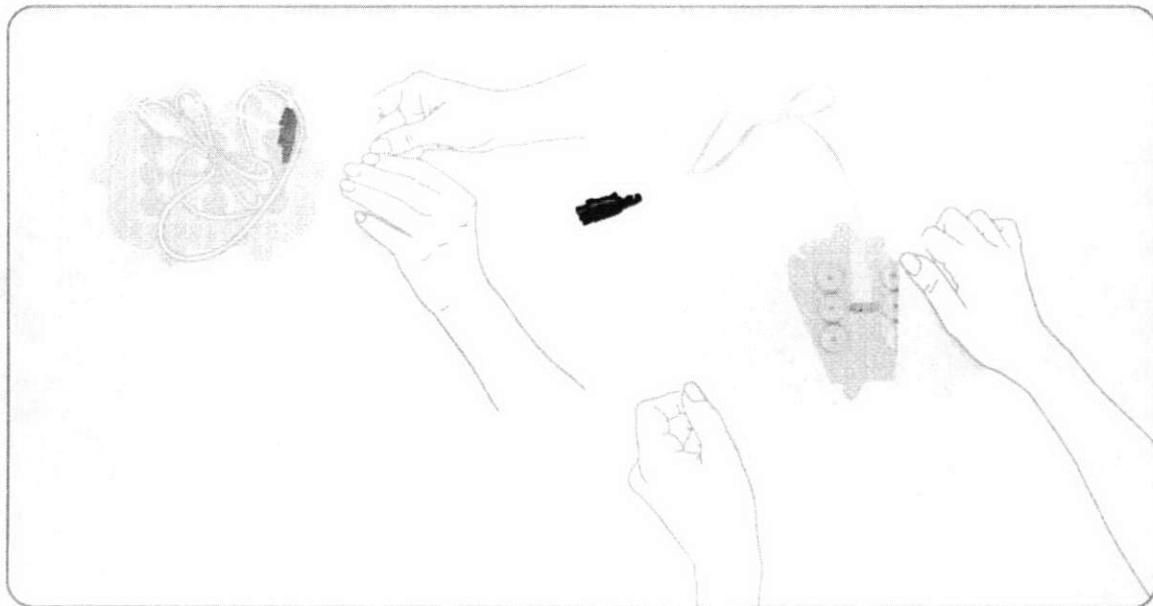
Please call technical support at 1-800-978-0265 to dispose of your used electrodes.

11 Before You Put on the Electrodes

You will need to use four (4) electrodes at one time. Change these 4 electrodes one to two times per week (every 4 to 7 days) to continue treatment with the NovoTTF-100A System. You may change the electrodes with the help of a doctor or caregiver if needed.

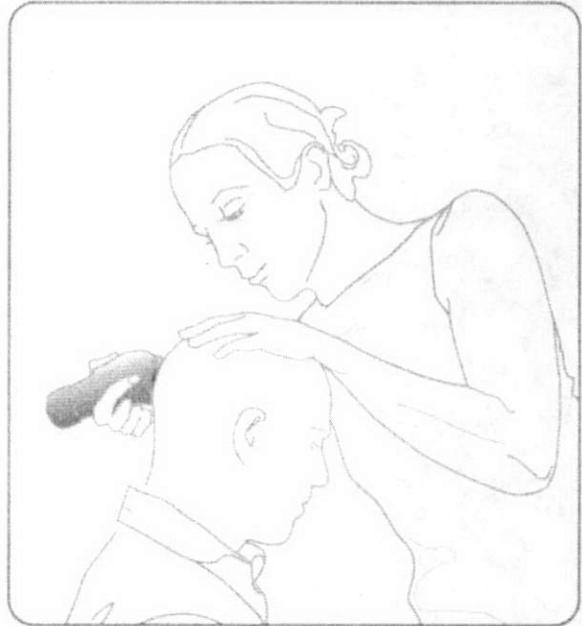
12 Removing the Electrodes from the Package

Open the clear envelope of four (4) electrodes by gently pulling apart the edges of the envelope (see the picture below).



13 Prepare Your Head for Electrode Placement

1. Wash your head with a gentle shampoo.
2. If this is the first time you have used the electrodes, ignore this step and go to step #3. If you are replacing electrodes, you, or your doctor or caregiver if needed, should wipe the skin with baby oil to remove any old adhesive from other electrodes. Baby oil is used to remove old adhesive. It will not stop the device from working.
3. Shave your entire scalp using an electric shaver. Do not leave any stubble.
4. Wipe your scalp with 70% Alcohol (available at your local pharmacy without a prescription).
5. Use an over-the-counter 0.1% hydrocortisone (steroid) cream if your scalp is red. Treat open sores on your scalp like your doctor told you. If you use this cream, wait at least 15 minutes and repeat step #4. Apply the electrodes after your scalp is dry.



14 Place the Electrodes on Your Head

After you prepare your scalp (Section 13), put the electrodes on your head with the help of a doctor or caregiver if needed. Every 4 to 7 days, remove the electrodes, prepare the scalp (as outlined in Section 13) and put on a new set of electrodes. You will know it is time to change electrodes when the device alarm beeps more often. This means that the device is not able to work properly because of hair growth. Hair growth keeps the electrodes from making good contact with your scalp.

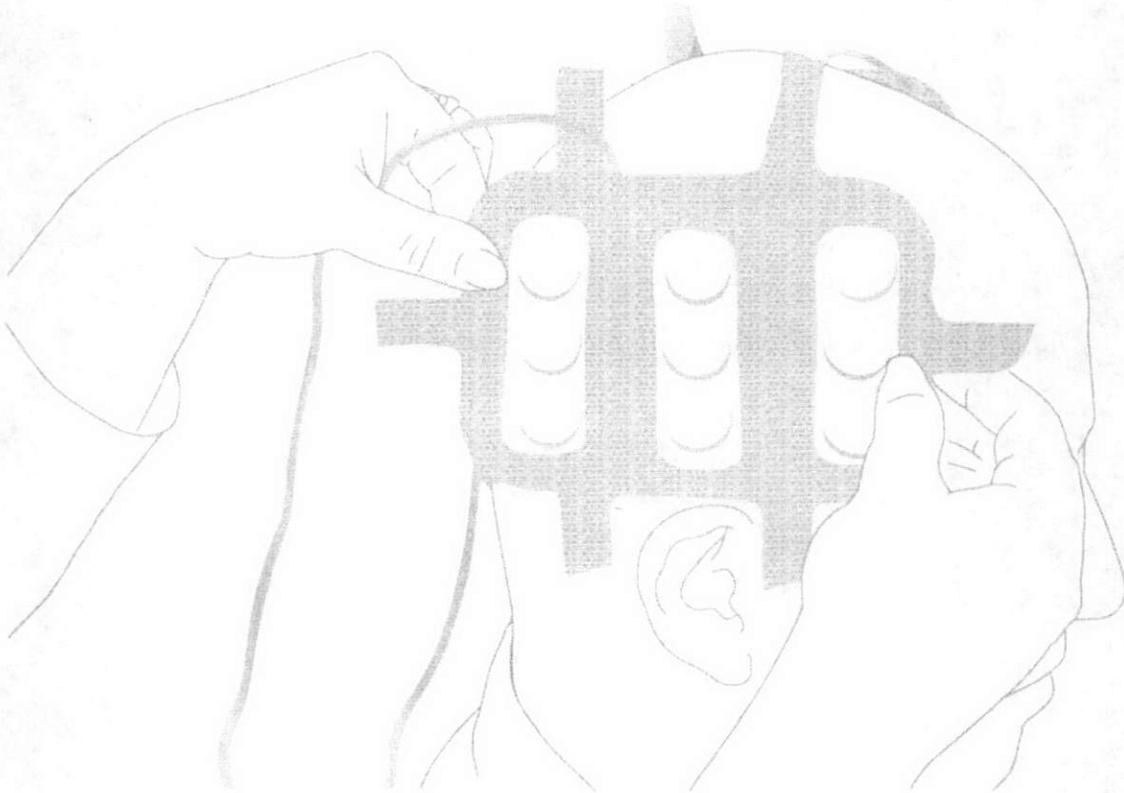
To place the electrodes on your head, with the help of a caregiver or doctor if needed, follow the steps below.

Note, if this is the first time you have used the electrodes, ignore step #1 and go to step #2.

1. Remove the electrodes from your head by peeling the medical tape away from your scalp.
2. Note which color electrode goes where on your head. The electrode locations and colors are: front (blue), back (red), right (yellow), left (white).
3. In the Treatment Kit, there are small, plastic rings in four different colors. These colors match the color coding of the electrode placement diagram that your doctor gave you. Snap the rings over the body of the connector. Place the color coded rings on the electrode connectors of the four electrodes you have opened.
4. Prepare your skin for the electrodes, as described in Section 13.
5. Peel off the white layer (liner) covering the gel from the first electrode.
6. If this is the first time you have used the electrodes, put the electrodes on your head as shown in the electrode placement diagram that your doctor gave you. Placement is based on the location of your tumor. When changing the electrodes, place the electrodes on your head in the same general location as before, but shift the electrodes less than an inch in the direction of the arrow on your electrode placement diagram. To reduce skin irritation under the

electrodes, move the electrodes a small amount. Shifting the electrodes is not required for the device to work properly.

7. Place the other three electrodes in the same way.
8. Pull the tabs on each side of the electrodes and press them firmly to your scalp.
9. Press the entire edge of the electrode tape to your scalp.



15 Connect the Electrodes to the Device

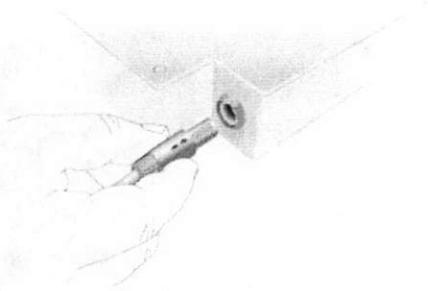
1. Connect each of the four electrode connectors with the color coded rings to the matching color coded socket on the connection cable. For example, plug the electrode connector with the red ring into the red socket (labeled "N1"; see diagram).
2. Connect the other three electrode connectors in the same way.
3. Press firmly to be sure the connectors are pushed in all the way.
4. Hold the electrode wires together. Wrap them with a small piece of tape, if you wish.



16 Disposal

Please contact NovoCure to arrange for proper disposal of used electrodes. Do not throw them in the trash.

17 Connecting & Disconnecting the Portable Battery



The NovoTTF-100A Treatment Kit comes with 4 rechargeable batteries. Each battery has a cord that connects to the device. The NovoTTF-100A uses one (1) battery at a time. The other three (3) batteries should stay in the battery charger. Each battery lasts 2 to 3 hours. Replace the battery each time it runs out (when the yellow Low Battery indicator light is on, as described in Section 22). If you plan to be away from home for more than 2 hours, carry extra batteries or a power supply.

Recharge the batteries in the charger (see Section 18) for four to five hours. The batteries will only stay charged if they are off the charger for a short time (hours, but not days). For this reason, keep the extra batteries in the charger at all times, if possible. You can charge and use the batteries many times for about six to nine months. Over time, the length of time the batteries can run the device (before the low battery alarm beeps) will get shorter. When this happens, contact technical support (see Section 27) to get replacement batteries.

When the yellow Low Battery indicator light lights up, replace the battery using these steps:

1. Turn off the alarm by pressing the TTFIELDS button once.

2. Turn OFF the device using the power button.
3. Unplug the battery connector from the blue socket on the front panel.
4. Hold the connector by its sleeve (as shown). Do not pull on the cord.
5. Remove the battery from the bag. Do not lift or pull the battery by the cord.
6. Put a fully charged battery into the device bag.
7. Connect the battery connector of the fully charged battery to the blue socket on the front panel. Hold the arrows on the connector up toward the "DC IN" label on the device.
8. Turn ON the device and start treatment by turning the power button on and pressing the TTFields button (see Section 22).
9. Connect the used battery to the charger for recharging (as described in Section 18).



18 Charging the Portable Battery

The battery charger recharges used batteries. The battery charger uses power from a standard wall outlet. Each battery has a cord that connects to the device or to the charger.

Before charging the batteries, plug the charger power cord into a standard wall outlet and turn on the power button at the back of the charger.

To recharge a used battery:

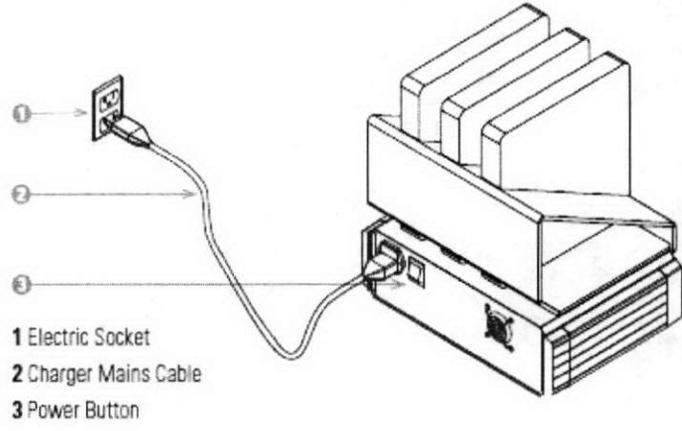
1. Place the used battery in the charger.
2. Plug the connector into an open charger socket (see diagram on the next page). If plugged in correctly, the Charge light on the front of the charger will light up in red. A red light means the battery is charging.
3. When the battery is fully charged (about 4 to 5 hours), the Charge light will turn from red to green.

Put all three (3) extra batteries in the charger and connect the cables to the charging sockets at all times. Keep the batteries in the charger even after they are fully charged. This will not harm the batteries.

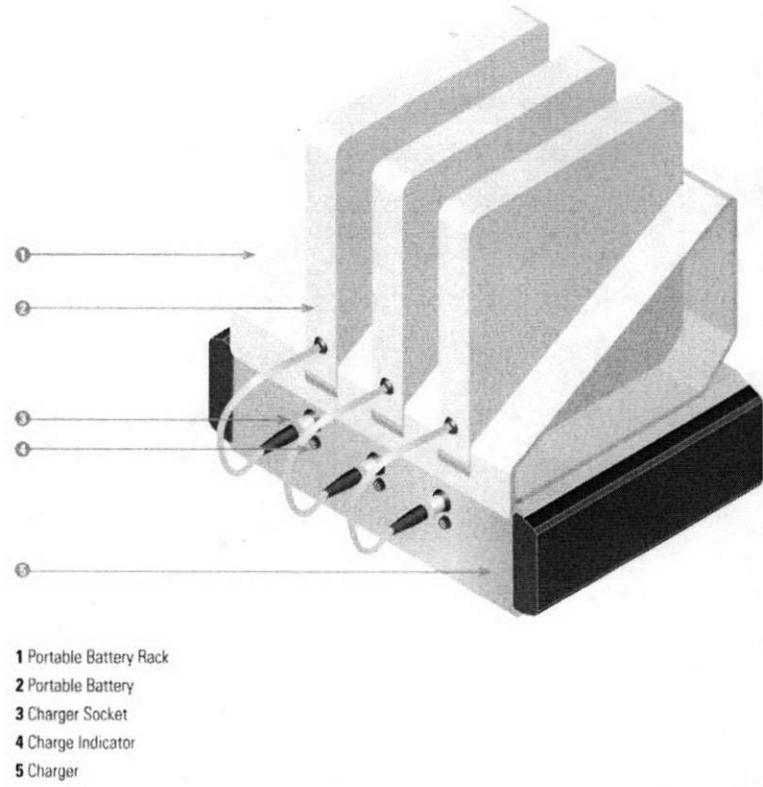
Always start with a fully charged battery. A fully-charged battery will have a bright green Charge light.

To remove a battery from the charger:

1. Unplug the battery cable from the charger by pulling the connector out of the socket on the charger.
2. Hold the connector by the sleeve. Do not pull on the cord.



Back view of the battery charger and rack showing where to turn the charger on and off and where to connect the charger power cord



Front view of the battery charger and rack showing where the battery cords connect to the charger sockets

19 Using the Plug-In Power Supply

When you plan to stay in one place for a while, like when you are sleeping, you may use the plug-in power supply instead of the batteries. Unlike the batteries, there is no limit to how long the device can work when you use the plug-in power supply. The plug-in power supply will work with either U.S. (120V AC) or European (230V AC) outlets.

Note: It is normal for the power supply to become warm when in use. If the power supply becomes too hot to touch, unplug it and contact technical support (Section 27).

Connecting the Plug-In Power Supply

1. Plug in the power supply to a standard wall outlet using the power cord that comes with it.
2. Press the TTFields button and turn off the power switch to stop the device (as described in Section 22).
3. Unplug the battery cord from the device. To do this, take the battery connector out of the blue socket on the front of the device.
4. Plug the blue connector of the plug-in power supply line to the blue socket on the front of the device (where the battery was plugged in).
5. Turn on the power switch and push the TTFields button to start the device (as described in Section 22).
6. Check that the filter box is not hanging from the line to the blue connector.

Note: The filter is part of the power cord. It cannot be taken off.

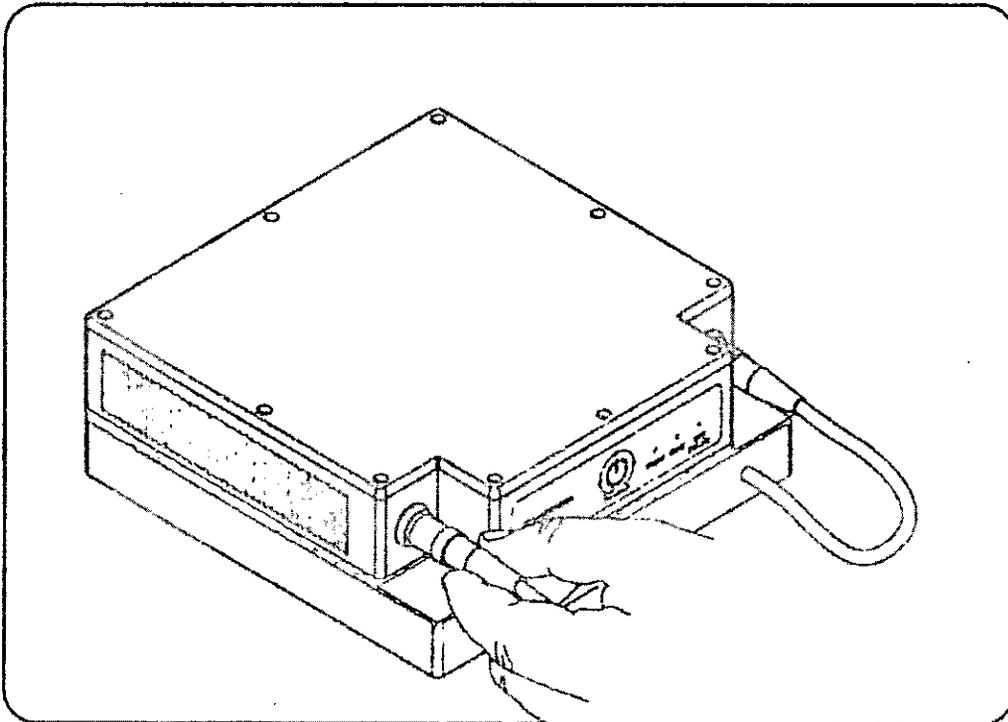
To Disconnect the Plug-In Power Supply and Go Back to Battery Power

1. Stop the device by stopping the TTFields and switching off the power.
2. Remove the blue connector of the plug-in power supply from the blue socket on the front of the device.
3. Put a charged battery in the device bag.
4. Plug the battery connector into the blue socket on the front of the device.
5. Turn on the power switch and push the TTFields button to start the device by.
6. Store the plug-in power supply for future use.

20 The Connection Cable & Connection Box

The connection cable is the coiled, stretchy cord that runs from the device to the connection box. The four color-coded electrode connectors plug into the connection box on the other side. The color coding matches with the electrode position on the head.

The connection cable plugs into the device in the P1 socket. The P1 socket has a picture of a person next to it and a grey ring around it. Note that the battery socket has a blue ring around it. The connection cable plugs into the socket with the arrows facing up to the P1 label. Push in the connector until you hear a snap. The snap means it is in the right place.



There are two ways to unplug from the device to take a break from treatment:

1. Unplug the connection cable from the device.
2. Unplug the electrodes from the connection cable.

To Unplug the connection cable from the device:

1. Stop treatment by pressing the TTFields button.
2. Turn off the NovoTTF device using the power button.
3. Unplug the connection cable from the socket by holding the sleeve and pulling. Do not pull on the cord.

You may now move around without the device, but you will still be connected to the connection cable and box. To start treatment again after your break:

1. Plug the connection cable into the P1 (grey) socket with the arrows pointing to the P1 label.
2. Turn on the NovoTTF device using the power button.
3. Turn on the TTFields using the TTFields button.

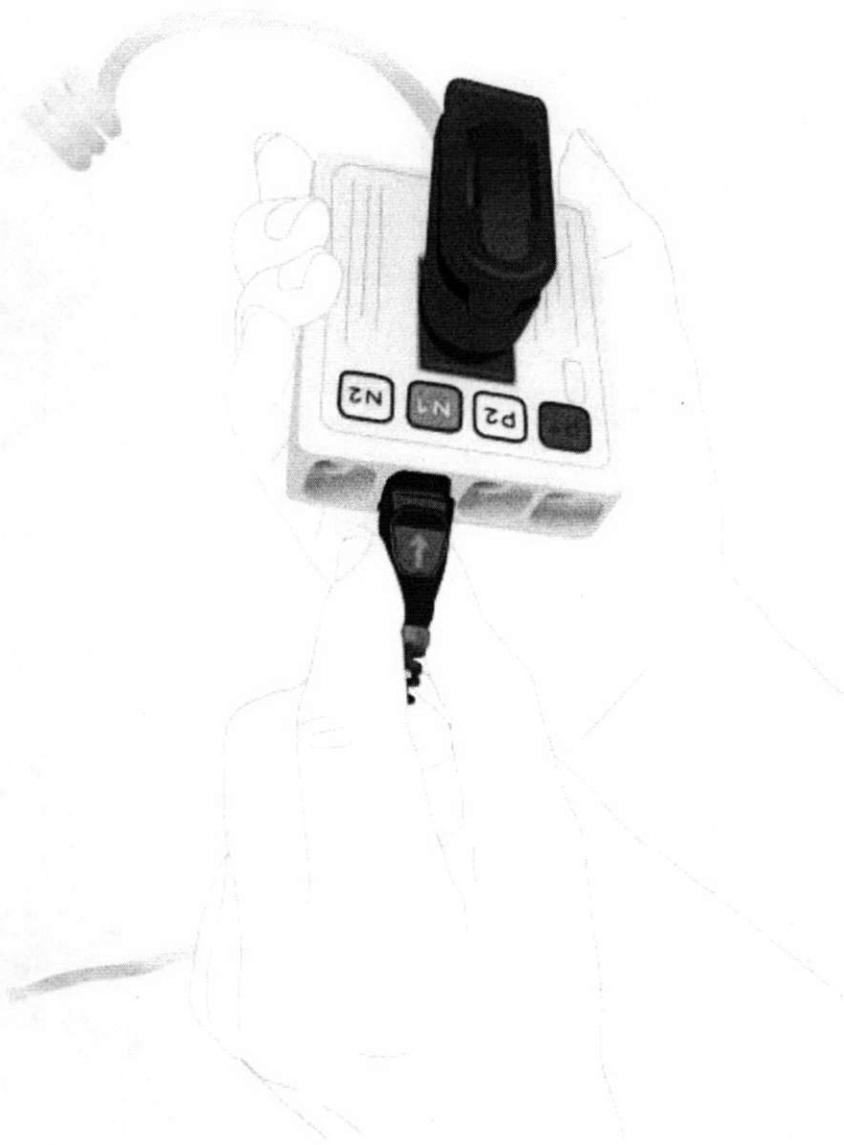
To Unplug the electrodes from the connection cable:

To take a break from treatment and completely disconnect from the device, unplug the electrodes from the connection cable box. The four electrodes are plugged into the connection cable box as described in Section 15. The connection cable is plugged into the device at the P1 (patient) socket.

1. Stop treatment by pressing the TTFields button.
2. Turn off the NovoTTF device using the power button.
3. Unplug the electrode connectors from the connection box by pulling as shown in the picture below. You may have to wiggle the electrode cables to remove them.

To restart treatment, plug the electrodes into the connection box. Plug each electrode into its matching color that goes with the electrode's position on the head (as described in Section 15).

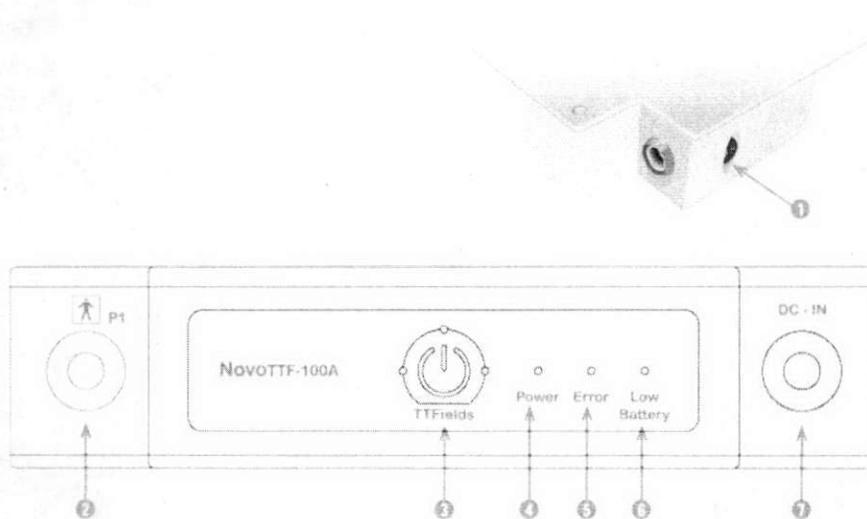
4. When all 4 electrodes are plugged in, turn on the power switch and push the TTFields button to restart treatment.



21 The Electric Field Generator (the Device)

Keep the TTFIELD treatment on all the time, as much as possible, when awake and when sleeping. Keep breaks from treatment as short as possible.

The picture below shows the device controls to work the system. You do not need to adjust any settings. You only need to turn the device and the therapy off and on.

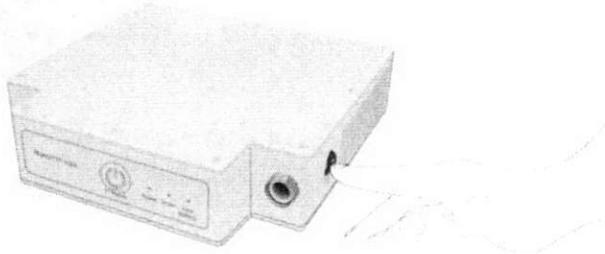


1 NovoTTF-100A power button **2** Connection cable socket (P1) **3** TTFIELD therapy ON/OFF button **4** Power ON indicator light **5** Error indicator light **6** Low Battery indicator light **7** Battery connector socket

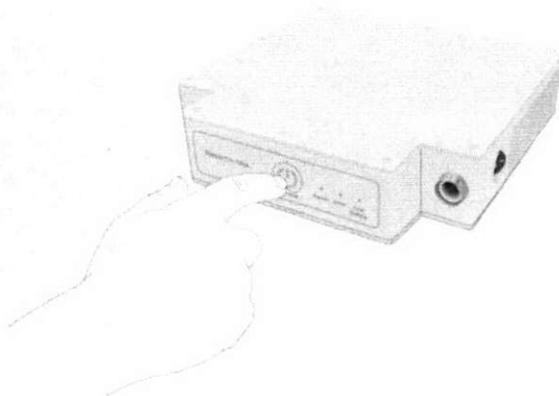
22 To Start & Stop the Electric Field Generator

To start treatment,

1. Put the electrodes on the scalp (with the help of a caregiver if needed). Plug the electrodes into the connection cable box (Sections 14 and 15).
2. Plug the connection cable into the device with the arrows on the connector up, facing the "P1" label (as described in Section 20).
3. Plug a charged battery into the device (see Section 17).
4. Turn the power button on the side of the device to the ON position.



5. Wait about 3 seconds for the blue lights around the TTFields button to stop blinking.
6. Press the TTFields therapy button once – this will start treatment.

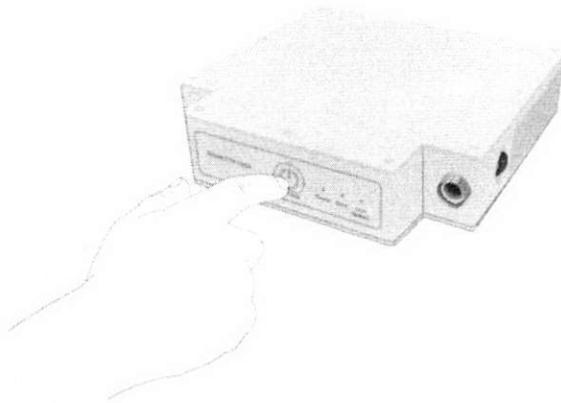


The three blue lights around the TTFields therapy button will turn on and stay on while the treatment is on. If the three blue lights are not on, then the treatment is not running and you should check the setup and restart the procedure. If, after this, the indicator lights do not light up, consult the Troubleshooting Guide (Section 26). If you still have problems, call the technical support center at 1-800-978-0265.

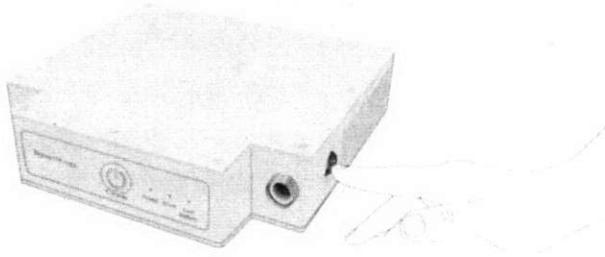
You may **stop treatment** if the following happens:

A. If the Device is Running Properly, But You Need to Stop Treatment to Take a Break:

Press the TTFields button. The three blue lights around the button will turn off. This turns the TTField therapy off, but the device power is still on.



Then, turn off the device by turning the power button on the side of the device to the OFF position.

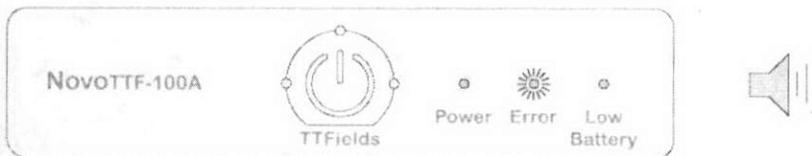


B. If an Error Occurs:

If an error occurs, the device will turn off the TTFields and make a loud beeping noise. The red Error light will light up (as shown below).

To turn off the device:

1. Press the TTFields button on the front of the device to stop the alarm. The red Error light will turn off.
2. Turn off the device by turning the power button to the OFF position.
3. See the Troubleshooting Guide (Section 26) for instructions on fixing problems. Restart the device and restart treatment if no problem is found. If the alarm does not stop, contact technical support at 1-800-978-0265.

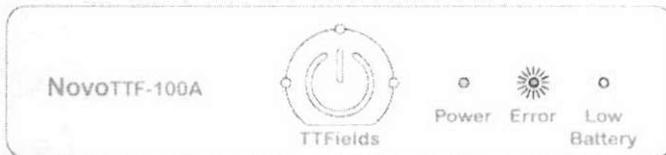


C. If the Low Battery Indicator Light Lights Up:

When your battery runs out (after about 2-3 hours), an alarm will beep, the TTFields therapy will stop and both the yellow Low Battery light and red Error light will light up. This alarm sound is the same alarm sound the device makes for an error. However, in this case *both the yellow and red lights* will light up instead of just the red light.

To turn off the device:

1. Press the TTFIELDS button on the front of the device to stop the alarm. The red Error and the yellow Low Battery lights will turn off.
2. Replace the battery using the steps in Section 18.

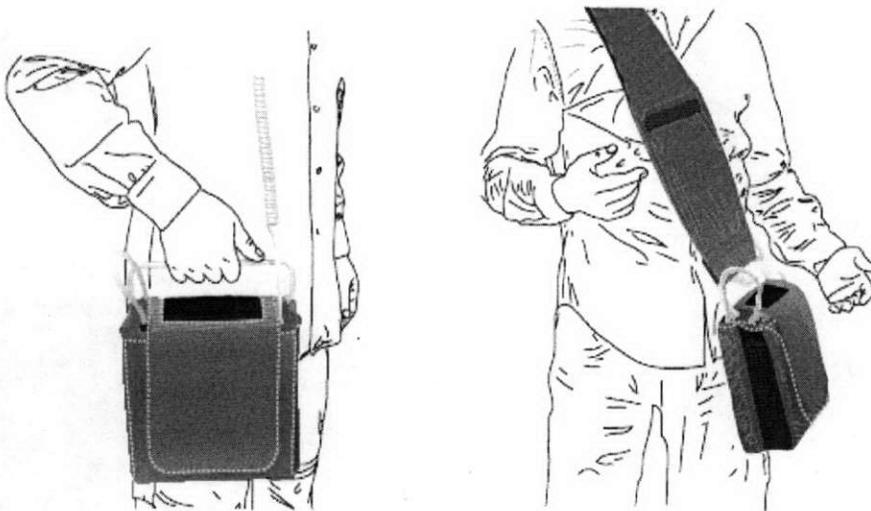


23 Carrying the Electric Field Generator

Both the electric field generator and the battery fit in a carrying bag with a handle and a shoulder strap that can be taken off.

To wear the bag:

1. Place the strap over your shoulder.
2. Grab the snap hook at the end of the strap with your other hand.
3. Connect the snap hook to the handle as shown.



Note: Do not place the device in a different bag. The NovoTTF-100A device has a fan on the inside that needs air flow. The bag that comes with the device is designed to allow for proper air flow. If you put the device in a bag without proper air flow, it could overheat and stop the treatment. If this happens, you will hear an alarm.

24 Glossary of Graphic Symbols



Attention – consult accompanying documents



Date of Manufacturing



Fragile – handle with care



Do not enter rooms with high humidity or danger of direct exposure to water while wearing the device.

Do not carry the device outdoors if not within its carrying bag.

Do not expose the device to direct rain.



The charger is for indoor use only



Batteries are Lithium Ion. Contact technical support to arrange for proper disposal of batteries that are used up or no longer in use.



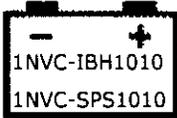
The NovoTTF-100A device and Treatment Kit parts should be kept away from extreme heat and sources of radiation



BF type applied part – symbolizes the part which comes in contact with the patient

1NVC-CAD1010

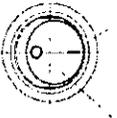
Specifies the P/N of the applied part to be used with this device



Battery socket – connect only 1NVC-IBH1010 Lithium Ion batteries or 1NVC-SPS1010 power supply manufactured by NovoCure Ltd.



Expiration date – do not use beyond this date



Power ON / OFF switch for the NovoTTF-100A device:
When the switch is in the — position the device is ON
When the switch is in the O position the device is OFF



Power ON / OFF switch for the portable battery and overnight battery chargers:

When the switch is in the | position the device is ON and will light up green. When the switch is in the O position the device is OFF.



Do not use the INE electrodes if their packaging is breached.



The INE Electrodes are for single use and should not be re-used.



The INE Electrodes are sterilized by Gamma irradiation

25 Storage and Transportation by the Distributer

Storage Conditions

Temperature range: 23°F to 104°F for the device and additional parts

Temperature range: 41°F to 81°F for the electrodes

Relative Humidity range: 15-75% for the device and additional parts

Relative Humidity range: 35-50% for the electrodes

Transport Conditions

Transportation of the device and additional parts is possible using air/ground transportation in weather protected conditions as specified below:

- Temperature range: -13°F to 104°F
- Maximal relative humidity 15-75%
- No direct exposure to water

Transportation of the electrodes is possible using air/ground transportation in weather protected conditions as specified below:

- Temperature range: 32°F to 104°F
- Maximal relative humidity 15-75%
- No direct exposure to water

26 Troubleshooting

Problem	Possible Causes	Actions to be Taken
Device power indicator light does not light up after turning ON the device	<ol style="list-style-type: none"> 1. Battery dead 2. Battery malfunction 3. Charger malfunction 4. Device malfunction 	<ol style="list-style-type: none"> 1. Replace battery. If problem is not fixed: <ol style="list-style-type: none"> 1. Turn OFF power switch 2. Call technician
Any cable detached from electrode/connection cable/device	<ol style="list-style-type: none"> 1. Too much physical force to cables 2. Device malfunction 	<ol style="list-style-type: none"> 1. Replace electrode. If problem is not fixed: <ol style="list-style-type: none"> 1. Press TFields button to stop therapy. 2. Turn OFF power switch 3. Call technician
Device dropped or wet	Incorrect use	<ol style="list-style-type: none"> 1. Press TFields button to stop therapy. 2. Turn OFF power switch 3. Call technician
Device alarm on	<ol style="list-style-type: none"> 1. Low battery 2. Cable loose or disconnected 3. Vents on the sides of the device and the front of the charger are blocked 4. Local hot spot on electrode from laying on a pillow, for example 5. Poor electrode contact due to hair growth or other reason 6. Device malfunction 	<p>If Low Battery light is on:</p> <ol style="list-style-type: none"> 1. Replace battery as described Above in Section 18 2. Turn on treatment <p>If the Error light lights up but the Low Battery light is not lit:</p> <ol style="list-style-type: none"> 1. Press the TFields button to stop the alarm 2. Turn off power switch 3. Check all plugs to make sure nothing is loose 4. Check vents on device and charger to make sure they are not blocked 5. If lying down, move your head 6. Make sure electrodes are well

Problem	Possible Causes	Actions to be Taken
		<p>stuck to the head, add tape if needed</p> <p>7. Restart treatment</p> <p>8. If alarm keeps going, turn off the device and call technician</p>
<p>Low Battery indicator light remains on after battery replaced</p>	<p>1. Charger malfunction</p> <p>2. Battery malfunction</p> <p>3. Device malfunction</p>	<p>1. Replace battery with an additional charged battery.</p> <p>2. If problem is not fixed – call technician.</p>
<p>Redness of the skin under the electrodes</p>	<p>Common side effect</p>	<p>1. Use over-the-counter 0.1% hydrocortisone cream when switching electrodes.</p> <p>2. Shift electrodes 3/4 of an inch from the last location (so the adhesive gel is between the red marks).</p> <p>If the redness gets worse:</p> <p>1. See your doctor</p>
<p>Blisters under the electrodes</p>	<p>Rare side effect</p>	<p>See your doctor for a prescription antibacterial cream. Use as your doctor tells you.</p>
<p>Itching under the electrodes</p>	<p>Rare side effect</p>	<p>1. Use over-the-counter 0.1% hydrocortisone cream when switching electrodes.</p> <p>2. Shift electrodes over 3/4 of an inch from the last location (so the adhesive gel is between the red marks).</p> <p>If the itching gets worse:</p>

Problem	Possible Causes	Actions to be Taken
		1. See your doctor.
Pain under the electrodes	Rare side effect	Stop treatment See your doctor

27 Assistance & Information

Technical support:

For technical support call at 1-800-978-0265. Call technical support for help with operation of the system, troubleshooting alarms, or to get replacement parts or electrodes.

Medical support:

If you feel any change in your health or any side effects from the treatment call your doctor right away.



28 Traveling with the NovoTTF-100A

NovoCure, Ltd. is not aware of any limitations regarding air, ground or sea travel when using the NovoTTF-100A.

Note: The NovoTTF-100A System and electrodes will activate metal detectors.

29 Brain Cancer

What is Brain Cancer?

In simple terms, brain cancer is a growth of cells that form a tumor in the brain. Just like any other form of cancer, brain tumors can spread to other parts of the brain. They do not usually spread outside of the brain. Even before the brain cancer grows and spreads, the tumor could cause problems inside the brain. The brain controls the functions of the body. Any problem in the brain will affect normal functioning. Therefore, symptoms of brain cancer depend on where and how big the tumor is.

Close to 10,000 patients in the U.S. are diagnosed with GBM every year. It is still unknown what causes GBM. GBM is a very serious disease. Less than 10% of patients with GBM are alive after 5 years even using the best available treatments.

Can Brain Cancer Be Treated?

There are currently four main options to treat GBM:

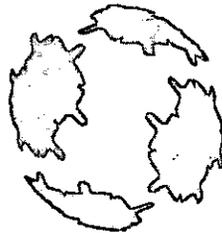
- *Operation* – Treatment of patients with GBM usually begins with taking out all or some of the tumor.
- *Radiation* – Following an operation, many patients have radiation therapy.
- *Local Chemotherapy* – During the operation, the surgeon can put a wafer that delivers cancer drugs to the site where the tumor was taken out.
- *Systemic Chemotherapy* – Many GBM patients take cancer drugs. There are several approved drugs to treat GBM.

Radiation therapy and cancer drugs can allow patients to live longer than if they had no treatment. Radiation and cancer drugs have side effects. These side effects

include hair loss, skin irritation, possible hearing problems, nausea, vomiting, loss of appetite, effects related to the brain, and tiredness.

When Brain Cancer Returns (Recurrence of Brain Cancer)

GBM can come back even with operations and the treatments described above. In these cases, some of the above treatments (operation, radiation, cancer drugs) may still work to treat the cancer. In those cases, doctors may use a systemic cancer drug treatment, or, alternatively once a patient has had treatment with a cancer drug, the NovoTTF-100A System.



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novocure



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