

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-637/S-016

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-637/S-016

Guilford Pharmaceuticals Inc.
Attention: Louise M. Peltier
Senior Director, Regulatory Affairs
6611 Tributary Street
Baltimore, MD 21224

Dear Ms. Peltier:

Please refer to your supplemental new drug application dated and received April 6, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gliadel Wafer (polifeprosan 20 with carmustine implant).

We acknowledge receipt of your submissions dated November 27, 2002, February 3, 4 and 6, 2003.

Your submission of October 25, 2002 constituted a complete response to our March 19, 2002 action letter.

This supplemental new drug application proposes to expand the indication to include patients with malignant glioma undergoing primary surgical resection.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-637/S-016." Approval of this submission by FDA is not required before the labeling is used.

We remind you under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each postmarketing study commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to

the Division of Oncology Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Paul Zimmerman, Project Manager, at (301) 594-5775.

Sincerely,

{See appended electronic signature page}

Richard Nazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon labeling text

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Richard Pazdur
2/25/03 01:28:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-637/S-016

Approved Labeling

Guilford Pharmaceuticals Inc.
 6611 Tributary Street
 Baltimore, Maryland 21224

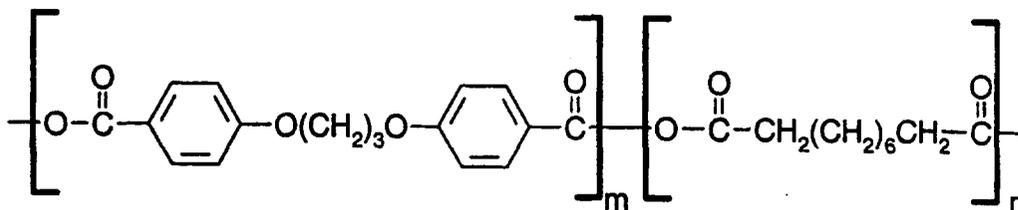
GLIADEL® WAFER
 (polifeprosan 20 with carmustine implant)

R only

DESCRIPTION

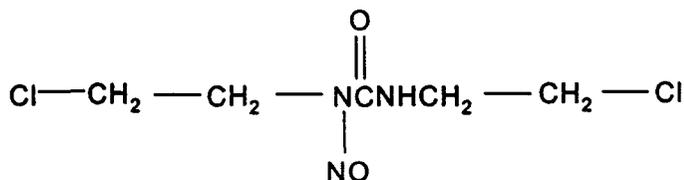
GLIADEL® Wafer (polifeprosan 20 with carmustine implant) is a sterile, off-white to pale yellow wafer approximately 1.45 cm in diameter and 1 mm thick. Each wafer contains 192.3 mg of a biodegradable polyanhydride copolymer and 7.7 mg of carmustine [1,3-bis (2-chloroethyl)-1-nitrosourea, or BCNU]. Carmustine is a nitrosourea oncolytic agent. The copolymer, polifeprosan 20, consists of poly[bis(4-carboxyphenoxy) propane: sebacic acid] in a 20:80 molar ratio and is used to control the local delivery of carmustine. Carmustine is homogeneously distributed in the copolymer matrix.

The structural formula for polifeprosan 20 is:



Ratio m:n = 20:80; random copolymer

The structural formula for carmustine is:



CLINICAL PHARMACOLOGY

GLIADEL[®] Wafer is designed to deliver carmustine directly into the surgical cavity created when a brain tumor is resected. On exposure to the aqueous environment of the resection cavity, the anhydride bonds in the copolymer are hydrolyzed, releasing carmustine, carboxyphenoxypropane, and **sebacic acid**. The carmustine released from GLIADEL[®] Wafer diffuses into the surrounding brain tissue and produces an antineoplastic effect by alkylating DNA and RNA.

Carmustine has been shown to degrade both spontaneously and metabolically. The production of an alkylating moiety, hypothesized to be chloroethyl carbonium ion, leads to the formation of DNA cross-links.

The tumoricidal activity of GLIADEL[®] Wafer is dependent on release of carmustine to the tumor cavity in concentrations sufficient for effective cytotoxicity.

More than 70% of the copolymer degrades by three weeks. The metabolic disposition and excretion of the monomers differ. Carboxyphenoxypropane is eliminated by the kidney and sebacic acid, an endogenous fatty acid, is metabolized by the liver and expired as CO₂ in animals.

The absorption, distribution, metabolism, and excretion of the copolymer in humans is unknown. Carmustine concentrations delivered by GLIADEL[®] Wafer in human brain tissue have not been determined. Plasma levels of carmustine after GLIADEL[®] Wafer implant were not determined. In rabbits implanted with wafers containing 3.85% carmustine, no detectable levels of carmustine were found in the plasma or cerebrospinal fluid.

Following an intravenous infusion of carmustine at doses ranging from 30 to 170 mg/m², the average terminal half-life, clearance, and steady-state volume of distribution were 22 minutes, 56 mL/min/kg, and 3.25 L/kg, respectively. Approximately 60% of the intravenous 200 mg/m² dose of ¹⁴C-carmustine was excreted in the urine over 96 hours and 6% was expired as CO₂.

GLIADEL[®] Wafers are biodegradable in human brain when implanted into the cavity after tumor resection. The rate of biodegradation is variable from patient to patient. During the biodegradation process, a wafer remnant may be observed on brain imaging scans or at re-operation even though extensive degradation of all components has occurred. Data obtained from review of CT scans obtained 49 days after implantation of GLIADEL[®] Wafer demonstrated that images consistent with wafers were visible to varying degrees in the scans of 11 of 18 patients. Data obtained at re-operation and autopsies have demonstrated wafer remnants up to 232 days after GLIADEL[®] Wafer implantation.

Wafer remnants removed at re-operation from two patients with recurrent malignant glioma, one at 64 days and the second at 92 days after implantation, were analyzed for content. The following table presents the results of analyses completed on these remnants.

**COMPOSITION OF WAFER REMNANTS REMOVED FROM
TWO PATIENTS ON RE-OPERATION**

<u>Component</u>	<u>Patient A</u>	<u>Patient B</u>
Days After GLIADEL [®] Wafer Implantation	64	92
Anhydride Bonds	None detected	None detected
Water Content (% of wafer remnant weight)	95-97%	74-86%
Carmustine Content (% of initial)	<0.0004%	0.034%
Carboxyphenoxypropane Content (% of initial)	9%	14%
Sebacic Acid Content (% of initial)	4%	3%

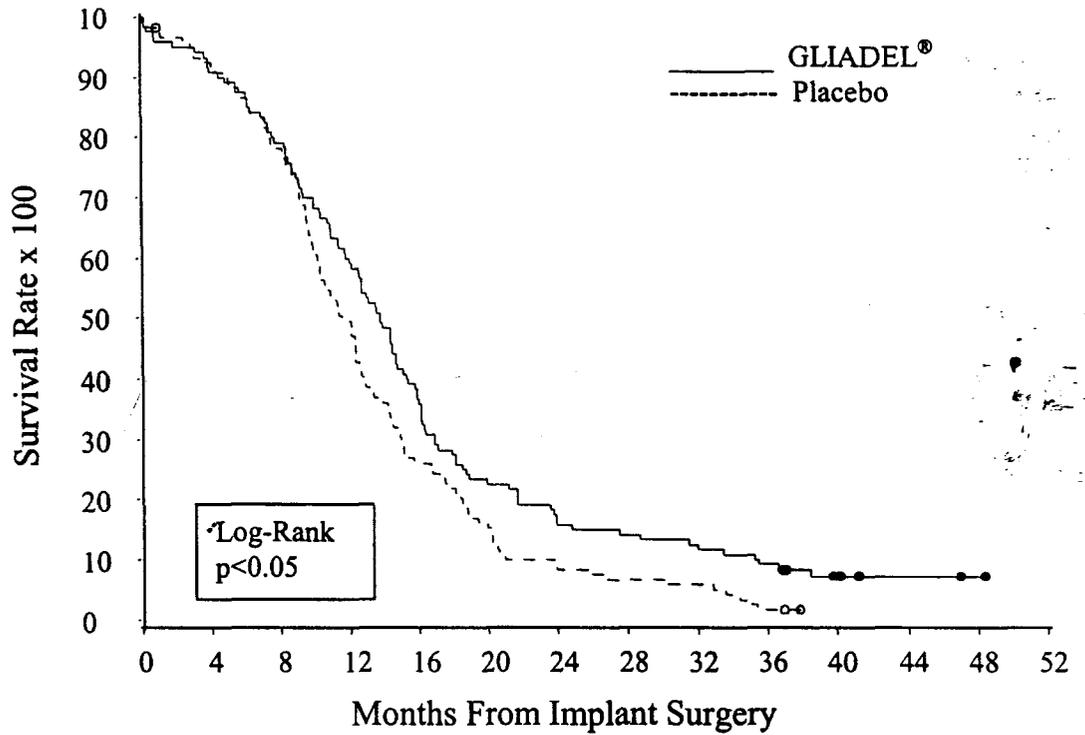
The wafer remnants consisted mostly of water and monomeric components with minimal detectable carmustine present.

CLINICAL STUDIES

Primary Surgery

A randomized, double-blind, placebo-controlled clinical trial was conducted in adult patients with newly-diagnosed high-grade malignant glioma undergoing initial craniotomy for tumor resection. This trial determined the safety and efficacy of GLIADEL[®] Wafer implants plus surgery and radiation therapy compared to placebo implants plus surgery and radiation therapy. Two hundred and forty patients with newly-diagnosed malignant glioma were enrolled. The most common tumor type was Glioblastoma Multiforme (GBM) (n=207), followed by anaplastic oligoastrocytoma (n=11), anaplastic oligodendroglioma (n=11), and anaplastic astrocytoma (n=2). GLIADEL[®] Wafers were implanted at the time of the surgery in 120 patients and placebo wafers were implanted in 120 patients. The majority of patients received 6-8 wafers. The majority of patients (93/120, 77.5% in the GLIADEL[®] Wafer group and 98/120, 81.7% in the placebo group) with newly-diagnosed malignant glioma received a standard course of radiotherapy (55 to 60 Gy) typically starting 3 weeks after surgery. There were 17 patients (14.2%) in the GLIADEL[®] Wafer group and 12 patients (10.0%) in the placebo group who received systemic chemotherapy during the study. All six patients with anaplastic oligodendroglioma received chemotherapy within 30 days of GLIADEL[®] wafer implantation. Patients were followed for at least three years or until death. Only one patient was lost to follow-up. Median survival increased from 11.6 months with placebo to 13.9 months with GLIADEL[®] Wafer (p-value <0.05, log-rank test). The hazard ratio for GLIADEL[®] Wafer treatment was 0.73 (95% CI: 0.56-0.95).

**Kaplan-Meier Overall Survival Curves for Patients Undergoing
INITIAL SURGERY FOR A HIGH-GRADE MALIGNANT GLIOMA**



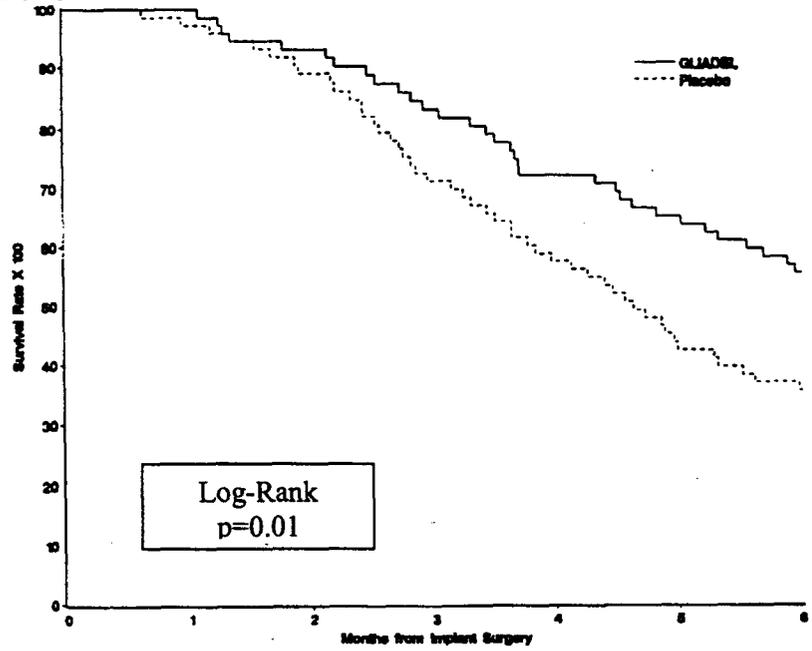
When only patients with Glioblastoma multiforme were included in the analysis, the hazard ratio with GLIADEL[®] Wafer treatment was 0.78 (95% CI: 0.59-1.03, p=0.08; log-rank test).

Surgery for Recurrent Disease

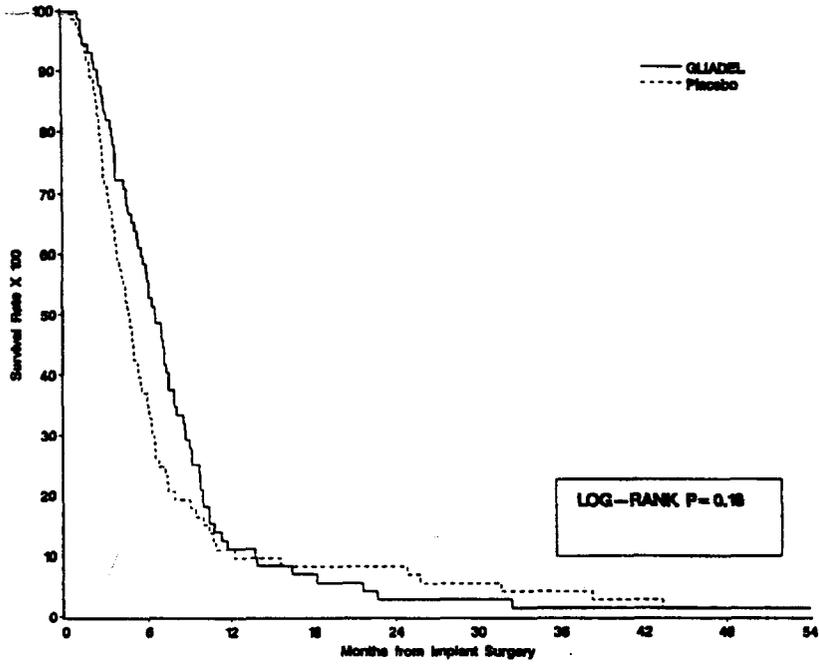
A randomized, double-blind, placebo-controlled clinical trial was conducted in adult patients with recurrent malignant glioma. This trial determined the safety and efficacy of GLIADEL[®] Wafer implants plus surgery compared to placebo implants plus surgery. Ninety-five percent of the patients treated with GLIADEL[®] had 7-8 wafers implanted. Chemotherapy was withheld at least four weeks (six weeks for nitrosoureas) prior to and two weeks after surgery in patients undergoing re-operation for malignant glioma. In 222 patients with recurrent malignant glioma who had failed initial surgery and radiation therapy, the six-month survival rate after repeat surgery increased from 47% (53/112) for patients receiving placebo to 60% (66/110) for patients treated with GLIADEL[®] Wafer. Median survival increased by 33%, from 24 weeks (5.5 months) with placebo to 32 weeks (7.4 months) with GLIADEL[®] Wafer treatment. In patients with GBM, the six-month survival rate increased from 36% (26/73) with placebo to 56% (40/72) with GLIADEL[®] Wafer treatment. Median survival of GBM patients increased by 41% from 20 weeks (4.6 months) with placebo to 28 weeks (6.4 months) with GLIADEL[®] Wafer treatment. In patients with pathologic diagnoses other than GBM at the time of surgery for tumor recurrence, GLIADEL[®] Wafer produced no survival prolongation.

**APPEARS THIS WAY
ON ORIGINAL**

6-MONTH KAPLAN-MEIER SURVIVAL CURVES FOR PATIENTS UNDERGOING SURGERY FOR RECURRENT GBM



KAPLAN-MEIER OVERALL SURVIVAL CURVES FOR PATIENTS UNDERGOING SURGERY FOR RECURRENT GBM



INDICATIONS AND USAGE

GLIADEL[®] Wafer is indicated in newly-diagnosed high grade malignant glioma patients as an adjunct to surgery and radiation. GLIADEL[®] Wafer is indicated in recurrent glioblastoma multiforme patients as an adjunct to surgery.

CONTRAINDICATIONS

GLIADEL[®] Wafer contains carmustine. GLIADEL[®] Wafer should not be given to individuals who have demonstrated a previous hypersensitivity to carmustine or any of the components of GLIADEL[®] Wafer.

WARNINGS

Patients undergoing craniotomy for malignant glioma and implantation of GLIADEL[®] Wafer should be monitored closely for known complications of craniotomy, including seizures, intracranial infections, abnormal wound healing, and brain edema. Cases of intracerebral mass effect unresponsive to corticosteroids have been described in patients treated with GLIADEL[®] Wafer, including one case leading to brain herniation.

Pregnancy: There are no studies assessing the reproductive toxicity of GLIADEL[®] Wafer. Carmustine, the active component of GLIADEL[®] Wafer, can cause fetal harm when administered to a pregnant woman. Carmustine has been shown to be embryotoxic and teratogenic in rats at i.p. doses of 0.5, 1, 2, 4, or 8 mg/kg/day when given on gestation days 6 through 15. Carmustine caused fetal malformations (anophthalmia, micrognathia, omphalocele) at 1.0 mg/kg/day (about 1/6 the recommended human dose (eight wafers of 7.7 mg carmustine/wafer) on a mg/m² basis). Carmustine was embryotoxic in rabbits at i.v. doses of 4.0 mg/kg/day (about 1.2 times the recommended human dose on a mg/m² basis). Embryotoxicity was characterized by increased embryo-fetal deaths, reduced numbers of litters, and reduced litter sizes.

There are no studies of GLIADEL[®] Wafer in pregnant women. If GLIADEL[®] Wafer is used during pregnancy, or if the patient becomes pregnant after GLIADEL[®] Wafer implantation, the patient must be warned of the potential hazard to the fetus.

PRECAUTIONS

General: Communication between the surgical resection cavity and the ventricular system should be avoided to prevent the wafers from migrating into the ventricular system and causing obstructive hydrocephalus. If a communication larger than the diameter of a wafer exists, it should be closed prior to wafer implantation.

Computed tomography and magnetic resonance imaging of the head may demonstrate enhancement in the brain tissue surrounding the resection cavity after implantation of GLIADEL[®] Wafers. This enhancement may represent edema and inflammation caused by GLIADEL[®] Wafer or tumor progression.

Therapeutic Interactions: Interactions of GLIADEL[®] Wafer with other drugs have not been formally evaluated.

The short-term and long-term toxicity profiles of GLIADEL[®] Wafer when given in conjunction with chemotherapy have not been fully explored. GLIADEL[®] Wafer, when given in conjunction with radiotherapy does not appear to have any short-term or chronic toxicities.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with GLIADEL[®] Wafer. Carcinogenicity, mutagenicity and impairment of fertility studies have been conducted with carmustine, the active component of GLIADEL[®] Wafer. Carmustine was given three times a week for six months, followed by 12 months observation, to Swiss mice at i.p. doses of 2.5 and 5.0 mg/kg (about 1/5 and 1/3 the recommended human dose (eight wafers of 7.7 mg carmustine/wafer) on a mg/m² basis) and to SD rats at i.p. dose of 1.5 mg/kg (about 1/4 the recommended human dose on a mg/m² basis). There were increases in tumor incidence in all treated animals, predominantly subcutaneous and lung neoplasms. *Mutagenesis:* Carmustine was mutagenic *in vitro* (Ames assay, human lymphoblast HGPRT assay) and clastogenic both *in vitro* (V79 hamster cell micronucleus assay) and *in vivo* (SCE assay in rodent brain tumors, mouse bone marrow micronucleus assay). *Impairment of Fertility:* Carmustine caused testicular degeneration at i.p. doses of 8 mg/kg/week for eight weeks (about 1.3 times the recommended human dose on a mg/m² basis) in male rats.

Pregnancy: Pregnancy Category D: see WARNINGS.

Nursing Mothers: It is not known if either carmustine, carboxyphenoxypropane, or sebacic acid is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from carmustine in nursing infants, it is recommended that patients receiving GLIADEL[®] Wafer discontinue nursing.

Pediatric Use: The safety and effectiveness of GLIADEL[®] in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reactions for the trials are described in the tables below.

Primary Surgery

The following data are the most frequently occurring adverse events observed in 5% or more of the newly-diagnosed malignant glioma patients during the trial.

**COMMON ADVERSE EVENTS OBSERVED IN \geq 5% OF PATIENTS
RECEIVING GLIADEL® AT INITIAL SURGERY**

Body System	GLIADEL® N=120	Placebo N=120
Adverse event	n (%)	n (%)
Body as a whole		
Aggravation reaction*	98 (82)	95 (79)
Headache	33 (28)	44 (37)
Asthenia	26 (22)	18 (15)
Infection	22 (18)	24 (20)
Fever	21 (18)	21 (18)
Pain	16 (13)	18 (15)
Abdominal pain	10 (8)	2 (2)
Back pain	8 (7)	4 (3)
Face edema	7 (6)	6 (5)
Abscess	6 (5)	3 (3)
Accidental injury	6 (5)	8 (7)
Chest pain	6 (5)	0
Allergic reaction	2 (2)	6 (5)
Cardiovascular system		
Deep thrombophlebitis	12 (10)	11 (9)
Pulmonary embolus	10 (8)	10 (8)
Hemorrhage	8 (7)	7 (6)
Digestive system		
Nausea	26 (22)	20 (17)
Vomiting	25 (21)	19 (16)
Constipation	23 (19)	14 (12)
Diarrhea	6 (5)	5 (4)
Liver function tests abnormal	1 (1)	6 (5)
Endocrine system		
Diabetes mellitus	6 (5)	5 (4)
Cushings syndrome	4 (3)	6 (5)
Metabolic and nutritional disorders		
Healing abnormal	19 (16)	14 (12)
Peripheral edema	11 (9)	11 (9)
Musculoskeletal system		
Myasthenia	5 (4)	6 (5)
Nervous system		
Hemiplegia	49 (41)	53 (44)
Convulsion	40 (33)	45 (38)
Confusion	28 (23)	25 (21)
Brain edema	27 (23)	23 (19)
Aphasia	21 (18)	22 (18)
Depression	19 (16)	12 (10)
Somnolence	13 (11)	18 (15)
Speech disorder	13 (11)	10 (8)
Amnesia	11 (9)	12 (10)

*Adverse events coded to the COSTART term "aggravation reaction" were usually events involving tumor/disease progression or general deterioration of condition (e.g. condition/health/Karnofsky/neurological/physical deterioration).

Nervous system (continued)

**COMMON ADVERSE EVENTS OBSERVED IN \geq 5% OF PATIENTS
RECEIVING GLIADEL® AT INITIAL SURGERY**

Body System	GLIADEL® N=120	Placebo N=120
Adverse event	n (%)	n (%)
Intracranial hypertension	11 (9)	2 (2)
Personality disorder	10 (8)	9 (8)
Anxiety	8 (7)	5 (4)
Facial paralysis	8 (7)	5 (4)
Neuropathy	8 (7)	12 (10)
Ataxia	7 (6)	5 (4)
Hypesthesia	7 (6)	6 (5)
Paresthesia	7 (6)	10 (8)
Thinking abnormal	7 (6)	10 (8)
Abnormal gait	6 (5)	6 (5)
Dizziness	6 (5)	11 (9)
Grand mal convulsion	6 (5)	5 (4)
Hallucinations	6 (5)	4 (3)
Insomnia	6 (5)	7 (6)
Tremor	6 (5)	8 (7)
Coma	5 (4)	6 (5)
Incoordination	3 (3)	8 (7)
Hypokinesia	2 (2)	8 (7)
Respiratory system		
Pneumonia	10 (8)	9 (8)
Dyspnea	4 (3)	8 (7)
Skin and appendages		
Rash	14 (12)	13 (11)
Alopecia	12 (10)	14 (12)
Special senses		
Conjunctival edema	8 (7)	8 (7)
Abnormal vision	7 (6)	7 (6)
Visual field defect	6 (5)	8 (7)
Eye disorder	3 (3)	6 (5)
Diplopia	1 (1)	6 (5)
Urogenital system		
Urinary tract infection	10 (8)	13 (11)
Urinary incontinence	9 (8)	9 (8)

Surgery for Recurrent Disease

The following post-operative adverse events were observed in 4% or more of the patients receiving GLIADEL® Wafer at recurrent surgery. Except for nervous system effects, where there is a possibility that the placebo wafers could have been responsible, only events more common in the GLIADEL®

Wafer group are listed. These adverse events were either not present pre-operatively or worsened post-operatively during the follow-up period. The follow-up period was up to 71 months.

COMMON ADVERSE EVENTS OBSERVED IN $\geq 4\%$ OF PATIENTS
RECEIVING GLIADEL® Wafer AT SURGERY FOR RECURRENT DISEASE

Body System Adverse Event	GLIADEL Wafer with Carmustine [N=110] n (%)	PLACEBO Wafer without Carmustine [N=112] n (%)
Body as a Whole		
Fever	13 (12)	9 (8)
Pain*	8 (7)	1 (1)
Digestive System		
Nausea and Vomiting	9 (8)	7 (6)
Metabolic and Nutritional Disorders		
Healing Abnormal*	15 (14)	6 (5)
Nervous System		
Convulsion	21 (19)	21 (19)
Hemiplegia	21 (19)	22 (20)
Headache	16 (15)	14 (13)
Somnolence	15 (14)	12 (11)
Confusion	11 (10)	9 (8)
Aphasia	10 (9)	12 (11)
Stupor	7 (6)	7 (6)
Brain Edema	4 (4)	1 (1)
Intracranial Hypertension	4 (4)	7 (6)
Meningitis or Abscess	4 (4)	1 (1)
Skin and Appendages		
Rash	6 (5)	4 (4)
Urogenital System		
Urinary Tract Infection	23 (21)	19 (17)

*p < 0.05 for comparison of GLIADEL® versus placebo groups

The following four categories of adverse events are possibly related to treatment with GLIADEL® Wafer. The frequency with which they occurred in the randomized trials along with descriptive detail is provided below.

1. Seizures: In the initial surgery trial, the incidence of seizures was 33.3% in patients receiving GLIADEL® Wafer and 37.5% in patients receiving placebo. Grand mal seizures occurred in 5% of GLIADEL® Wafer-treated patients and 4.2% of placebo treated patients. The incidence of seizures within the first 5 days after wafer implantation was 2.5% in the GLIADEL® Wafer group and 4.2% in the placebo group. The time from surgery to the onset of the first post-operative seizure did not differ between the GLIADEL® Wafer and placebo treated patients.

In the surgery for recurrent disease trial, the incidence of post-operative seizures was 19% in both patients receiving GLIADEL® Wafer and placebo. In this study, 12/22 (54%) of patients treated with GLIADEL® Wafer and 2/22 (9%) of placebo patients experienced the first new or worsened seizure within the first five post-operative days. The median time to onset of the first new or worsened post-operative seizure was 3.5 days in patients treated with GLIADEL® Wafer and 61 days in placebo patients.

2. Brain Edema: In the initial surgery trial, brain edema was noted in 22.5% of patients treated with GLIADEL® Wafer and in 19.2% of patients treated with placebo. Development of brain edema with mass effect (due to tumor recurrence, intracranial infection, or necrosis) may necessitate re-operation and, in some cases, removal of GLIADEL® Wafer or its remnants.

3. Healing Abnormalities: The following healing abnormalities have been reported in clinical trials of GLIADEL® Wafer: wound dehiscence, delayed wound healing, subdural, subgaleal or wound effusions, and cerebrospinal fluid leak. In the initial surgery trial, healing abnormalities occurred in 15.8% of GLIADEL® Wafer treated patients and in 11.7% of placebo recipients. Cerebrospinal fluid leaks occurred in 5% of GLIADEL® Wafer recipients and 0.8% of those given placebo. During surgery, a water-tight dural closure should be obtained to minimize the risk of cerebrospinal fluid leak.

In the surgery for recurrent disease trial, the incidence of healing abnormalities was 14% in GLIADEL® Wafer treated patients and 5% in patients receiving placebo wafers.

4. Intracranial Infection: In the initial surgery trial, the incidence of brain abscess or meningitis was 5% in patients treated with GLIADEL® Wafer and 6% in patients receiving placebo. In the recurrent setting, the incidence of brain abscess or meningitis was 4% in patients treated with GLIADEL® Wafer and 1% in patients receiving placebo.

The following adverse events, not listed in the table above, were reported in less than 4% but at least 1% of patients treated with GLIADEL® Wafer in all studies. The events listed were either not present pre-operatively or worsened post-operatively. Whether GLIADEL® Wafer caused these events cannot be determined.

Body as a Whole: peripheral edema (2%); neck pain (2%); accidental injury (1%); back pain (1%); allergic reaction (1%); asthenia (1%); chest pain (1%); sepsis (1%)

Cardiovascular System: hypertension (3%); hypotension (1%)

Digestive System: diarrhea (2%); constipation (2%); dysphagia (1%); gastrointestinal hemorrhage (1%); fecal incontinence (1%)

Hemic and Lymphatic System: thrombocytopenia (1%); leukocytosis (1%)

Metabolic and Nutritional Disorders: hyponatremia (3%); hyperglycemia (3%); hypokalemia (1%)

Musculoskeletal System: infection (1%)

Nervous System: hydrocephalus (3%); depression (3%); abnormal thinking (2%); ataxia (2%); dizziness (2%); insomnia (2%); monoplegia (2%); coma (1%); amnesia (1%); diplopia (1%); paranoid reaction (1%). In addition, cerebral hemorrhage and cerebral infarct were each reported in less than 1% of patients treated with GLIADEL[®] Wafer.

Respiratory System: infection (2%); aspiration pneumonia (1%)

Skin and Appendages: rash (2%)

Special Senses: visual field defect (2%); eye pain (1%)

Urogenital System: urinary incontinence (2%)

OVERDOSAGE

There is no clinical experience with use of more than eight GLIADEL[®] Wafers per surgical procedure.

DOSAGE AND ADMINISTRATION

Each GLIADEL[®] Wafer contains 7.7 mg of carmustine, resulting in a dose of 61.6 mg when eight wafers are implanted. It is recommended that eight wafers be placed in the resection cavity if the size and shape of it allows. Should the size and shape not accommodate eight wafers, the maximum number of wafers as allowed should be placed. Since there is no clinical experience, no more than eight wafers should be used per surgical procedure.

Handling and Disposal¹⁻⁷: Wafers should only be handled by personnel wearing surgical gloves because exposure to carmustine can cause severe burning and hyperpigmentation of the skin. Use of double gloves is recommended and the outer gloves should be discarded into a biohazard waste container after use. A surgical instrument dedicated to the handling of the wafers should be used for wafer implantation. If repeat neurosurgical intervention is indicated, any wafer or wafer remnant should be handled as a potentially cytotoxic agent.

GLIADEL[®] Wafer should be handled with care. The aluminum foil laminate pouches containing GLIADEL[®] Wafer should be delivered to the operating room and remain unopened until ready to implant the wafers. **The outside surface of the outer foil pouch is not sterile.**

Instructions for Opening Pouch Containing GLIADEL

Figure 1: To remove the sterile inner pouch from the outer pouch, locate the folded corner and slowly pull in an outward motion.

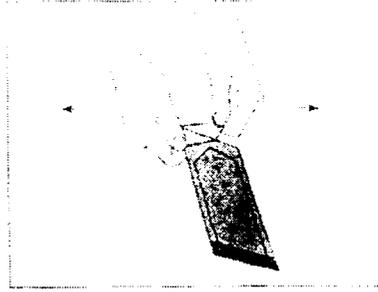


Figure 2: Do NOT pull in a downward motion rolling knuckles over the pouch. This may exert pressure on the wafer and cause it to break.

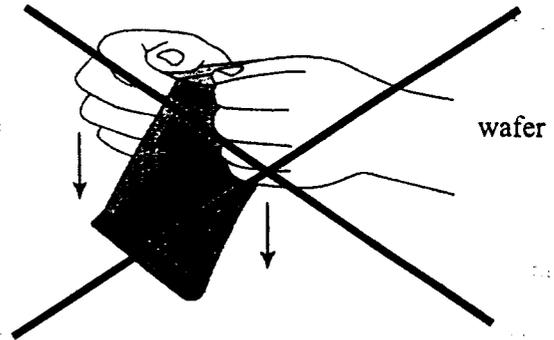


Figure 3: Remove the inner pouch by grabbing hold of the crimped edge and pulling upward.

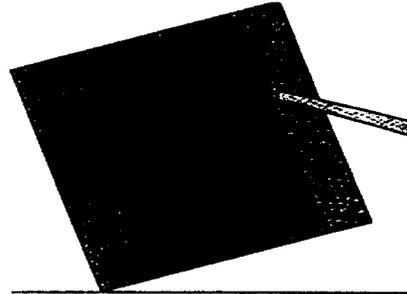


Figure 4: To open the inner pouch, gently hold the crimped edge and cut in an arc-like fashion around the wafer.

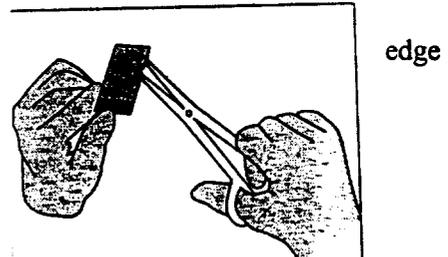
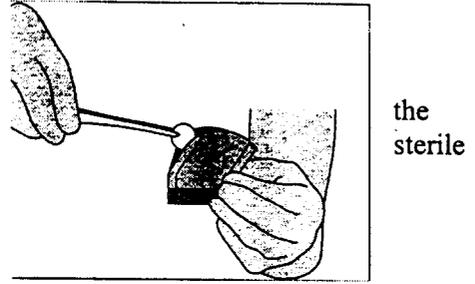


Figure 5: To remove the GLIADEL[®] Wafer, gently grasp wafer with the aid of forceps and place it onto a designated field.



Once the tumor is resected, tumor pathology is confirmed, and hemostasis is obtained, up to eight GLIADEL[®] Wafers (**polifeprosan 20 with carmustine implant**) may be placed to cover as much of the resection cavity as possible. Slight overlapping of the wafers is acceptable. Wafers broken in half may be used, but wafers broken in more than two pieces should be discarded in a biohazard container. Oxidized regenerated cellulose (**Surgicel[®]**) may be placed over the wafers to secure them against the cavity surface. After placement of the wafers, the resection cavity should be irrigated and the dura closed in a water tight fashion.

Unopened foil pouches may be kept at ambient room temperature for a maximum of **six hours** at a time.

HOW SUPPLIED

GLIADEL[®] Wafer is available in a single dose treatment box containing eight individually pouched wafers. Each wafer contains 7.7 mg of carmustine and is packaged in two **aluminum foil laminate** pouches. The inner pouch is sterile and is designed to maintain product sterility and protect the product from moisture. The outer pouch is a peelable overwrap. **The outside surface of the outer pouch is not sterile.**

GLIADEL[®] Wafer must be stored at or below -20°C (-4°F).

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CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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