CONSIDER
Is your patient an appropriate candidate for GLIADEL® Wafer (carmustine implant)?

Does your patient have a newly diagnosed high-grade glioma or recurrent GBM?
- YES
- NO

Is there an active, enrolling clinical trial for which your patient may fit the criteria?
- YES
- NO

Is your patient interested in a trial?
- YES
- NO

Is your patient able to comply with treatment and make the required study visits?
- YES
- NO

Does your patient meet the trial’s inclusion criteria?†
- KPS ≥70
- Age requirements
- Normal renal function
- Normal hepatic function
- Free from concomitant medication use (ie, use of CYP inducers/inhibitors)
- No prior chemotherapy
- Newly diagnosed or first recurrence
- NO

POTENTIAL GLIADEL WAFER CANDIDATE

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

IMPORTANT SAFETY INFORMATION
The following Warnings and Precautions have been associated with the use of GLIADEL Wafer: seizures, intracranial hypertension, impaired neurosurgical wound healing, meningitis, and wafer migration. GLIADEL Wafer can cause fetal harm when administered to a pregnant woman.

Please see additional Important Safety Information on reverse, as well as the enclosed full Prescribing Information.

*Clinical studies of GLIADEL Wafer included patients aged 18 to 80 with a KPS ≥60.†
†The presented trial criteria is typical. Every trial is different and should be considered separately.
INDICATIONS

GLIADEL® Wafer (carmustine implant) is indicated in patients with newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation.

GLIADEL Wafer is also indicated in patients with recurrent glioblastoma multiforme as an adjunct to surgery.

IMPORTANT SAFETY INFORMATION

GLIADEL Wafer (carmustine implant) can cause fetal harm when administered to a pregnant woman. It is recommended that patients receiving GLIADEL Wafer discontinue nursing. Female patients of reproductive potential should receive counseling on pregnancy planning and prevention. 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.

WARNINGS AND PRECAUTIONS

Seizures: Fifty-four percent (54%) of patients treated with GLIADEL Wafers in the recurrent disease trial experienced new or worsened seizures within the first five post-operative days. 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.

Intracranial Hypertension: Brain edema occurred in 23% of patients treated with GLIADEL Wafers in the initial surgery trial. Additionally, one GLIADEL-treated patient experienced intracerebral mass effect unresponsive to corticosteroids which led to brain herniation. 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.

Impaired Neurosurgical Wound Healing: Impaired neurosurgical wound healing including wound dehiscence, delayed wound healing, and subdural, subgaleal, or wound effusions occur with GLIADEL Wafer treatment. In the initial disease trial, 16% of GLIADEL Wafer-treated patients experienced impaired intracranial wound healing and 5% had cerebrospinal fluid leaks. In the recurrent disease trial, 14% of GLIADEL Wafer-treated patients experienced wound healing abnormalities. Monitor patients post-operatively for impaired neurosurgical wound healing.

Meningitis: Meningitis occurred in 4% of patients receiving GLIADEL Wafers in the recurrent disease trial. 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.

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.

ADVERSE REACTIONS

The most common adverse reactions in Newly-Diagnosed High Grade Malignant Glioma patients (incidence >10% and between arm difference ≥4%) are cerebral edema, asthenia, nausea, vomiting, constipation, wound healing abnormalities and depression.

The most common adverse reactions in Recurrent Glioblastoma Multiforme patients (incidence >10% and between arm difference ≥4%) are urinary tract infection, wound healing abnormalities and fever.


Please see enclosed insert or visit www.gliadel.com for full Prescribing Information.

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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

1 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)

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 (2.1). Follow preparation and handling recommendations (2.3).

2.2 Insertion Instructions

Following maximal tumor resection, confirmation of tumor pathology and establishment of hemostasis, place up to a maximum of eight GLIADEL Wafer into the resection cavity 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.

3 DOSAGE FORMS AND STRENGTHS

Each GLIADEL Wafer contains 7.7 mg of carmustine (B). Prepared for implantation, GLIADEL Wafer is a soft gelatin wafer.

4 CONTRAINDICATIONS

None (4)

5 WARNINGS AND PRECAUTIONS

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5.2 Intracranial Hypertension

5.3 Impaired Neurosurgical Wound Healing

5.4 Meningitis

5.5 Wafer Migration

5.6 Embryo-fetal Toxicity

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6.2 Post-marketing Surveillance

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

5.3 Impaired Neurosurgical Wound Healing

Impaired neurosurgical wound healing including wound dehiscence, delayed wound healing, and subdural, subgaleal, 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, 14.2% 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 Wafer in Study 2. Two cases of meningitis were bacterial; one patient required removal of the Wafer 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 Wafer 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/m² basis and embryotoxic in rabbits at exposures similar to the exposure at the recommended human dose on a mg/m² basis. Advise females of reproductive potential to avoid pregnancy after implantation of GLIADEL Wafer. 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 Wafer 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 Waters 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 waters and 78% received > 6 waters. 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 Wafer compared to 2 (2%) of patients receiving placebo. Deaths on the GLIADEL arm resulted from cerebral hemorrhage/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%)**

<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>GLIADEL Wafer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=120</td>
<td>N=120</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
</tbody>
</table>
| GASTROINTESTINAL DISORDERS
| Nausea      | 22           | 17      |
| Vomiting    | 21           | 16      |
| Constipation| 19           | 12      |
| Abdominal pain| 8        | 2       |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITION
| Asthma      | 22           | 15      |
| Chest pain  | 5            | 0       |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS
| Wound healing abnormalities* | 16 | 12 |
| BACKACHE
| Back pain   | 7            | 3       |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS
| Depression  | 16           | 10      |

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

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**Table 2. Incidence of Local Adverse Reactions, Study 1**

<table>
<thead>
<tr>
<th>Local Adverse Reactions</th>
<th>GLIADEL Wafer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=120</td>
<td>N=120</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Intracranial hypertension</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Brain cyst</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>23</td>
<td>19</td>
</tr>
</tbody>
</table>

*Not seen at baseline or worsened if present at baseline.

Recurrent Glioblastoma Multiforme

The safety of GLIADEL Wafer 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 Waters 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 nitrosourea) 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 waters and 98% received > 6 waters.

Sixty-four severe adverse reactions were reported in 43(39%) patients receiving GLIADEL Wafer. Adverse reactions in GLIADEL Wafer-treated patients are shown in Table 3. Meningitis occurred in four patients receiving GLIADEL Waters 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.
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 polyaspartamide copolymer. The copolymer, polyleopran 20, consists of poly (ε-carboxypropylene) and sebacic acid in a 20:80 molar ratio. Carmustine is homogeneously distributed in the copolymer matrix.

The structural formula for polyleopran 20 is:

![Structural formula](image)

The structural formula for carmustine is:

![Structural formula](image)

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 polyaspartamide copolymer. The copolymer, polyleopran 20, consists of poly (ε-carboxypropylene) and sebacic acid in a 20:80 molar ratio. Carmustine is homogeneously distributed in the copolymer matrix.

The structural formula for polyleopran 20 is:

![Structural formula](image)

The structural formula for carmustine is:

![Structural formula](image)

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, carbosphenosylpropionate, 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/m², the average terminal half-life, clearance and steady-state volume of distribution were 32 minutes, 56 mL/min/m² and 3.25 L/kg, respectively. Approximately 60% of the intravenous 200-mg/m² dose of ³¹C-carmustine was excreted in the urine over 96 hours and 9% was expired as CO₂. 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 (GCE assay in rodent brain tumors, mouse bone marrow micronucleus assay). In male rats carmustine caused testicular degeneration at intraoral doses of 8 mg/kg/week for eight weeks (about 1.3 times the recommended human dose on a mg/m² 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/m² day 1, procarbazine 60 mg/m² days 8-21, vincristine 1.4 mg/m² days 8 and 29). The population in Study 1 was 67% male, 97% white, the median age was 53 years (range: 21-72). Seventy-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; 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** | **Placebo Wafer** |
| (n=120) | (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) | <0.02* |

*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 Kornfeil 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 glioblastoma multiforme. Study 2.

<table>
<thead>
<tr>
<th>GLIABLASTOMA MULTIFORME</th>
<th>GliaLal Wafer</th>
<th>Placebo Wafer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6-Month Survival</strong></td>
<td>32 (92%)</td>
<td>47 (92%)</td>
</tr>
<tr>
<td>6-month survival rate (%)</td>
<td>56%</td>
<td>36%</td>
</tr>
<tr>
<td>Gehan’s generalized Wilcoxon Test p-value</td>
<td>0.013**</td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>71 (99%)</td>
<td>72 (99%)</td>
</tr>
<tr>
<td>Median overall survival (95% CI)</td>
<td>5.51 (3.52, 7.49)</td>
<td>4.63 (3.78, 5.52)</td>
</tr>
<tr>
<td>Log-Rank test p-value</td>
<td>0.181**</td>
<td></td>
</tr>
<tr>
<td>Gehan’s generalized Wilcoxon Test p-value</td>
<td>0.021**</td>
<td></td>
</tr>
</tbody>
</table>

*p-value not adjusted for multiple comparisons

15 REFERENCES


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 -20°C (-4°F).
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 (5.2)].

Meningitis: Advise patients to report symptoms of meningitis such as fever or stiff neck [see Warnings and Precautions (5.3)].

Emboz-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)].