PRODUCT MONOGRAPH

PrGLIADEL® WAFER

carmustine implant in polifeprosan 20

7.7 mg carmustine/implant

Antineoplastic
GLIADEL® WAFER

carmustine implant in polifeprosan 20
7.7 mg carmustine/implant

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>intralesional</td>
<td>Wafer / 7.7 mg</td>
<td>None. For a complete listing see Dosage Forms, Composition and Packaging section.</td>
</tr>
</tbody>
</table>

INDICATIONS AND CLINICAL USE

GLIADEL® Wafer (carmustine in polifeprosan) is indicated in recurrent glioblastoma multiforme patients for whom surgical resection is indicated as an adjunct to surgery. Presence of tumor should be confirmed by a pathologist prior to wafer implantation.

Pediatrics (< 18 years of age): The safety and effectiveness of GLIADEL in pediatric patients have not been established.

CONTRAINDICATIONS

GLIADEL® Wafer contains carmustine. It should not be implanted in individuals who have demonstrated a previous hypersensitivity to carmustine or any of the components of GLIADEL.
WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

GLIADEL® Wafers should only be used by a qualified surgeon.

Improper implantation of GLIADEL® Wafers may result in blockage of cerebrospinal fluid and consequent obstructive hydrocephalus (see General section below).

Clinically significant or life-threatening safety hazards associated with Gliadel implantation include (see General section below and Adverse Reactions):

- Obstructive hydrocephalus
- Seizures
- Intracranial infections, including meningitis
- Abnormal wound healing, including cerebrospinal fluid leaks, subdural, subgaleal or wound effusions, delayed wound healing, and wound breakdown or dehiscence
- Brain edema

**General**

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 cerebral edema/intracranial hypertension. Cases of intracerebral mass effect unresponsive to corticosteroids have been described in patients treated with GLIADEL, including one case leading to brain herniation. CSF leak was more common in GLIADEL-treated patients (see Adverse Reactions). Attention to a water-tight dural closure and local wound care is indicated. 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 (see Adverse Reactions).

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 the implant 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 GLIADEL implantation. This enhancement may represent edema and inflammation caused by the wafers rather than tumor progression.
Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with GLIADEL® Wafer. Carmustine was carcinogenic in mice and rats; mutagenic in vitro and clastogenic both in vitro and in vivo; and caused testicular degeneration in male rats (see Toxicology).

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.

Therapeutic Interactions

Interactions of GLIADEL® Wafer with other drugs or chemotherapy have not been formally evaluated. In the clinical trial in patients with recurrent malignant gliomas, few patients have received systemic chemotherapy within 30 days of GLIADEL (6). 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.

Special Populations

Pregnant Women:
Carmustine, the active component of GLIADEL, is embryotoxic and teratogenic in animals (see Toxicology). There are no studies assessing the reproductive toxicity of GLIADEL and there are no studies with GLIADEL in pregnant women. However, carmustine, the active component of GLIADEL, can cause fetal harm when administered to pregnant women. GLIADEL® Wafer should therefore not be used during pregnancy. Women of childbearing potential should be advised to avoid pregnancy while receiving GLIADEL® Wafer. In the event a patient becomes pregnant during treatment with GLIADEL® Wafer, the patient should be informed of the potential risk to the fetus and genetic counseling should be obtained.

Nursing Women:
It is not known whether carmustine, carboxyphenoxypropane, or sebacic acid are 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

GLIADEL® WAFER (carmustine implant in polifeprosan 20) - Product Monograph
receiving GLIADEL® Wafer discontinue nursing.

**Pediatrics (< 18 years of age):** The safety and effectiveness of GLIADEL in pediatric patients have not been established.

**ADVERSE REACTIONS**

**Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*
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 it is possible that the placebo wafers were 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 ≥4% of Patients Receiving GLIADEL® Wafer at Surgery for Recurrent Disease

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

*p < 0.05 for comparison of GLIADEL® Wafer versus placebo groups
Other Clinical Trials

GLIADEL® Wafer is indicated in recurrent glioblastoma multiforme patients as an adjunct to surgery. Adverse drug reaction information from a study in newly-diagnosed malignant glioma patients was generally consistent with that from the study in recurrent glioma patients. Important information from both studies is included below.

In the initial surgery trial, intracranial hypertension was present in more GLIADEL-treated patients than in placebo patients (9.2% vs. 1.7%). It was typically observed late, and at the time of tumor recurrence.

Adverse Drug Reactions Known to be Complications of Craniotomy
The following four categories of adverse events were found possibly related to treatment with GLIADEL® Wafer. The frequency with which they occurred in the clinical trials is presented below.

Convulsions:
In the initial surgery trial, the incidence of treatment-emergent convulsions was 33.3% in patients given GLIADEL and 37.5% in patients given placebo. Grand mal convulsions occurred in 5% of GLIADEL® Wafer-treated patients and 4.2% of placebo treated patients. The incidence of convulsions 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 convulsions 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 convulsion 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 51 days in placebo patients.

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.

Healing Abnormalities:
The following healing abnormalities have been reported in clinical trials of GLIADEL® Wafer: cerebrospinal fluid leaks, subdural, subgaleal or wound effusions, delayed wound healing, and wound breakdown or dehiscence. 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.

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.
**Intracranial Infection:**
In the initial surgery trial, the incidence of intracranial infection (meningitis or brain abscess) 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 and 1% in patients receiving placebo. In GLIADEL-treated patients, there were three cases of bacterial meningitis, one case of chemical meningitis, and one case of meningitis which was not further specified. A brain abscess was diagnosed in one placebo-treated patient 76 days after wafer implant surgery.

**Less Common Clinical Trial Adverse Drug Reactions (<4%)**

The following treatment-emergent 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.

**Body as a Whole:** pain (4%); peripheral edema (3%); neck pain (2%); back pain (2%); allergic reaction (1%); asthenia (1%); chest pain (1%); sepsis (1%);

**Cardiovascular:** hypertension (3%); hypotension (2%); tachycardia (2%);

**Digestive:** oral moniliasis (3%); diarrhea (3%); vomiting (2%); constipation (1%); dysphagia (1%); gastrointestinal hemorrhage (1%); fecal incontinence (1%)

**Hemic and Lymphatic:** anemia (4%); thrombocytopenia (1%); leukocytosis (1%)

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

**Musculoskeletal:** infection (2%);

**Nervous:** stupor (4%); hydrocephalus (4%); meningitis (4%); depression (3%); thinking abnormal (3%); ataxia (2%); dizziness (2%); coma (2%); insomnia (2%); monoplegia (2%); amnesia (1 %); diplopia (1 %); necrosis (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:** infection (3%); aspiration pneumonia (1%)

**Skin and Appendages:** rash (3%);

**Special Senses:** visual field defect (3%); eye pain (1%);

**Urogenital:** urinary incontinence (2%);
**Post-Market Adverse Drug Reactions**

Post-marketing experience includes spontaneous reports of cyst formation after GLIADEL® Wafer implantation. These occurred at varying time intervals post-implantation.

**DRUG INTERACTIONS**

**Overview**

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.

**DOSAGE AND ADMINISTRATION**

**Recommended Dose and Dosage Adjustment**

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 its size and shape allow. Alternately, the maximum possible number of wafers should be placed. The maximum dose should not exceed 8 wafers per surgical procedure.

Once the tumor is resected, tumor pathology is confirmed, and hemostasis is obtained, up to eight GLIADEL® Wafers 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. Oxidizing regenerated cellulose (Surgicel®) may be placed over the wafers to secure them against the cavity surface. After placement of wafers, the resection cavity should be irrigated and the dura closed in a water tight fashion.

**OVERDOSAGE**

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

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.
ACTION AND CLINICAL PHARMACOLOGY

GLIADEL® Wafer (carmustine in polifeprosan) 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 and release the carmustine. The tumoricidal activity of GLIADEL® Wafer is dependent on release of carmustine to the tumor cavity in concentrations sufficient for effective cytotoxicity. The carmustine released from the GLIADEL® Wafers 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 alkylating moiety hypothesized to be chloroethyl carbonium ion, leads to the formation of DNA cross-links.

GLIADEL® Wafers are biodegradable in human brains at a variable rate from patient to patient. Data obtained at reoperation and autopsies have demonstrated wafer remnants up to 232 days after GLIADEL implantation.

Analysis performed on wafer remnants showed there was minimal detectable carmustine present.

STORAGE AND STABILITY

Gliadel must be stored at or below -15°C (5°F). Unopened foil pouches may be kept at ambient room temperature for a maximum of six hours.

SPECIAL HANDLING INSTRUCTIONS

Handling and Disposal

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® Wafers should be handled with care; the aluminum foil laminate pouches containing GLIADEL 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.
Opening the Pouch Containing the GLIADEL® Wafer

**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 the wafer with the aid of forceps and place onto a designated sterile field.
DOSAGE FORMS, COMPOSITION AND PACKAGING

GLIADEL® Wafer (carmustine in polifeprosan, implant) 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 (3.85%) of carmustine.

Non Medicinal Ingredients: Each wafer contains 192.3 mg of a biodegradable polyanhydride copolymer polifeprosan 20 (copolymer of carboxyphenoxypropane and sebacic acid). The copolymer polifeprosan 20, consists of poly[bis(p-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.

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.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:  Carmustine

Chemical name:  1,3-bis(2-chloroethyl)-1-nitrosurea

Molecular formula:  C₅H₉Cl₂N₃O₂

Molecular mass:  214.06

Structural formula:

\[
\begin{align*}
\text{Cl} - \text{CH}_2 - \text{CH}_2 - \text{NCH}_2 - \text{CH}_2 - \text{Cl} \\
\text{NO}
\end{align*}
\]

Physicochemical properties:  Light yellow powder, soluble in water (4.1 mg/mL),
Melting Point:  30-32°C, Partition Coefficient:
Octanol/Water=34.7

CLINICAL TRIALS

Surgery for Recurrent Disease
A randomized, double-blind, placebo-controlled clinical trial was conducted in adult patients
with recurrent malignant glioma who had previously received definitive external beam radiation
therapy sufficient to disqualify the patient from further radiation therapy and for whom
reoperation was considered an appropriate therapy.  At the time of surgery, patients were
required to have a unilateral single focus of tumor of at least 1.0 cm in diameter, as determined
by tumor imaging studies.  Randomization into the study occurred during surgery after
pathologic examination of the tumor established the presence of malignant glioma.  This trial
determined the safety and efficacy of GLIADEL® Wafer implants plus surgery with maximal
tumor resection compared to placebo implants plus surgery.  The primary efficacy parameter was
the cumulative survival rate at six months from the time of surgery; secondary efficacy
parameters included overall survival at the end of the post-surgery observation period (up to 6
years).

Two hundred and twenty-two patients were enrolled in the study; 110 were treated with
GLIADEL and 112 were treated with placebo.  The median age of patients was 49 years (range:
27-79 years) in the GLIADEL group and 48 years (range 19-80 years) in the placebo group. The majority of patients were male (64%) and Caucasian (92%). Sixty-five percent were diagnosed as having glioblastoma multiforme (GBM). All patients had undergone surgery for malignant glioma at least once before study enrollment, and the median interval from first operation was approximately 12 months. All patients had received prior radiation therapy; 48% had received local radiotherapy, 23% had received diffuse (whole brain) and 28% had received both. Fifty percent of patients had received prior chemotherapy, in most cases with one or more nitrosoureas. Ninety-two percent of the patients treated with GLIADEL® Wafer had 7-8 wafers implanted. Subtotal tumor resection was performed in 76% of patients. 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.

The primary efficacy endpoint in this study was six-month survival. In 222 patients with recurrent malignant glioma who had failed initial surgery and radiation therapy, the six-month survival rate after repeat surgery was 47% (53/112) for patients receiving placebo and 60% (66/110) for patients treated with GLIADEL® Wafer (p=0.061, Fisher’s Exact Test). A secondary endpoint in this study was overall survival. Median survival was 24 weeks (5.5 months) in patients treated with placebo and 32 weeks (7.4 months) in patients treated with GLIADEL® Wafer treatment (p=0.30, Log-rank test).

In the subgroup of 145 patients with GBM, the six-month survival rate increased from 36% (26/73) with placebo to 56% (40/72) with GLIADEL® Wafer treatment (p=0.020, Fisher’s Exact Test, see Figure 6). Median survival of GBM patients was 20 weeks (4.6 months) in patients treated with placebo and 28 weeks (6.4 months) in patients treated with GLIADEL® Wafer treatment (p=0.18, Log-rank test, see Figure 7). In the subgroup of 77 patients with pathologic diagnoses other than GBM at the time of surgery for tumor recurrence, GLIADEL® Wafer produced no improvement in survival at six months (69% for patients receiving placebo versus 68% for patients receiving Gliadel) and no overall survival prolongation.
Figure 6: 6-Month Kaplan-Meier Survival Curves for Patients Undergoing Surgery for Recurrent GBM
DETAILED PHARMACOLOGY

Animals
The pharmacology and pharmacokinetic profile of GLIADEL® Wafer, which contain 3.85% of carmustine, has been based on studies conducted in animals; primarily rats, rabbits and monkeys.

The selection of effective doses of carmustine in GLIADEL for tumoricidal treatment was determined with a rat brain tumor model. In this model, 9L gliosarcoma tumor cells are implanted intracerebrally in the rat. The resulting solid tumor mass will enlarge, leading to the death of all untreated animals within 10-30 days post-inoculation. To evaluate different concentrations of carmustine in the GLIADEL polymer matrix, 4-5 days after a 9L gliosarcoma tumor implant, groups of Fischer 344 rats were surgically implanted with increasing concentrations of carmustine in the polymer matrix ranging from 4%-32%. The resulting efficacy was observed as a dose-related increase in mean survival time when compared to the untreated tumor-bearing rat group.

In a 150 day survival study, wafers containing 30% of carmustine were effective in extending survival in a 9L gliosarcoma rat tumor model from a mean survival of 13.5 days to 122.5 days. In a 200 day survival study, wafers containing 4, 8, or 12% of carmustine were effective in extending survival from no survival beyond 25 days in untreated rats to a 10-25% survival after...
200 days. With wafers containing 20 or 32% of carmustine, survival was extended to 200 days for 50-60% of the rats.

Intracerebral carmustine dose delivery is dependent on polymer degradation following GLIADEL® Wafer implantation. GLIADEL® Wafers degrade by surface erosion in a sharp, slowly advancing front from the exterior to the interior of the wafer. The dynamics of the biodegradation process include the penetration of body water into the outer layers of compressed wafer microspheres, which begin to degrade thereby releasing carmustine into the surrounding brain tissue.

To understand the biodistribution and clearance of GLIADEL’s components, a study was conducted in the male and female adult Sprague-Dawley rat and New Zealand White rabbit. Three types of GLIADEL® Wafers with carmustine were prepared, each containing a different \textsuperscript{14}C-labeled component (\textsuperscript{14}C-PPCP, \textsuperscript{14}C-SA, and \textsuperscript{14}C-Carmustine). The concentrations of carmustine varied from 0.18-0.27 mg (1-2.5%). The results indicated that greater than 80% of the radiolabel for carmustine is released from the wafer within the first week of implantation and that more than 70% of the radiolabel for the polymer components is released from the wafer by three weeks post-implantation. The major route of excretion of the radiolabel from carmustine and PCPP is the kidneys, and from SA is the lungs as CO\textsubscript{2}.

In another study conducted in the New Zealand White rabbit, GLIADEL was implanted in the animal's brain to determine the levels of carmustine in the whole blood, cerebrospinal fluid, and brain tissue exclusive of the implantation site. Six rabbits per group were sacrificed at 1, 3, and 5 days post-implantation and on these days no carmustine was detected from the analysis of the whole blood, cerebrospinal fluid, or brain tissue of the implantation site (assay sensitivity, > 2 g). By day 5, 14% of the original carmustine content was present in the wafer remnants.

The plasma and cerebrospinal levels of carmustine were evaluated during a 28 day brain implantation study in the New Zealand White rabbits. Fifteen rabbits received a 12 mg wafer implant of GLIADEL. Three rabbits per group were sacrificed on days 1, 3, 5, 14, and 28. Bioanalytical results indicated that no carmustine was detected in the plasma or cerebrospinal fluid on any of the assay days.

More than 70% of the copolymer degrades by three weeks. The metabolic disposition and excretion of the monomers differ. Carboxyphenoxypropane is eliminated unchanged by the kidney and sebacic acid, an endogenous fatty acid, is metabolized by the liver and expired as CO\textsubscript{2} in animals.

**Human Pharmacology**

The absorption, distribution, metabolism, and excretion of the copolymer in humans is unknown. Carmustine concentrations delivered by GLIADEL in human brain tissue and plasma levels of carmustine after implant have not been determined.
Following an intravenous infusion of carmustine in man 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.

TOXICOLOGY

An in vitro study evaluated the effects of carmustine on the competency of B6C3Fl mouse macrophage cells. Carmustine produced macrophage toxicity at very low concentrations (5 M to 0.1 mM). These findings reflect the known cytotoxicity of carmustine on normal cells possibly associated with carbamoylation of nucleoprotein lysine residues.

The GLIADEL® Wafer polymer matrix with different dose percents of carmustine and/or the GLIADEL copolymer, P(CPP:SA, 20:80) alone, were evaluated in a series of safety studies by brain implantation in the rat, rabbit, and monkey.

Wafer containing 10, 20 or 30% of carmustine implanted in the Fischer 344 rat brain resulted in either a reduced weight gain or loss in weight, but no mortality over a four week period. Wafers containing 40% of carmustine resulted in a significant weight loss and death in 1 of 4 rats over the same period.

In a one month study with New Zealand White rabbits, P(CPP:SA, 20:80) alone and GLIADEL were implanted in the brain ventricle. Both implants produced a region of focal necrosis, which was increased in the presence of carmustine. These findings were resolved at one month. In a ten-month rabbit brain cortex implantation study, animals received an implant of wafers containing 4.0% of carmustine or P(CPP:SA, 20:80) and subsequent evaluation with or without brain radiation. At the one-month time interval, implant- and irradiation-related brain necrosis was observed. In the non-radiated groups of animals at ten months, the effects of wafers containing 4.0% of carmustine, or P(CPP:SA, 20:80) implants, were comparable to the sham surgery control group in the non-radiated animals. In the radiated groups, brain necrosis was observed in all of the treatment groups with comparable incidence and severity. Brain radiation treatment did not result in a significant change in the pathology findings associated with wafers containing 4.0% of carmustine or P(CPP:SA, 20:80).

Ten week (with wafers containing 1.9% of carmustine) and 26 week (with GLIADEL) cynomologous monkey studies were completed to evaluate the effects of the 1.9% wafers and GLIADEL and P(CPP:SA, 20:80) alone following brain implantation. No meaningful neurological or histological findings were observed in either study, except for localized necrosis around the implanted wafer. In the 26 week study, two monkeys were irradiated, with one monkey sacrificed after 10 weeks and the second monkey sacrificed at 26 weeks. Microscopic pathology in the first monkey indicated focal necrosis at the wafer site which was not found in the second monkey at 26 weeks. Radiation treatment in the monkey implanted with GLIADEL and sacrificed after 10 weeks did not result in a greater severity of brain necrosis than was
observed in the non-irradiated monkeys implanted with 1.9% wafers in the ten week monkey study.

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with Gliadel. 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.

There are no studies assessing the reproductive toxicity of Gliadel. Carmustine, the active component of Gliadel, 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.

**Biocompatibility**

The polymer in Gliadel consists of 20% CPP and 80% SA by molar ratio [P(CPP:SA, 20:80)]. Sebacic acid is a natural body constituent in man. The biocompatibility of these two polymer components was evaluated in a series of in vitro and in vivo studies.

P(CPP:SA, 45:55) was evaluated in vitro in the Salmonella typhimurium mutation assay. The cell findings in this study indicated that these two polymer components are biocompatible. PCPP alone was evaluated in the ascitic mouse ovarian tumor cell assay and the bovine aorta cell assay. These studies also indicated that PCPP is biocompatible.

P(CPP) was evaluated for local tissue response for six weeks following corneal implantation in the NZW rabbit and for six months following subcutaneous injection in the Sprague-Dawley rat. The results from these studies indicated that PCPP is biocompatible.

P(CPP:SA, 20:80) with 3.85% carmustine (Gliadel) and without carmustine were evaluated in a series of intramuscular biocompatibility studies in NZW rabbits. P(CPP:SA, 20:80) exhibited a greater foreign body granulomatous response than was found with the USP Negative Control Plastic Reference Standard*. Partial dissolution of the P(CPP:SA, 20:80) was observed
by seven days post-implantation. GLIADEL exhibited a greater intramuscular response in NZW rabbits than P(CPP:SA, 20:80), which included necrosis, heterophil infiltration with mononuclear cells, and increased fibrous tissue. These findings reflect the known tissue effects of carmustine.

*High density polyethylene plastic
REFERENCES


PART III: CONSUMER INFORMATION

GLIADEL® Wafer
Carmustine implant in polifeprosan 20

This leaflet is part III of a three-part "Product Monograph" published when GLIADEL® Wafer was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about GLIADEL® Wafer. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
- GLIADEL® Wafer is used with surgery, in the treatment of glioblastoma multiforme (a form of brain cancer) if it comes back.

What it does:
Carmustine helps to kill any leftover tumor cells that are not taken out by the surgery. Polifeprosan 20 works by controlling the release of carmustine into the area where the brain tumor was taken out.

When it should not be used:
You should not be given GLIADEL® Wafer if you are allergic to carmustine or any of the other ingredients in GLIADEL® Wafer.

What the medicinal ingredient is:
Carmustine

What the important nonmedicinal ingredients are:
Polifeprosan 20 (a copolymer of carboxyphenoxypropane and sebacic acid).

What dosage forms it comes in:
GLIADEL® Wafer is an implant in the form of 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.

WARNINGS AND PRECAUTIONS

GLIADEL® Wafer should only be placed by a qualified surgeon during brain surgery.

Possible serious side effects with GLIADEL® Wafer implant include the following:
- Obstructive hydrocephalus (an abnormal accumulation of cerebrospinal fluid in the brain), especially if GLIADEL® Wafers are not properly implanted.
- New seizures and worsening of seizures
- Brain infections, including meningitis
- Abnormal wound healing
- Brain swelling (edema)

BEFORE you have treatment with GLIADEL® Wafer talk to your doctor or pharmacist if any of the conditions apply to you:
- Are pregnant or planning to get pregnant. Gliadel can cause harm to an unborn baby, therefore pregnancy should be avoided while receiving Gliadel treatment.
- Are breastfeeding. Breastfeeding should be discontinued while receiving Gliadel treatment.
- You have any allergies to this drug or its ingredients or components of the container.

Gliadel should not be used in patients under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Before using this medication, tell your doctor or pharmacist of all prescription and nonprescription/herbal products you may use. During your treatment with GLIADEL® Wafer, do not start taking a new medicine before checking with your doctor or pharmacist.

The safety of GLIADEL® Wafer when given with other cancer treatments has not been fully studied.

PROPER USE OF THIS MEDICATION

GLIADEL® Wafer is placed by a surgeon during brain surgery into the area where the brain tumor was taken out. The implant will dissolve slowly, releasing the medication to the surrounding area. Follow all your doctor’s instructions on what to do before and after surgery.

Usual dose:
The number of implants placed is based on the size of the area to cover. The maximum recommended dose is 8 implants placed at each surgery.

Since this drug can be absorbed through the skin, women who are pregnant or who may become pregnant should not handle this medication.

Overdose:
In case of a suspected drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
Not applicable

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

#### Very common side effects (>4%

- nausea, vomiting
- fever (signs of an infection), pain
- swelling/redness/warmth at surgery site, wound at surgery site that is opening or not healing properly
- seizures, severe headache
- extreme tiredness/weakness, confusion, weakness on one side of the body, slurred speech, stiff neck, fainting
- rash
- mental/mood changes (e.g., depression, anxiety)

#### Common side effects (1%):

- constipation
- bleeding in the stomach
- chest pain

Seek immediate medical attention if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

This is not a complete list of possible side effects. If you notice any other effects not listed above, contact your doctor or pharmacist.

### HOW TO STORE IT

Store in a freezer at or below -15 degrees C (5 degrees F). Unopened foil pouches may be kept at room temperature for up to 6 hours. Consult your pharmacist for details. Keep all medicines away from children and pets.

Do not flush medications down the toilet or pour them into a drain unless instructed to do so. Properly discard this product when it is expired or no longer needed. Consult your pharmacist or local

**Symptom / effect** | **Talk with your doctor or pharmacist** | **Call your doctor immediately**
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**Very Common** | | |
Swelling, redness, warmth at surgery site (14%) | | |
Signs of an infection (e.g., fever, pain) (7 -12%) | | |
Nausea or vomiting (8%) | | |
Stomach, abdominal, back pain (7%) | | |
Mood changes (4%) | | |
**Common** | | |
Constipation (1%) | T | |
Chest pain (1%) | T | |
Allergic reaction: rash, itching, swelling, dizziness or trouble breathing (rare) | T | |

This is not a complete list of side effects. For any unexpected effects while taking GLIADEL® Wafer, contact your doctor or pharmacist.
waste disposal company for more details about how to safely discard your product.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

**NOTE:** Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Eisai Limited, at: 1-877-873-4724

This leaflet was prepared by Eisai Limited.

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