HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GLIADEL WAFER safely and effectively. See full prescribing information for GLIADEL WAFER.

GLIADEL® WAFER (carmustine implant) for intracranial use
Initial U.S. Approval: 1996

----------INDICATIONS AND USAGE----------
GLIADEL Wafer is an alkylating drug indicated for the treatment of:
- newly-diagnosed high-grade-malignant glioma as an adjunct to surgery and radiation (1) and
- recurrent glioblastoma multiforme as an adjunct to surgery (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose: Eight 7.7 mg wafers (61.6 mg total dose) implanted intracranially (2.1, 2.2)
- Follow preparation and handling recommendations (2.3).

----------DOSAGE FORMS AND STRENGTHS----------
- Each GLIADEL Wafer contains 7.7 mg of carmustine (3).

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Seizures: Monitor patients for seizures following implantation (5.1).
- Intracranial hypertension: Monitor patients for signs of increased intracranial pressure (5.2).
- Impaired neurosurgical wound healing: Monitor patients for complications of craniotomy (5.3).
- Meningitis: Monitor patients for signs of bacterial or chemical meningitis (5.4).
- Wafer migration: Monitor patients for signs of obstructive hydrocephalus (5.5).
- Embryo-fetal toxicity: Can cause fetal harm (5.6)

----------ADVERSE REACTIONS----------
- Newly-Diagnosed High-Grade Malignant Glioma: Most common adverse reactions (incidence >10% and between arm difference ≥4%) are cerebral edema, asthenia, nausea, vomiting, constipation, wound healing abnormalities and depression (6.1).
- Recurrent Glioblastoma Multiforme: Most common adverse reactions (incidence >10% and between arm difference ≥4%) are urinary tract infection, wound healing abnormalities and fever (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Arbor Pharmaceuticals, LLC at 1-866-516-4950 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------
- Pediatric use: Safety and effectiveness not established (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GLIADEL Wafer is indicated for the treatment of patients with:

- newly-diagnosed high-grade malignant glioma as an adjunct to surgery and radiation, and
- recurrent glioblastoma multiforme as an adjunct to surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of GLIADEL Wafer is eight 7.7 mg wafers for a total of 61.6 mg implanted intracranially. The safety and effectiveness of repeat administration have not been studied.

2.2 Insertion Instructions

Following maximal tumor resection, confirmation of tumor pathology and establishment of hemostasis, place up to a maximum of eight GLIADEL Wafers to cover as much of the resection cavity as possible. Should the size and shape of the resected cavity not accommodate eight wafers, place the maximum number of wafers feasible within the cavity. Slight overlapping of the wafers is acceptable. Wafers broken in half may be used, but discard wafers broken in more than two pieces. Oxidized regenerated cellulose (Surgicel®) may be placed over the wafers to secure them against the cavity surface. After placement of the wafers, irrigate the resection cavity and close the dura in a water-tight fashion.

2.3 Preparation and Safe Handling

GLIADEL Wafers contain a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Each wafer is packaged within two nested aluminum foil laminate pouches. The inner pouch is sterile and is designed to maintain product sterility and protect the product from moisture. The outside surface of the outer laminated aluminum foil pouch is a peelable overwrap and is not sterile.

Deliver GLIADEL Wafers to the operating room in their outer aluminum foil pouch, unopened. Do not open the pouch until the wafers are ready to be implanted**.** GLIADEL Wafers in unopened outer foil pouches are stable at room temperature for six hours at a time for up to three cycles within a 30-day period.

Exposure to carmustine can cause severe burning and hyperpigmentation of the skin. Use double gloves when handling GLIADEL Wafers. Discard the outer gloves into a biohazard waste container after use. Use a dedicated surgical instrument for wafer implantation. If repeat neurosurgical intervention is indicated, handle residual wafers or wafer remnants as potential cytotoxic agents.

Instructions for Opening Pouch Containing GLIADEL Wafer

Read all steps of the instructions prior to opening the pouch.

Instructions for opening the pouch containing GLIADEL Wafer can be viewed at the following website: *http://gliadel.com/hcp/pouch-opening-instructions*. Illustrations are also pictured below.

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: The inner pouch is a multi-layered, silver colored, foil laminate. Remove the inner pouch by grabbing hold of the crimped edge of the inner pouch using a sterile instrument 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 the wafer with the aid of forceps and place it onto a designated sterile field.

3 DOSAGE FORMS AND STRENGTHS

GLIADEL Wafer is an off-white to pale yellow round wafer. Each GLIADEL Wafer contains 7.7 mg of carmustine.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Seizures

Fifty-four percent (54%) of patients treated with GLIADEL Wafers for recurrent glioma in Study 2 experienced new or worsened seizures within the first five post-operative days *[see Adverse Reactions (6.1)]*. The median time to onset of the first new or worsened post-operative seizure was 4 days. Optimize anti-seizure therapy prior to surgery. Monitor patients for seizures postoperatively.

5.2 Intracranial Hypertension

Brain edema occurred in 23% of patients with newly diagnosed glioma treated with GLIADEL Wafers in Study 1. Additionally, one GLIADEL-treated patient experienced intracerebral mass effect unresponsive to corticosteroids which led to brain herniation (*see Adverse Reactions (6.1)*). Monitor patients closely for intracranial hypertension related to brain edema, inflammation, or

necrosis of the brain tissue surrounding the resection. In refractory cases, consider re-operation and removal of GLIADEL Wafers or Wafer remnants.

5.3 Impaired Neurosurgical Wound Healing

Impaired neurosurgical wound healing including wound dehiscence, delayed wound healing, and subdural, subgleal, or wound effusions occur with GLIADEL Wafer treatment. In Study 1, 16% of GLIADEL Wafer-treated patients with newly diagnosed glioma experienced impaired intracranial wound healing and 5% had cerebrospinal fluid leaks. In Study 2, 14% of GLIADEL Wafer-treated patients with recurrent glioma experienced wound healing abnormalities *[see Adverse Reactions (6.1)]*. Monitor patients post-operatively for impaired neurosurgical wound healing.

5.4 Meningitis

Meningitis occurred in 4% of patients with recurrent glioma receiving GLIADEL Wafers in Study 2. Two cases of meningitis were bacterial; one patient required removal of the Wafers four days after implantation; the other developed meningitis following reoperation for recurrent tumor. One case was diagnosed as chemical meningitis and resolved following steroid treatment. In one case the cause was unspecified, but meningitis resolved following antibiotic treatment. Monitor postoperatively for signs of meningitis and central nervous system infection.

5.5 Wafer Migration

GLIADEL Wafer migration can occur. To reduce the risk of obstructive hydrocephalus due to wafer migration into the ventricular system, close any communication larger than the diameter of a Wafer between the surgical resection cavity and the ventricular system prior to Wafer implantation. Monitor patients for signs of obstructive hydrocephalus.

5.6 Embryo-Fetal Toxicity

GLIADEL Wafers can cause fetal harm when administered to a pregnant woman. Carmustine, the active component of GLIADEL Wafer, is embryotoxic and teratogenic in rats at exposures less than the exposure at the recommended human dose on a mg/m^2 basis and embryotoxic in rabbits at exposures similar to the exposure at the recommended human dose on a mg/m^2 basis. Advise females of reproductive potential to avoid pregnancy after implantation of GLIADEL Wafers. If the patient becomes pregnant after GLIADEL Wafer implantation, warn the patient about the potential hazard to the fetus [*see Use in Specific Populations (8.1 and 8.6)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the label:

- Seizures [(see *Warnings and Precautions (5.1)*]
- Intracranial Hypertension [(see *Warnings and Precautions (5.2)*]
- Impaired Neurosurgical Wound Healing [(see *Warnings and Precautions (5.3)*]
- Meningitis [(see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly-Diagnosed High-Grade Malignant Glioma

The safety of GLIADEL Wafers was evaluated in a multicenter, randomized (1:1), double-blind, placebo controlled trial of 240 adult patients with newly-diagnosed high-grade malignant glioma who received up to eight GLIADEL Wafers or matched placebo implanted against the resection surfaces after maximal tumor resection (Study 1).

The population in Study 1 was 67% male, 97% white, the median age was 53 years (range: 21-72). Eighty-seven percent had a Karnofsky performance status ≥ 70 and 71% had a Karnofsky performance status of ≥ 80%. Seventy-eight percent had a histologic subtype of glioblastoma multiforme as determined by central pathology review. Thirty-eight percent of patients received 8 wafers and 78% received ≥ 6 wafers. Starting three weeks after surgery, 80% of patients received standard limited field radiation therapy (RT) described as 55-60 Gy delivered in 28 to 30 fractions over six weeks; an additional 11% received no radiotherapy and the remainder received non-standard radiotherapy or a combination of standard and non-standard radiotherapy. At the time of progression, 24% received systemic chemotherapy.

Deaths occurred within 30 days of wafer implantation in 5 (4%) of patients receiving GLIADEL Wafers compared to 2 (2%) of patients receiving placebo. Deaths on the GLIADEL arm resulted from cerebral hematoma/edema (n=3), pulmonary embolism (n=1) and acute coronary event (n=1). Deaths on the placebo arm resulted from sepsis (n=1) and malignant disease (n=1).

The incidence of common adverse reactions in GLIADEL Wafer-treated patients is listed in Table 1. The incidence of local adverse reactions is shown in Table 2.

Table 1. Per-Patient Incidence of Adverse Reactions Occurring in Gliadel Wafer-Treated Patients with Newly-Diagnosed High Grade Malignant Glioma (Study 1) (Between Arm Difference of ≥ 4%)		
BODY SYSTEM	GLIADEL Wafer N=120	Placebo N=120
	%	%
GASTROINTESTINAL DISORDERS		
Nausea	22	17
Vomiting	21	16
Constipation	19	12
Abdominal pain	8	2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITION		
Asthenia	22	15
Chest pain	5	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Wound healing abnormalities*	16	12
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	7	3
PSYCHIATRIC DISORDERS		
Depression	16	10
*included (1) Fluid, CDS, or subdural fluid collection; (2) CSF leak; (3) Wound dehiscence, breakdown, or poor healing; and (4) Subgaleal or wound effusions (including yellow discharge at the incision)		

Table 2. Incidence of Local Adverse Reactions, Study 1*		
Local Adverse Reactions	GLIADEL Wafer N=120	Placebo N=120
	%	%
Intracranial hypertension	9	2
Cerebral hemorrhage	6	4
Brain abscess	6	4
Brain cyst	2	3
Cerebral edema	23	19
*Not seen at baseline or worsened if present at baseline.		

Recurrent Glioblastoma Multiforme

The safety of GLIADEL Wafers was evaluated in a multicenter, randomized (1:1), double-blind, placebo controlled trial of 222 patients with recurrent high-grade malignant glioma who received up to eight GLIADEL Wafers or matched placebo implanted against the resection surfaces after maximal tumor resection (Study 2) . Patients were required to have had prior definitive external beam radiation therapy sufficient to disqualify them from additional radiation therapy. All patients were eligible to receive chemotherapy which was withheld at least four weeks (six weeks for nitrosoureas) prior to and two weeks after surgery.

The population in Study 2 was 64% male, 92% white, and had a median age of 49 years (range: 19-80). Sixty-five percent had a histologic subtype of glioblastoma multiforme, 26% had anaplastic astrocytoma or another anaplastic variant, 73% had a Karnofsky performance status ≥ 70, 53% had a Karnofsky performance status of ≥ 80%, 73% had only one prior surgery, and 46% had prior treatment with nitrosourea. Eighty-one percent of patients received 8 wafers and 96% received ≥ 6 wafers.

Sixty-four severe adverse reactions were reported in 43(39%) patients receiving GLIADEL Wafers. Adverse reactions in GLIADEL Wafer-treated patients are shown in Table 3. Meningitis occurred in four patients receiving GLIADEL Wafers and in no patients receiving placebo. Bacterial meningitis was confirmed in two patients: the first with onset four days following GLIADEL Wafer implantation; the second following resection for tumor recurrence 155 days following GLIADEL Wafer implantation. One case, attributed to chemical meningitis resolved following steroid treatment. The cause of the fourth case was undetermined but resolved following antibiotic treatment.

Table 3. Per-Patient Incidence of Adverse Reactions in Gliadel Wafer-Treated Patients with Glioblastoma Multiforme (Study 2) (Between Arm Difference of ≥ 4%)

BODY SYSTEM	GLIADEL Wafer N=110	Placebo N=112
	%	%
GENERAL		
Fever	12	8
INFECTIOUS		
Urinary tract infections	21	17
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Wound healing abnormalities*	14	5

*included (1) Fluid, CDS, or subdural fluid collection; (2) CSF leak; (3) Wound dehiscence, breakdown, or poor healing; and (4) Subgaleal or wound effusions (including yellow discharge at the incision)

The incidence of seizures is shown in Table 4. The incidence of hydrocephalus, cerebral edema and intracranial hypertension is shown in Table 5.

Table 4. Incidence of Seizures, Study 2

Adverse Reaction	GLIADEL Wafer N=110	Placebo N=112
	%	%
Patients with seizures		
Any seizures after wafer implantation	37	29
New or worsening seizures	20	20
Time to new or worsening seizures (days)*		
Mean (SD)	26.09 (0.75)	62.36 (48.66)
Median	3.5	61.0

*Days from implantation to onset of first new or worsening seizure.

Table 5. Hydrocephalus and Cerebral Edema, Study 2*		
Adverse Reaction	GLIADEL Wafer N=110	Placebo N=112
	%	%
Hydrocephalus	5	2
Cerebral edema	4	1
*Not seen at baseline or worsened if present at baseline.		

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

GLIADEL Wafer can cause fetal harm when administered to a pregnant woman. There have been no studies with GLIADEL Wafer; however, carmustine, the active component of GLIADEL Wafer, is embryotoxic and teratogenic in rats at exposures less than the exposure at the recommended human dose on a mg/m^2 basis and embryotoxic in rabbits at exposures similar to exposures at the recommended human dose on a mg/m^2 basis. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Animal Data

There are no studies assessing the reproductive toxicity of GLIADEL Wafer; however, carmustine, the active component of GLIADEL Wafer, is embryotoxic and teratogenic in rats at intraperitoneal doses of 0.5mg/kg/day or greater when given on gestation days 6 through 15. Carmustine caused fetal malformations (anophthalmia, micrognathia, omphalocele) at 1.0 mg/kg/day (about 0.12 the recommended human dose, eight wafers of 7.7 mg carmustine/wafer, on a mg/m^2 basis). Carmustine was embryotoxic in rabbits at intravenous doses of 4.0 mg/kg/day (about 1.2 times the recommended human dose on a mg/m^2 basis). Embryotoxicity was characterized by increased embryo-fetal deaths, reduced numbers of litters, and reduced litter sizes.

8.3 Nursing Mothers

It is not known if carmustine, the active component of GLIADEL Wafer, is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from carmustine, a decision should be made whether to discontinue nursing or not to administer the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of GLIADEL Wafer in pediatric patients have not been established.

8.5 Geriatric Use

Clinical trials of GLIADEL Wafer did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients.

8.6 Females and Males of Reproductive Potential

Contraception

Females
GLIADEL Wafer can cause fetal harm when administered during pregnancy (*see Use in Specific Populations, 8.1*). Counsel patients on pregnancy planning and prevention. Advise female patients of reproductive potential to use effective contraception after implantation of GLIADEL Wafer. Advise patients to inform their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking GLIADEL.

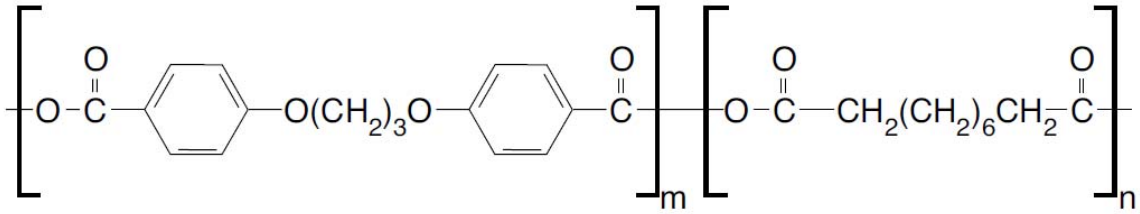
Infertility

Males
Carmustine caused testicular degeneration in animals. Advise male patients of the potential risk of infertility, and to seek counseling on fertility and family planning options prior to implantation of GLIADEL Wafer. (*see Nonclinical Toxicology, 13.1*)

11 DESCRIPTION

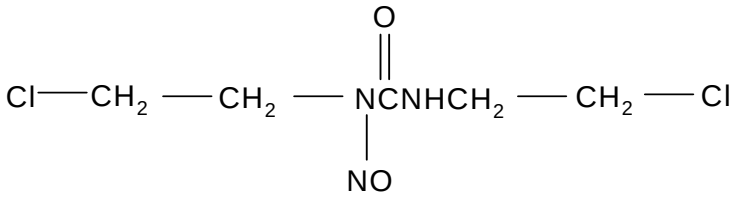
GLIADEL Wafer is an implant for intracranial use, containing carmustine, a nitrosourea alkylating agent, and polifeprosan, a biodegradable copolymer used to control the release of carmustine. It is a sterile, off-white to pale yellow wafer approximately 1.45 cm in diameter and 1 mm thick. Each wafer contains 7.7 mg of carmustine [1, 3-bis (2-chloroethyl)-1-nitrosourea, or BCNU] and 192.3 mg of a biodegradable polyanhydride copolymer. The copolymer, polifeprosan 20, consists of poly [bis (p-carboxyphenoxy)] propane and sebacic acid in a 20:80 molar ratio. 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:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The activity of GLIADEL Wafer is due to release of cytotoxic concentrations of carmustine, a DNA and RNA alkylating agent, into the tumor resection cavity. On exposure to the aqueous environment of the resection cavity, the anhydride bonds in the copolymer are hydrolyzed, releasing carmustine, carboxyphenoxypropane, and sebacic acid into the surrounding brain tissue.

12.3 Pharmacokinetics

Carmustine concentrations delivered by GLIADEL Wafer in human brain tissue have not been determined.

Following an intravenous infusion of carmustine at doses ranging from 30 to 170 mg/m^2, 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/m^2 dose of ^{14}C-carmustine was excreted in the urine over 96 hours and 6% was expired as CO_2. Carmustine degrades both spontaneously and metabolically. The relevance of these data to elimination of intracranial implant-delivered carmustine are unknown.

GLIADEL Wafers are biodegradable when implanted into the human brain. Wafer remnants may be observed on brain imaging scans or at re-operation. Wafer remnants were visible in 11 of 18 patients on CT scans obtained 49 days after implantation of GLIADEL Wafer. More than 70% of the copolymer degrades within three weeks. Wafer remnants have been present at re-operation and autopsy up to 232 days after GLIADEL Wafer implantation, and consisted mostly of water and monomeric components with minimal detectable carmustine present.

13 NONCLINICAL TOXICOLOGY

13.1 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 carcinogenic in rats and mice when delivered by intraperitoneal injection at doses lower than those delivered by GLIADEL Wafer at the recommended dose. There were increases in tumor incidence in all treated animals. 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).

In male rats carmustine caused testicular degeneration at intraperitoneal doses of 8 mg/kg/week for eight weeks (about 1.3 times the recommended human dose on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Newly-Diagnosed High-Grade Malignant Glioma

Study 1 was a multicenter, double-blind, placebo-controlled, clinical trial in adult patients with newly-diagnosed high-grade malignant glioma. A total of 240 patients were randomized (1:1) to receive up to eight GLIADEL Wafers or matched placebo wafers following maximal tumor resection. Patients received post-operative radiation therapy (55-60 Gy delivered in 28 to 30 fractions over six weeks) starting three weeks after surgery. Patients with anaplastic oligodendroglioma also received systemic chemotherapy (6 cycles of PCV- lomustine 110 mg/m^2 day 1, procarbazine 60 mg/m^2 days 8-21, vincristine 1.4 mg/m^2 days 8 and 29).

The population in Study 1 was 67% male, 97% white, the median age was 53 years (range: 21-72). Eighty-seven per cent had a Karnofsky performance status ≥ 70% and 71% had a Karnofsky performance status of ≥ 80%. Seventy-eight percent had a histologic subtype of glioblastoma multiforme as determined by central pathology review. Thirty-eight percent of patients received 8 wafers and 78% received ≥ 6 wafers. Starting three weeks after surgery, 80% of patients received standard limited field radiation therapy (RT) described as 55-60 Gy delivered in 28 to 30 fractions over six weeks; 11% received radiotherapy and the remainder received non-standard radiotherapy or a combination of standard and non-standard radiotherapy. At the time of progression, 12% received systemic chemotherapy. Patients were followed for at least three years or until death.

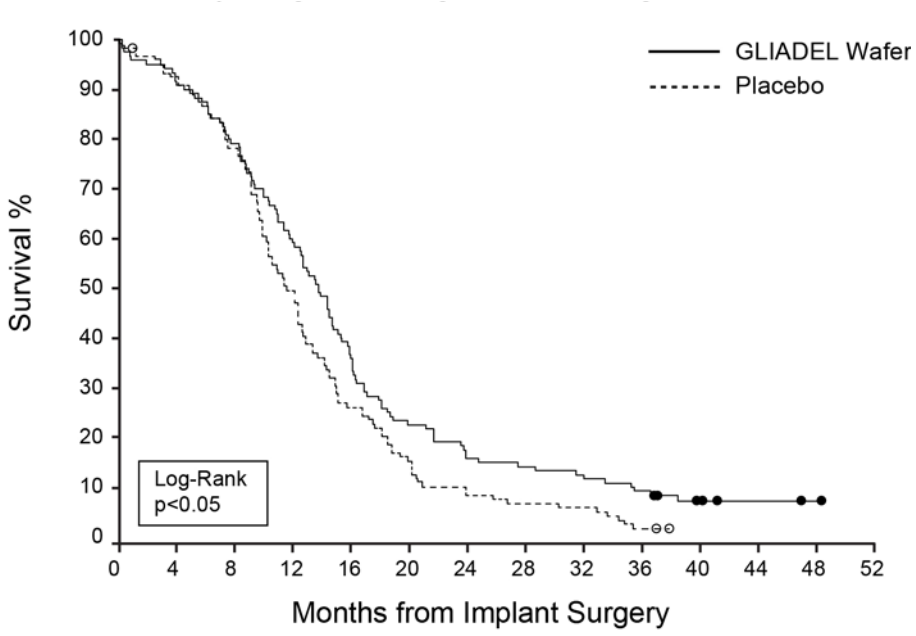
Efficacy results for patients randomized in Study 1 are summarized in Table 6 and Figure 6. Overall survival among all patients with newly diagnosed high grade glioma, the primary outcome measure, was prolonged in the GLIADEL arm. Overall survival in the subset of patients with glioblastoma multiforme, a secondary outcome measure, was not significantly prolonged.

Table 6. Overall Survival in Patients with Newly Diagnosed Glioma, Study 1.

Overall Survival – ITT*	Gliadel Wafer (n=120)	Placebo Wafer (n=120)
Number of deaths, n (%)	111 (93%)	117(98%)
Median overall survival, months (95% CI)	13.9 (12.1, 15.1)	11.6 (10.2, 12.7)
Hazard ratio (95% CI)	0.73 (0.56, 0.95)	
Log-Rank test p-value	<0.02**	

*Based on a post-final analysis, protocol specified non-stratified log-rank test.
**p-value not adjusted for multiple comparisons

Figure 6 – Overall Survival for Patients with Newly Diagnosed High-Grade Malignant Glioma – Kaplan-Meier Curves by Treatment Group*



*Based on a post-final analysis, protocol specified non-stratified log-rank test; p-value not adjusted for multiple comparisons

14.2 Recurrent Glioblastoma Multiforme

Study 2 was a multicenter, double-blind, placebo controlled, clinical trial in adult patients with recurrent malignant glioma. Patients were required to have had prior definitive external beam radiation therapy sufficient to disqualify them from additional radiation therapy. Following maximal tumor resection and confirmation of malignant glioma, a total of 222 patients were randomized (1:1) to receive a maximum of eight GLIADEL Wafers (n=110) or matched placebo wafers (n=112) positioned to cover the entire resection surface. All patients were eligible to receive chemotherapy which was withheld at least four weeks (six

weeks for nitrosoureas) prior to and two weeks after surgery. Patients were followed for up to 71 months.

The population in Study 2 was 64% male, 92% white, and had a median age of 49 years (range: 19-80). Sixty-five percent had a histologic subtype of glioblastoma multiforme, 26% had anaplastic astrocytoma or another anaplastic variant, 73% had a Karnofsky performance status ≥ 70, 53% had a Karnofsky performance status of ≥ 80%, 73% had only one prior surgery, and 46% had prior treatment with nitrosourea. Eighty-one percent of patients received 8 wafers and 96% received ≥ 6 wafers.

Survival and 6-month mortality rate in the subgroup of patients with recurrent glioblastoma multiforme, were exploratory outcome measures and are summarized in Table 7 and Figures 7 and 8. No survival prolongation was observed in patients with pathologic diagnoses other than glioblastoma multiforme.

Table 7. Main Efficacy Outcome Measures in Patients with Recurrent Gliomablastoma Multiforme, Study 2.

	Gliadel Wafer	**Placebo Wafer**
GLIOBLASTOMA MULTIFORME	n=72	n=73
6-Month Survival		
Number of deaths, n (%)	32	47
6-month survival rate (%)	56%	36%
Log-Rank test p-value Gehan's generalized Wilcoxon Test p-value	0.013** 0.015**	
Overall Survival		
Number of deaths, n (%)	71 (99%)	72 (99%)
Median overall survival (95% CI (months)	6.51 (5.32, 7.49)	4.63 (3.78, 5.52)
Log-Rank test p-value Gehan's generalized Wilcoxin Test p-value	0.181** 0.021**	

**p-value not adjusted for multiple comparisons

Figure 7: **6-Month Survival for Patients with Recurrent Glioblastoma Multiforme– Kaplan-Meier Curves by Treatment Group**

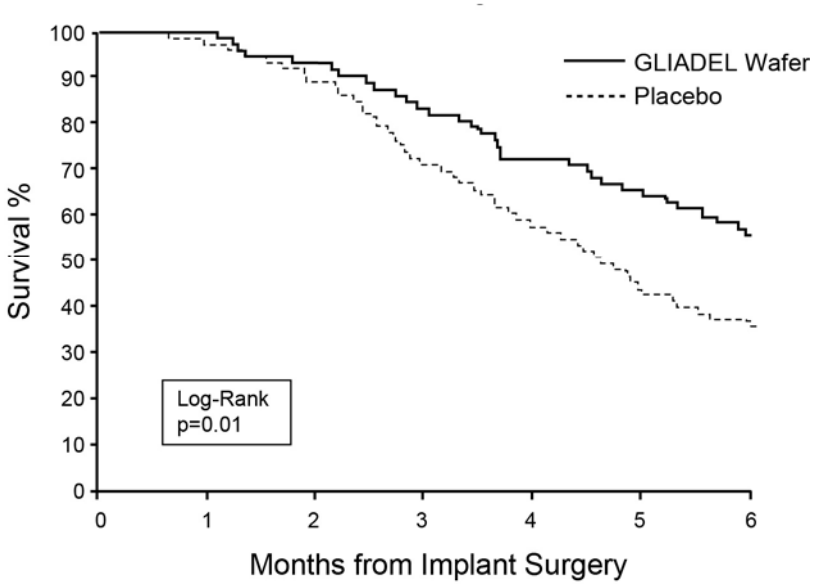
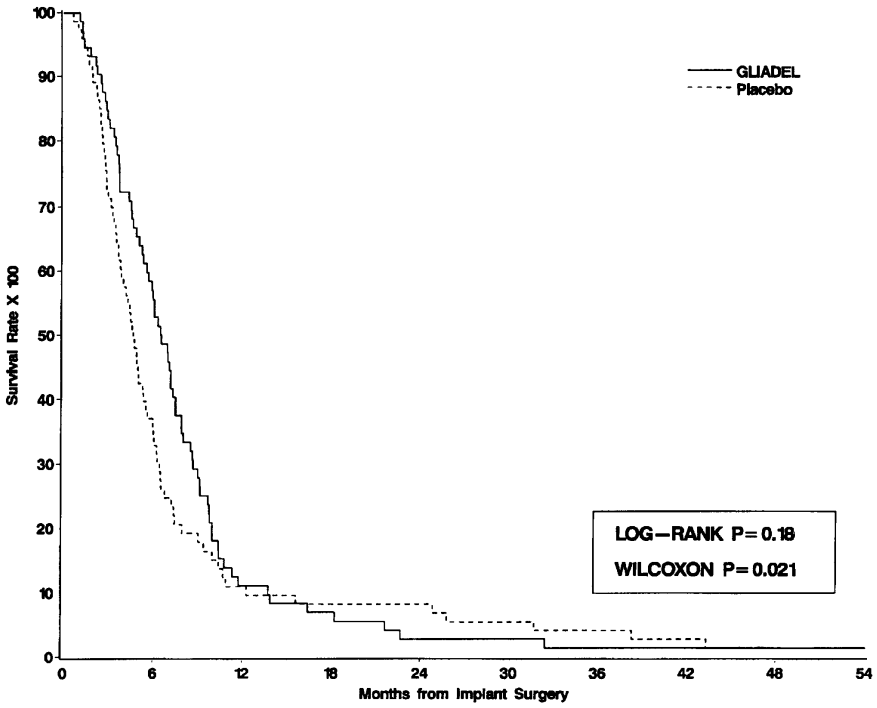


Figure 8: **Overall Survival (months) for Patients with Recurrent Glioblastoma Multiforme– Kaplan-Meier Curves by Treatment Group**



15 REFERENCES

1. OSHA Hazardous Drugs". *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

GLIADEL Wafer is supplied 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.

NDC for single dose treatment box: 24338-050-08

Store GLIADEL Wafer at or below -20ºC (-4ºF).

Do not keep unopened foil pouches at ambient room temperature for more than six hours at a time for up to three cycles within a 30-day period.

GLIADEL Wafer is a cytotoxic drug and special handling and disposal procedures should be considered.[1]

17 PATIENT COUNSELING INFORMATION

Seizures: Advise patients to report any new or change in their seizure activity [(*see Warnings and Precautions (5.1)*].

Intracranial Hypertension: Advise patients to report severe headaches, nausea, vomiting or new onset visual disturbances [(*see Warnings and Precautions (5.2)*].

Impaired Neurosurgical Wound Healing: Advise patients to report any evidence of wound dehiscence, fever or cerebrospinal fluid leak *[see Warnings and Precautions (5.3)]*.

Meningitis: Advise patients to report symptoms of meningitis such as fever or stiff neck *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity: Counsel patients on pregnancy planning and prevention. Advise females of reproductive potential to use effective contraception during treatment with GLIADEL *[see Warnings and Precautions (5.6)]*.

Nursing Infants: Advise nursing mothers to discontinue nursing after GLIADEL WAFER implantation *[see Use in Specific Populations (8.3)]*.

Manufactured by
Eisai Inc.
Woodcliff Lake, NJ 07677

Distributed by
Arbor Pharmaceuticals, LLC
Atlanta, GA 30328

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GL-PI-01