GLIADEL® WAFER (carmustine implant), for intracranial use

HIGHLIGHTS OF PRESCRIBING INFORMATION

DISPOSAL PROCEDURES.1

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

CONTRAINDICATIONS

GLIADEL Wafers can cause fetal harm when administered to a pregnant woman. GLIADEL Wafers should not be used in women who are pregnant or who may become pregnant. Hormonal contraceptives are ineffective in preventing fetal exposure. All women of reproductive potential should be counseled about the potential anticonception issues associated with GLIADEL Wafers. GLIADEL Wafers should be used, but discard wafers broken in more than two pieces. Oxidized regenerated cellulose (including yellow discharge at the incision) is excrated with the fascia. Do not attempt to identify source of fascial edema or infection with the aid of forceps and place it onto a designated sterile field.

In the multicenter, randomized (1:1), double-blind, placebo controlled trial of 222 patients with recurrent high-grade glioma who were treated with GLIADEL Wafers compared to 2 (2%) of patients receiving placebo. Deaths on the placebo arm were due primarily to disease progression. The most frequent serious adverse reactions were:

Table 3. Per-Patient Incidence of Adverse Reactions in Gliadel Wafer-Treated Patients with Recurrent High-Grade Glioma (Study 2)*

INJURY, POISONING AND PROCEDURAL COMPLICATIONS

Brain abscess 6 4

*Includes major and minor reaction

Table 1. Per-Patient Incidence of Adverse Reactions in Patients Receiving GLIADEL Wafers (Study 1)**

GENERAL AND ADMINISTRATION SITE CONDITION

Adult seizures: Seizures, if controlled, may recur if the dosage is reduced or the interval between doses is increased. seizure, status, or prolonged convulsions may occur at any time after implantation of GLIADEL Wafers.

Urinary tract infections 21 17

MUSCULOSKELETAL AND CONNECTIVE TISSUE

Urinary tract infections 21 17

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

Roentgenogram, CT scan, or MRI scan of the area around the site of implantation should be performed immediately after the procedure to confirm the position of the wafers and excise any wafer remnants into the cavity. Slight overlapping of the wafers is acceptable. Wafers broken in half may

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May 2019

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Table 2. Incidence of Local Adverse Reactions, Study 1*
The incidence of seizures is shown in Table 4. The incidence of hydrocephalus, central eminence and intraventricular hemorrhage is shown in Table 5.

### Table 4. Incidence of Seizures, Study 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo Wafer</th>
<th>GLIADEL Wafer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with seizures (%)</td>
<td>32</td>
<td>47</td>
</tr>
<tr>
<td>Nearest observed symptoms</td>
<td>42</td>
<td>48</td>
</tr>
</tbody>
</table>

### Table 5. Hydrocephalus and Central Eminence, Study 2

<table>
<thead>
<tr>
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<th>Placebo Wafer</th>
<th>GLIADEL Wafer</th>
</tr>
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<tr>
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<td>42</td>
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### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

The activity of GLIADEL Wafer is due to release of tyrosine conjugates of carmustine (BCNU) and N-methyl-BCNU ablating agent. The absorbance of BCNU effects the neuronal cancerous tissue. A loss of microscopic exposure of the nerve tissue in the xenograft models in the human brain will start the cell lysis and cellular death.

#### 12.2 Pharmacokinetics

Carmustine concentrations delivered by GLIADEL Wafer in human brain tissue have not been determined. Following wafer insertion, the mean whole blood IC50 was 0.34 mg/mL (9.4 1.9 mg/mL).

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Summary**

GLIADEL Wafer can cause fetal harm when administered to a pregnant woman. There are no available data on GLIADEL use in pregnant women. There has been no animal reproductive studies with GLIADEL Wafer. Carmustine (active metabolite of GLIADEL Wafer) is embryotoxic and teratogenic in rats at exposures less than the recommended human dose based on body surface area (BSA) and embrittlement in rabbits at exposures similar to or less than the recommended human dose based on BSA. (See Data). Advise pregnant women of the potential risk to fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Data**

Animal Data

There are no studies assessing the reproductive toxicity of GLIADEL Wafer, however, the active component of GLIADEL Wafer, is embryotoxic and teratogenic. In rats at intraperitoneal doses of 4 mg/kg or greater when given once daily for 5 to 6 days through 15. Carmustine caused fetal malformations (sphinchnitis, microphthalmia, anophthalmia, persistent cloacal fistula, cleft palate, and cleft palate) at 2 to 3 times the recommended human dose based on BSA. Embryotoxicity was characterized by increased embryonic death and skeletal defects and increased numbers of litters and litter size in the fœtuses.

#### 8.2 Lactation

**Summary**

GLIADEL Wafer can cause fetal harm when administered to a pregnant woman (see Data in Specific Populations (8.1)).

**Data**

Animal Data

Carmustine causative teratogenic in animals. Advise male patients of the potential risk of infertility [see Data Toxicological (13.1)].

#### 8.3 Females and Males of Reproductive Potential

**Warning**

Verify pregnancy status of females of reproductive potential prior to implantation with GLIADEL Wafer. (See Data Specific Populations (8.1)).

**Females**

Advise females of reproductive potential to use effective contraception for 3 months after implantation of GLIADEL Wafer.

**Males**

Based on its mechanism of action, advise males with female partners of reproductive potential to use effective contraception for 3 months following implantation of GLIADEL Wafer. (See Data Clinical Pharmacology (12.1).) [Clinical Toxicology (13.1)].

**Immunology**

Carmustine cause teratogenic degeneration in animals. Advise male patients of the potential risk of infertility [see Data Toxicological (13.1)].

#### 8.4 Safety and Effectiveness of GLIADEL Wafer in Pediatric Patients

**Summary**

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

**Data**

Animal Data

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

### 14 CLINICAL STUDIES

#### 14.1 Newly-Diagnosed High Grade Glioma

Study 1 was a multicenter, double-blind, placebo-controlled, clinical trial in adult patients with newly-diagnosed high-grade 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 (50-60 Gy delivered in 25 to 30 fractions over 6 weeks) starting three weeks after surgery. Patients with anaplastic oligodendroglia also received systemic chemotherapy (6 cycles of PCV: lomustine 110 mg/1 day p.o., procarbazine 60 mg/1 day p.o. days 1-5, vincristine 1.4 mg/days 1 and 8). The population in Study 1 was 67% male and 94% White, and the median age was 53 years (range: 21-87). Eighty-seven percent of patients had a Karnofsky performance status of 70% or better at the Karnofsky performance status of 80%. Seventy percent of patients had a histologic subtypes of glioblastomas as determined by central pathology review. Eighty percent of patients received 8 wafers and 36% received 6 wafers. Starting three weeks after surgery, 96% of patients received standard limited field radiation therapy (RT) described on 55-65 Gy delivered in 28 to 30 fractions over 6 weeks; 11% received RT and chemotherapy and the remainder received standard non-radiation chemotherapy or a combination of standard and non-standard radiation therapy. At the time of progression, 11% received systemic chemotherapy. Patients were followed for at least three years or until death.

#### 14.2 Recurrent Glioblastoma

Study 2 was a multinational, double-blind, placebo controlled, clinical trial in adult patients with recurrent high-grade gliomas. 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 high-grade gliomas, a total of 222 patients were randomized (1:1) to receive a maximum of eight GLIADEL Wafer wafers or matched placebo wafers (n=110) positioned to cover the entire resection surface. All patients were eligible to receive chemotherapy which was withheld for hospital stay less than four weeks prior to and two weeks after surgery. Patients were followed for up to 7.5 months.

The population in Study 2 was 64% male and 95% White, and the median age was 49 years (range: 18-79). Study 2 had a total of 122 patients with glioblastoma (71%) and 100 patients with anaplastic glioma (29%). 71% had a Karnofsky performance status of ≥ 70. 51% had a Karnofsky performance status of ≤ 50 who had only one prior surgery, and 49% had prior treatment with radiation. Eighty-four percent of patients received chemotherapy in Study 1.waits.

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

### Table 6. Overall Survival in Patients with Newly-Diagnosed High Grade Glioma, Study 1

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Placebo Wafer</th>
<th>GLIADEL Wafer</th>
</tr>
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<tbody>
<tr>
<td>Overall Survival</td>
<td>11.6 (9.1,12.8)</td>
<td>12.1 (10.1,13.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.73 (0.56, 0.95)</td>
<td>0.70 (0.53, 0.90)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.02**</td>
<td>&lt;0.002**</td>
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**Based on a post-analysis, protocol specified non-stratified log-rank test.**

### Figure 6: Kaplan-Meier Curves of Overall Survival in Patients with Newly-Diagnosed High Grade Glioma, Study 1

#### Log-Rank Test for GLIADEL Wafer versus Placebo Wafer

![Kaplan-Meier Curves of Overall Survival in Patients with Newly-Diagnosed High Grade Glioma, Study 1.](image)

#### Log-Rank (p<0.001)

### Figure 7: Kaplan-Meier Curves of Overall Survival for Patients with Recurrent Glioblastoma, Study 2

#### Log-Rank Test for GLIADEL Wafer versus Placebo Wafer

![Kaplan-Meier Curves of Overall Survival for Patients with Recurrent Glioblastoma, Study 2.](image)

#### Log-Rank (p<0.01)

### References


### How Supplied/Storage and Handling

GLIADEL Wafer is supplied in a single dose treatment box containing eight individually packaged wafers. Each wafer contains 7.7 mg of carmustine and is packaged in two aluminum foil laminated pouches. The inner pouch is sterile and is designed to maintain product integrity and protect the product from moisture. The outer pouch is a permeable overwrap. The outside surface of the outer pouch is not sterile.

### Administrators

NDC for single dose treatment box: 23436-050-00

Store GLIADEL Wafer at or below -20°C (-4°F).

### Storage

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

GLIADEL Wafer is a specialty drug and special handling and disposal procedures should be considered.

### Patient Counseling Information

**Nursing Mothers**

Advises patients to any evidence of wound dermal, fistula or cerebrospinal fluid leak [see Warnings and Precautions (5.2)].

### Warnings

Advises patients to report symptoms of weakness or allergy [see Drug Interactions (6.4)].

### FAQs

Advises patients to ask their health care provider of a known or suspected pregnancy [see Warnings and Precautions (5.1)].

### How to administer

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### Usage

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