### Injections and Usage

GLIADEL Wafer is indicated for the treatment of:
- newly diagnosed high-grade glioma as an adjunct to surgery and radiation
- recurrent glioblastoma as an adjunct to surgery

### Dosage and Administration

2.1 Recommended Dose

The recommended dose of GLIADEL Wafer is one 7.7 mg wafer per day with newly diagnosed glioblastoma treated with GLIADEL Wafer (8). GLIADEL treated patients with newly diagnosed glioblastoma received 1-2 wafers daily for up to 14 days. GLIADEL-treated patients with newly diagnosed glioblastoma received 1-2 wafers daily for up to 14 days.

2.2 Recommended Route

The recommended route of administration is subarachnoid as a single dose.

### Warnings and Precautions

5.1 Seizures

Seizures occur in 17% of patients treated with GLIADEL Wafer. GLIADEL-treated patients with newly diagnosed glioblastoma received 1-2 wafers daily for up to 14 days. GLIADEL treated patients with newly diagnosed glioblastoma received 1-2 wafers daily for up to 14 days.

5.2 Impaired Neurosurgical Wound Healing

Monitor patients for impaired wound healing and report any delayed wound healing or related clinical findings.

5.3 Infection

Monitor patients for signs and symptoms of infection.

5.4 Meningitis

GLIADEL Wafers may cause meningitis. Monitor patients post-operatively for signs of meningitis.

5.5 Intracranial Hypertension

Monitor patients for signs and symptoms of intracranial hypertension.

### Adverse Reactions

### Table 1: Post-Presentation of Adverse Reactions Resulting in Global Wafer-Treated Patients with Newly Diagnosed High-Grade Glioma (Study 1) (All Adverse Events of ≥0.1%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>GLIADEL Wafer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>General adverse events</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Abnormalities</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

### Table 2: Common Adverse Reactions in GLIADEL Wafer-Treated Patients with Newly-Diagnosed High-Grade Glioma

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>GLIADEL Wafer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>51</td>
<td>41</td>
</tr>
<tr>
<td>Constipation</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Anorexia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table 3: Post-Prescription of Adverse Reactions in Global Wafer-Treated Patients with Newly Diagnosed High-Grade Glioma (Study 2) (All Adverse Events of ≥0.1%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>GLIADEL Wafer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Abnormalities</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Hypotension</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>41</td>
<td>31</td>
</tr>
<tr>
<td>Constipation</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

### Instructions for Opening Pouch Containing GLIADEL Wafer

3.1 Follow all steps of the opening procedure in a timely manner to prevent wafer migration.

### Instructions for Use

When administering GLIADEL Wafer, check the下列 guidelines:
- Discard the outer gloves into a designated waste container after use.

### Instructions for Disposing of Residual Waste

If repeat neurosurgical intervention is indicated, handle residual wafers as biohazard waste.

### Instructions for Handling GLIADEL Wafers

Use double gloves when handling GLIADEL Wafers. Discard the outer gloves into a designated waste container after use.

### Instructions for Use

When administering GLIADEL Wafer, check the下列 guidelines:
- Discard the outer gloves into a designated waste container after use.

### Instructions for Disposing of Residual Waste

If repeat neurosurgical intervention is indicated, handle residual wafers as biohazard waste.
The incidence of seizures is shown in Table 4. The incidence of hydrocephalus, exposure to the aqueous environment of the resection cavity, the anhydride bonds in the copolymer, the degradation of the wafer, and the slow release of the drug are all factors that contribute to the formation of new or worsening seizures.

### 12.6 Wafer Biodegradation

Carmustine degrades both spontaneously and metabolically. More than 70% of the copolymer degrades within three weeks. Wafer remnants are homogenously distributed in the copolymer matrix. The structural formula for polifeprosan 20 is:

\[
\text{Carmustine} \quad \text{Polifeprosan 20}
\]

**Table 12.6**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with seizures (%)</td>
<td>20.2 (29.2)</td>
</tr>
<tr>
<td>Time to new or worsening seizures (days)</td>
<td>10 (11.8)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>11 (12.3)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.1 (0.95-1.3)</td>
</tr>
</tbody>
</table>

**Figure 12.6**

### 13. NONCLINICAL TOXICOLOGY

#### 13.1 Mechanism of Action

GLIADEL Wafer is an implant for intracranial use, containing carmustine, a nitrosourea chemotherapeutic agent. In the clinical setting, carmustine is administered intrathecally or into a resection cavity in the brain. GLIADEL Wafer is administered via a controlled release delivery system that slowly releases carmustine into the brain. The implant is designed to release carmustine in a controlled and sustained manner.

#### 13.2 Pharmacokinetics

Carmustine concentrations delivered by GLIADEL Wafer in human tissue have not been systematically assessed. Prior to the following earlier insertions, the mean whole blood Cmax was 0.02 (0.01) ng/mL, with a maximum of 0.48 ng/mL.

#### 13.3 Mechanism of Action

1. GLIADEL Wafer is biodegradable when implanted in the human brain. waist. Remnants have been found in both cerebrospinal fluid and extracranial tissues after removal. After removal of carmustine, wafer remnants have been detected in cerebrospinal fluid and extracranial tissues by autoradiography and electron microscopy.

#### 13.4 Toxicity

Toxicity is summarized in Table 12.4. GLIADEL Wafer is administered via a controlled release delivery system that slowly releases carmustine into the brain. The implant is designed to release carmustine in a controlled and sustained manner.

#### 13.5 Preclinical Pharmacology

In vitro studies have demonstrated that GLIADEL Wafer inhibits the growth of human tumor cell lines derived from glioblastoma multiforme and anaplastic astrocytoma.

#### 13.6 Clinical Pharmacology

In clinical trials, GLIADEL Wafer was administered to patients with newly diagnosed high-grade glioma and recurrent high-grade glioma. The population in Study 1 was 67% male and 97% White, and the median age was 49 years (range: 19-80). Sixty-five percent had a histologic subtype of glioblastoma, and 35% had a histologic subtype of gliosarcoma. In Study 2, 72% of patients received ≥ 6 wafers, and 96% received ≥ 6 wafers. Median age was 49 years (range: 19-80). Sixty-five percent had a histologic subtype of glioblastoma, and 35% had a histologic subtype of gliosarcoma.

#### 13.7 Clinical Experience

Efficacy results for patients randomized in Study 1 are summarized in Table 6 and shown in Figure 6. Overall survival for patients randomized in Study 1 was significantly improved in the carmustine arm compared with the placebo arm.

#### 13.8 Dosage and Administration

GLIADEL Wafer is administered via a controlled release delivery system that slowly releases carmustine into the brain. The implant is designed to release carmustine in a controlled and sustained manner.

#### 13.9 Contraindications

Contraindications include patients with a history of seizures, those with a history of radiation therapy in the current treatment cycle, or those with prior history of radiation therapy.

#### 13.10 Adverse Reactions

Adverse reactions observed in clinical studies of GLIADEL Wafer in patients with newly diagnosed glioblastoma multiforme or anaplastic astrocytoma are shown in Table 3. Local adverse reactions include pain and irritation at the site of implantation. Other systemic adverse reactions include gastrointestinal reactions such as nausea and vomiting, and headache.

#### 13.11 Warnings and Precautions

Warnings and precautions include the potential for neurotoxicity, seizures, and intracranial pressure.

#### 13.12 Use in Specific Populations

Use in specific populations includes pediatric patients, patients with impaired renal function, and patients with other underlying conditions.

#### 13.13 Nonclinical Toxicology

Nonclinical toxicology includes studies to evaluate the safety and effectiveness of GLIADEL Wafer in pediatric patients, patients with impaired renal function, and patients with other underlying conditions.

#### 13.14 References

References include studies to evaluate the safety and effectiveness of GLIADEL Wafer in pediatric patients, patients with impaired renal function, and patients with other underlying conditions.

### 15. REFERENCES

#### 15.1_INFOGRAPHIC

Includes an infographic with data on the effectiveness and safety of GLIADEL Wafer.

#### 15.2_INFOGRAPHIC

Includes an infographic with data on the effectiveness and safety of GLIADEL Wafer.

#### 15.3_INFOGRAPHIC

Includes an infographic with data on the effectiveness and safety of GLIADEL Wafer.

#### 15.4_INFOGRAPHIC

Includes an infographic with data on the effectiveness and safety of GLIADEL Wafer.

#### 15.5_INFOGRAPHIC

Includes an infographic with data on the effectiveness and safety of GLIADEL Wafer.

#### 15.6_INFOGRAPHIC

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#### 15.7_INFOGRAPHIC

Includes an infographic with data on the effectiveness and safety of GLIADEL Wafer.

#### 15.8_INFOGRAPHIC

Includes an infographic with data on the effectiveness and safety of GLIADEL Wafer.

#### 15.9_INFOGRAPHIC

Includes an infographic with data on the effectiveness and safety of GLIADEL Wafer.

### 16. HOW SUPPLIED/STORAGE AND HANDLING

How supplied includes the form and strength of the drug.

### 17. PATIENT COUNSELING INFORMATION

Counseling includes information on patient counseling.

#### 17.1 SPECIFIC COUNSELING

Specific counseling includes information on specific counseling.

#### 17.2 PATIENT COUNSELING INFORMATION

Patient counseling includes information on patient counseling.

#### 17.3 PATIENT COUNSELING INFORMATION

Patient counseling includes information on patient counseling.

#### 17.4 PATIENT COUNSELING INFORMATION

Patient counseling includes information on patient counseling.

#### 17.5 PATIENT COUNSELING INFORMATION

Patient counseling includes information on patient counseling.