

## PRODUCT INFORMATION

### GLIADEL® Implants (Carmustine implant with Polifeprosan 20)

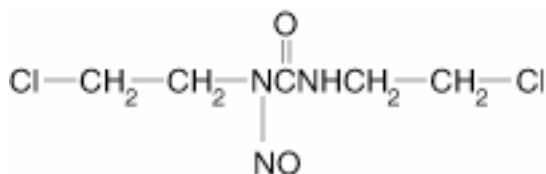
#### NAME OF THE DRUG

##### Chemical name

The chemical name of carmustine is 1,3-bis (2-chloroethyl)-1-nitrosourea (or BCNU).

##### Chemical structure

The structural formula for carmustine is:



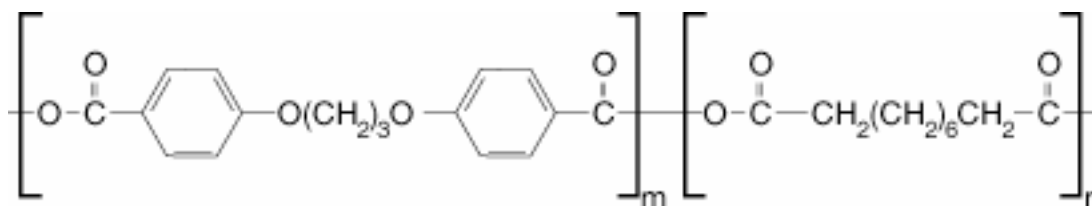
CAS: 154-93-8

#### DESCRIPTION

GLIADEL Implants are sterile, off-white to pale yellow implants approximately 1.45 cm in diameter and 1 mm thick. Each implant contains 7.7 mg of carmustine and 192.3 mg of a biodegradable polyanhydride copolymer (Polifeprosan 20).

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.

The structural formula for Polifeprosan 20 is:



Ratio m:n = 20:80; random copolymer

## PHARMACOLOGY

GLIADEL is designed to deliver carmustine directly into the surgical cavity created after tumour resection. On exposure to the aqueous environment of the cavity, the anhydride bonds in the copolymer are hydrolysed, releasing carmustine, carboxyphenoxypropane, and sebacic acid. The carmustine released from GLIADEL 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 an alkylating moiety, hypothesised to be chloroethyl carbonium ion, leads to the formation of DNA cross-links.

The tumouricidal activity of GLIADEL is dependent on release of carmustine to the tumour cavity in concentrations sufficient for effective cytotoxicity.

More than 70% of the copolymer degrades by three weeks. The metabolic disposition and excretion of the monomers differ. Carboxyphenoxypropane is predominantly eliminated by the kidney and sebacic acid (an endogenous fatty acid) is metabolised by the liver and expired as CO<sub>2</sub> in animals.

### Pharmacokinetics

The absorption, distribution, metabolism, and excretion of the copolymer in humans are unknown. Carmustine concentrations delivered by GLIADEL in human brain tissue have not been determined. Plasma levels of carmustine after GLIADEL implantation were not determined. Animal studies suggest that nearly all the carmustine in the implants is released within 7 days of implantation.

Following an intravenous infusion of carmustine at doses ranging from 30 to 170 mg/m<sup>2</sup>, the average terminal half-life, clearance, and steady-state volume of distribution were 22 minutes, 56 mL/min/kg, and 3.25 L/kg, respectively. Approximately 60% of the intravenous 200 mg/m<sup>2</sup> dose of <sup>14</sup>C-carmustine was excreted in the urine over 96 hours and 6% was expired as CO<sub>2</sub>.

GLIADEL implants are biodegradable in the human brain when placed into the cavity after tumour resection. The rate of biodegradation is variable from patient to patient. During the biodegradation process, an implant remnant may be observed on brain imaging scans or at re-operation even though extensive degradation of all components has occurred. Data obtained from review of CT scans obtained 49 days after implantation of GLIADEL demonstrated that images consistent with implants were visible to varying degrees in the scans of 11 of 18 patients. Data obtained at re-operation and autopsies have demonstrated implant remnants up to 232 days after GLIADEL implantation.

Implant remnants removed at re-operation from two patients with recurrent malignant glioma, one at 64 days and the second at 92 days after implantation, were analysed for content. The following table presents the results of analyses completed on these remnants.

### COMPOSITION OF IMPLANT REMNANTS REMOVED FROM TWO PATIENTS ON RE-OPERATION

Component	Patient A	Patient B
Days After GLIADEL Implantation	64	92
Anhydride Bonds	None detected	None detected
Water Content (% of implant remnant weight)	95-97%	74-86%
Carmustine Content (% of initial)	<0.0004%	0.034%
Carboxyphenoxypropane Content (% of initial)	9%	14%
Sebacic Acid Content (% of initial)	4%	3%

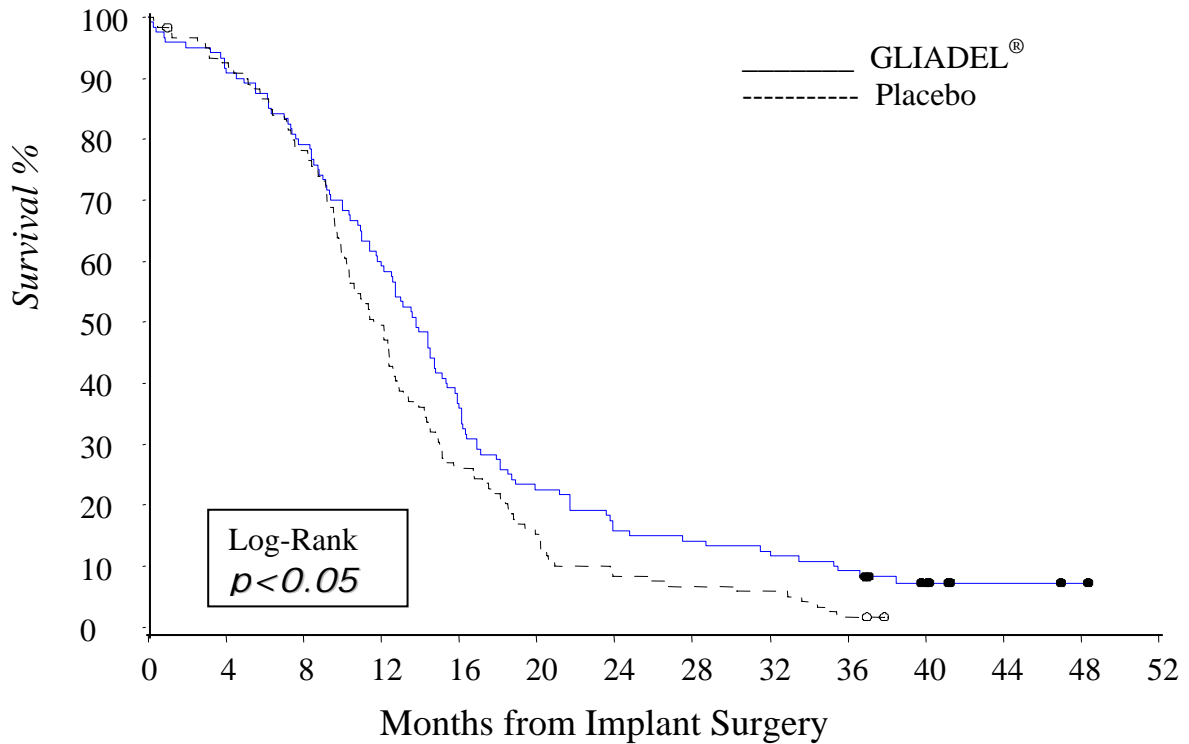
The implant remnants consisted mostly of water and monomeric components with minimal detectable carmustine present.

### Clinical Trials

#### Primary Surgery

A randomised, double-blind, placebo-controlled clinical trial was conducted in adult patients with newly-diagnosed high-grade malignant glioma undergoing initial craniotomy for tumour resection. The trial determined the safety and efficacy of GLIADEL implants plus surgery and radiation therapy compared to placebo implants plus surgery and radiation therapy. Two hundred and forty patients with newly-diagnosed malignant glioma were enrolled. The most common tumour type was Glioblastoma Multiforme (GBM) (n=207), followed by anaplastic oligoastrocytoma (n=11), anaplastic oligodendroglioma (n=11), and anaplastic astrocytoma (n=2). GLIADEL wafers were implanted at the time of the surgery in 120 patients and placebo were implanted in 120 patients. The majority of patients received 6-8 wafers. The majority of patients (93/120, 77.5% in the GLIADEL group and 98/120, 81.7% in the placebo group) with newly-diagnosed malignant glioma received a standard course of radiotherapy (55 to 60 Gy) typically starting 3 weeks after surgery. There were 17 patients (14.2%) in the GLIADEL group and 12 patients (10.0%) in the placebo group who received systemic chemotherapy during the study. All six patients with anaplastic oligodendroglioma received chemotherapy within 30 days of GLIADEL implantation. Patients were followed for at least three years or until death. Only one patient was lost to follow-up. Median survival increased from 11.6 months with placebo to 13.9 months with GLIADEL (p-value <0.05, log-rank test). The hazard ratio for GLIADEL treatment was 0.73 (95% CI: 0.56-0.95).

### Kaplan-Meier Overall Survival Curves for Patients Undergoing Initial Surgery for a High-Grade Malignant Glioma



When only patients with Glioblastoma multiforme were included in the analysis, the hazard ratio with GLIADEL treatment was 0.78 (95% CI: 0.59-1.03,  $p=0.08$ , log-rank test).

#### Surgery for Recurrent Disease

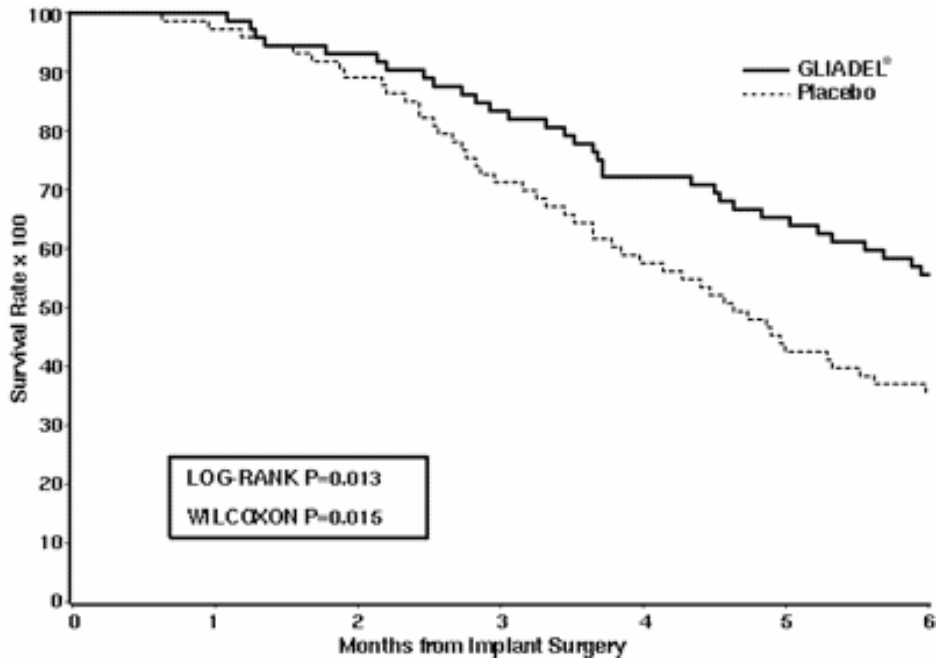
A randomised, double-blind, placebo-controlled clinical trial was conducted in adult patients with recurrent malignant glioma. This trial determined the safety and efficacy of GLIADEL implants plus surgery compared to placebo implants plus surgery.

Ninety-five percent of the patients treated with GLIADEL had 7-8 wafers implanted.

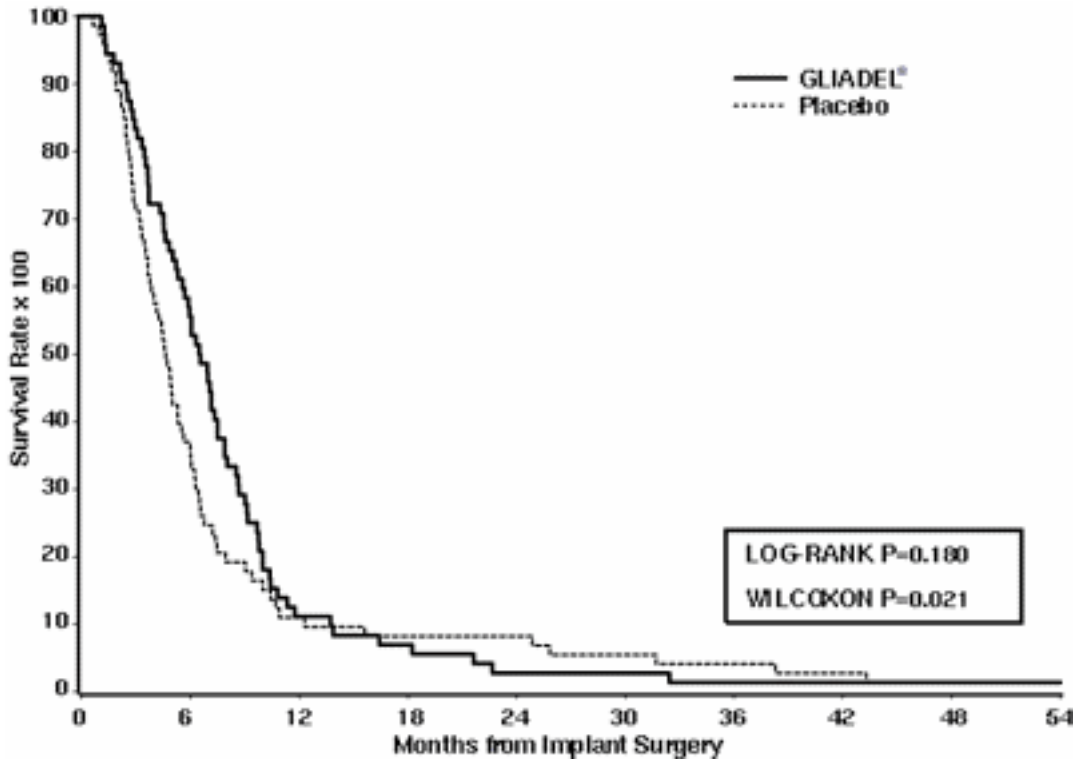
Chemotherapy was withheld at least four weeks (six weeks for nitrosoureas) prior to and two weeks after surgery in patients undergoing re-operation for malignant glioma.

In 222 patients with recurrent malignant glioma who had failed initial surgery and radiation therapy, the six-month survival rate after repeat surgery increased from 47% (53/112) for patients receiving placebo to 60% (66/110) for patients treated with GLIADEL. Median survival increased by 33%, from 24 weeks (5.5 months) with placebo to 32 weeks (7.4 months) with GLIADEL treatment. In patients with GBM, the six-month survival rate increased from 36% (26/73) with placebo to 56% (40/72) with GLIADEL treatment. Median survival of GBM patients increased by 41% from 20 weeks (4.6 months) with placebo to 28 weeks (6.4 months) with GLIADEL treatment. In patients with pathologic diagnoses other than GBM at the time of surgery for tumour recurrence, GLIADEL produced no survival prolongation.

### 6-MONTH KAPLAN-MEIER SURVIVAL CURVES FOR PATIENTS UNDERGOING SURGERY FOR RECURRENT GBM



### OVERALL KAPLAN-MEIER SURVIVAL CURVES FOR PATIENTS UNDERGOING SURGERY FOR RECURRENT GBM



## INDICATIONS

GLIADEL is indicated in newly-diagnosed high-grade malignant glioma patients as an adjunct to surgery and radiation. GLIADEL is also indicated for use as adjunct to surgery to prolong survival in patients with recurrent glioblastoma multiforme (GBM) for whom surgical resection is indicated.

## CONTRAINDICATIONS

GLIADEL is contraindicated in patients with a history of hypersensitivity to carmustine or any of the components of GLIADEL. GLIADEL is also contraindicated in breast-feeding mothers.

## PRECAUTIONS

### *Surgery*

Patients undergoing craniotomy for malignant glioma and implantation of GLIADEL should be monitored closely for known complications of craniotomy which include seizures/convulsions, intra-cranial infections, abnormal wound healing, and brain oedema (see “Adverse Events”). Cases of intracerebral mass effect unresponsive to corticosteroids have been described in patients treated with GLIADEL, including one case leading to brain herniation.

Communication between the surgical resection cavity and the ventricular system should be avoided to prevent the implants from migrating into the ventricular system and causing obstructive hydrocephalus. If a communication larger than the diameter of a wafer exists, it should be closed at operation prior to implantation.

### *Imaging Studies*

Computed tomography (CT) and magnetic resonance imaging (MRI) of the head may demonstrate enhancement in the brain tissue surrounding the resection cavity after placement of GLIADEL implants. This enhancement may represent oedema and inflammation caused by GLIADEL or tumour progression.

## **Carcinogenicity, Mutagenicity and Impairment of Fertility**

No carcinogenicity, mutagenicity or impairment of fertility studies have been conducted with GLIADEL. However, such studies have been conducted with carmustine, the active component of GLIADEL, when administered systemically. Carcinogenicity studies were conducted in rats and mice, with the data indicating an increased incidence of pulmonary neoplasms in rats and possible tumorigenic activity in mice. Carmustine was mutagenic *in vitro* and clastogenic *in vitro* and *in vivo*. Carmustine has also been shown to affect fertility in male rats, with conception rate being reduced in females mated to treated males, as carmustine can cause testicular degeneration.

## **Use in Pregnancy - Category D**

There are no studies in either pregnant women or laboratory animals on GLIADEL, but the active component, carmustine, when administered systemically, can cause foetal harm when administered to a pregnant woman and has been shown to be embryotoxic in rats and rabbits and teratogenic in rats.

Although it is preferable that GLIADEL is not used in pregnancy, if it is, or if the patient becomes pregnant after GLIADEL implantation, the patient must be warned of the potential hazard to the fetus.

### **Use in Lactation**

It is not known if either carmustine, carboxyphenoxypropane or sebacic acid are excreted in human milk. Since some drugs are excreted in human milk and because of the potential for serious adverse reactions from carmustine in nursing infants, women being treated with GLIADEL should not breast-feed their infants. For women who wish to breast-feed their infants, GLIADEL is contraindicated.

### **Interactions with other drugs or radiotherapy**

Interactions of GLIADEL with other drugs have not been formally evaluated.

The short and long-term toxicity profiles of GLIADEL when given in conjunction with chemotherapy have not been fully explored. GLIADEL, when given in conjunction with radiotherapy does not appear to have any short-term or chronic toxicities.

#### *Systemic Chemotherapy*

Some patients (n=6) in the clinical trials have received systemic chemotherapy. 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.

#### *Radiotherapy*

Some patients in the clinical trials have received external beam radiation therapy (n=36). External beam radiation therapy was initiated no sooner than three weeks after GLIADEL implantation. Of the 36 patients who received GLIADEL at initial surgery for newly diagnosed malignant glioma followed by external beam radiation therapy, 3/15 (20%) in one study and 11/21 (52%) in the other study experienced new or worsened seizures.

### **Use in Children**

The safety and efficacy of GLIADEL in children has not been established.

### **Recommendations for Safe Handling**

Implants should 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 dedicated biohazard waste container after use. A surgical instrument dedicated to the handling of the implants should be used for implant placement. If repeat neurosurgical intervention is required, any implant or implant remnant should be handled as a potentially cytotoxic agent and discarded into the biohazard container.

Each implant is wrapped in a double foil system for use in operating theatres, with the outer pouch acting as a NON STERILE overwrap and the inner pouch only being sterile.

**ADVERSE REACTIONS**

Adverse reactions for the trials are described in the tables below.

**Primary Surgery**

The following data are some of the most frequently occurring adverse events observed in 5% or more of the newly-diagnosed malignant glioma patients during the trial.

**COMMON ADVERSE EVENTS OBSERVED IN ≥ 5% OF PATIENTS  
RECEIVING GLIADEL AT INITIAL SURGERY**

<b>Body System</b>	<b>GLIADEL N=120</b>	<b>Placebo N=120</b>
Adverse event	n (%)	n (%)
<b>Body as a whole</b>		
Aggravation reaction*	98(82)	95(79)
Asthenia	26(22)	18(15)
Abdominal pain	10(8)	2(2)
Back pain	8(7)	4(3)
Face oedema	7(6)	6(5)
Abscess	6(5)	3(3)
Chest pain	6(5)	0
<b>Cardiovascular system</b>		
Deep thrombophlebitis	12(10)	11(9)
Haemorrhage	8(7)	7(6)
<b>Digestive system</b>		
Nausea	26(22)	20(17)
Vomiting	25(21)	19(16)
Constipation	23(19)	14(12)
Diarrhoea	6(5)	5(4)
Liver function tests abnormal	1(1)	6(5)
<b>Endocrine system</b>		
Diabetes mellitus	6(5)	5(4)
<b>Metabolic and nutritional disorders</b>		
Healing abnormal	19(16)	14(12)

\* Adverse events coded to the COSTART term "aggravation reaction" were usually events involving tumour/disease progression or general deterioration of condition (eg. condition/health/Karnofsky/neurological/physical deterioration).

**COMMON ADVERSE EVENTS OBSERVED IN ≥ 5% OF PATIENTS  
RECEIVING GLIADEL AT INITIAL SURGERY**

<b>Body System</b>	<b>GLIADEL N=120</b>	<b>Placebo N=120</b>
Adverse event	n (%)	n (%)
<b>Nervous system</b>		
Hemiplegia	49(41)	53(44)
Convulsion	40(33)	45(38)
Confusion	28(23)	25(21)
Brain oedema	27(23)	23(19)
Aphasia	21(18)	22(18)
Depression	19(16)	12(10)
Somnolence	13(11)	18(15)
Speech disorder	13(11)	10(8)
Amnesia	11(9)	12(10)
Intracranial hypertension	11(9)	2(2)
Personality disorder	10(8)	9(8)
Anxiety	8(7)	5(4)
Facial paralysis	8(7)	5(4)
Neuropathy	8(7)	12(10)
Ataxia	7(6)	5(4)
Hypesthesia	7(6)	6(5)
Paresthesia	7(6)	10(8)
Thinking abnormal	7(6)	10(8)
Abnormal gait	6(5)	6(5)
Dizziness	6(5)	11(9)
Grand mal convulsion	6(5)	5(4)
Hallucinations	6(5)	4(3)
Insomnia	6(5)	7(6)
Tremor	6(5)	8(7)
Coma	5(4)	6(5)
Incoordination	3(3)	8(7)
Hypokinesia	2(2)	8(7)
<b>Respiratory system</b>		
Pneumonia	10(8)	9(8)
<b>Skin and appendages</b>		
Rash	14(12)	13(11)

## Surgery for Recurrent Disease

The following post-operative adverse events were observed in 4% or more of the patients receiving GLIADEL at recurrent surgery. Except for nervous system effects, where there is a possibility that the placebo wafers could have been responsible, only events more common in the GLIADEL 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.

<b>Adverse events</b>	<b>GLIADEL treated Patients (%)</b>	<b>Placebo treated Patients(%)</b>
<i>Body as a Whole</i>		
Fever	12	8
Infection	7	8
Pain	7	1
<i>Cardiovascular System</i>		
Deep thrombophlebitis	9	11
Pulmonary embolism	6	7
<i>Digestive System</i>		
Nausea	6	5
Nausea and Vomiting	8	6
Oral moniliasis	6	5
<i>Haemic and Lymphatic System</i>		
Anaemia	7	11
<i>Metabolic and Nutritional Disorders</i>		
Healing Abnormal	14	5
Hyponatraemia	5	6
<i>Nervous System</i>		
Aphasia	9	11
Ataxia	2	5
Brain Oedema	4	1
Confusion	10	8
Convulsion	19	19
Headache	15	13
Hemiplegia	19	20
Intracranial Hypertension	4	6
Meningitis or Abscess	4	1
Somnolence	14	11
Stupor	6	6
<i>Respiratory System</i>		
Pneumonia	6	6
<i>Skin and Appendages</i>		
Rash	5	4
<i>Urogenital System</i>		
Urinary Tract Infection	21	17

The following four categories of adverse events are possibly related to treatment with GLIADEL. The frequency with which they occurred in the randomised trials along with descriptive detail is provided below.

**1. Seizures:** In the initial surgery trial, the incidence of seizures was 33.3% in patients receiving GLIADEL and 37.5% in patients receiving placebo. Grand mal seizures occurred in 5% of GLIADEL-treated patients and 4.2% of placebo-treated patients. The incidence of seizures within the first 5 days after wafer implantation was 2.5% in the GLIADEL 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- and placebo-treated patients.

In the surgery for recurrent disease trial, the incidence of post-operative seizures was 19% in both patients receiving GLIADEL and placebo. In this study, 12/22 (54%) of patients treated with GLIADEL and 2/22 (9%) of placebo patients experienced the first new or worsened seizure 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 and 61 days in placebo patients.

**2. Brain Oedema:** In the initial surgery trial, brain oedema was noted in 22.5% of patients treated with GLIADEL and in 19.2% of patients treated with placebo. Development of brain oedema with mass effect (due to tumour recurrence, intracranial infection, or necrosis) may necessitate re-operation and, in some cases, removal of GLIADEL or its remnants.

**3. Healing Abnormalities:** The following healing abnormalities have been reported in clinical trials of GLIADEL: wound dehiscence, delayed wound healing, subdural, subgaleal or wound effusions, and cerebrospinal fluid leak. In the initial surgery trial, healing abnormalities occurred in 15.8% of GLIADEL-treated patients and in 11.7% of placebo recipients. Cerebrospinal fluid leaks occurred in 5% of GLIADEL recipients and 0.8% of those given placebo.

During surgery, a water-tight dural closure should be obtained to minimise the risk of cerebrospinal fluid leak.

In the surgery for recurrent disease trial, the incidence of healing abnormalities was 14% in GLIADEL-treated patients and 5% in patients receiving placebo.

**4. Intracranial Infection:** In the initial surgery trial, the incidence of brain abscess or meningitis was 5% in patients treated with GLIADEL 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.

The following adverse events, not listed in the table above, were reported in less than 4% but at least 1% of patients treated with GLIADEL in all studies. The events listed were either not present pre-operatively or worsened post-operatively. Whether GLIADEL caused these events cannot be determined.

*Body as a Whole:* peripheral oedema (2%); neck pain (2%); accidental injury (1%); back pain (1%); allergic reaction (1%); asthenia (1%); chest pain (1%); sepsis (1%)

*Cardiovascular System:* hypertension (3%); hypotension (1%)

*Digestive System:* diarrhoea (2%); constipation (2%); dysphagia (1%); gastrointestinal haemorrhage (1%); faecal incontinence (1%)

*Haemic and Lymphatic System:* thrombocytopenia (1%); leukocytosis (1%)

*Metabolic and Nutritional Disorders:* hyponatraemia (3%); hyperglycaemia (3%); hypokalaemia (1%)

*Musculoskeletal System:* infection (1%)

*Nervous System:* hydrocephalus (3%); depression (3%); abnormal thinking (2%); ataxia (2%); dizziness (2%); insomnia (2%); monoplegia (2%); coma (1%); amnesia (1%); diplopia (1%); paranoid reaction (1%). In addition, cerebral haemorrhage and cerebral infarct were each reported in less than 1% of patients treated with GLIADEL.

*Respiratory System:* infection (2%); aspiration pneumonia (1%)

*Skin and Appendages:* rash (2%)

*Special Senses:* visual field defect (2%); eye pain (1%)

*Urogenital System:* urinary incontinence (2%)

In a published clinical study, cyst formation after GLIADEL Implant treatment has been reported. This reaction occurred in 10% of the patients observed in the study, however, the formation of cyst is possible after resection of a malignant glioma.

## DOSAGE AND ADMINISTRATION

Each GLIADEL implant contains 7.7 mg of carmustine, resulting in a dose of 61.6 mg when eight implants are placed in the tumour resection cavity. It is recommended that a maximum of eight implants be placed if the size and shape of the resection cavity allows it. Otherwise, use the maximum number of implants possible. No more than eight implants should be used per surgical procedure, as there is no clinical experience with this dose.

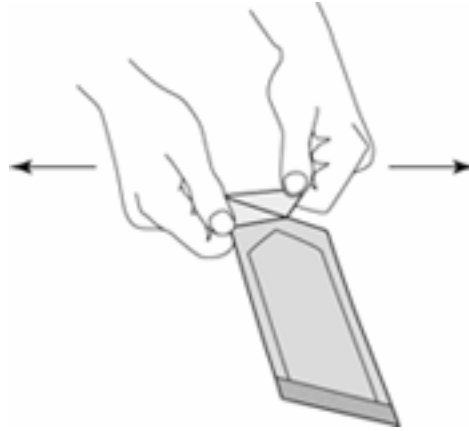
## Handling and Disposal

GLIADEL implants should be handled with care (refer to “PRECAUTIONS” section on safe handling).

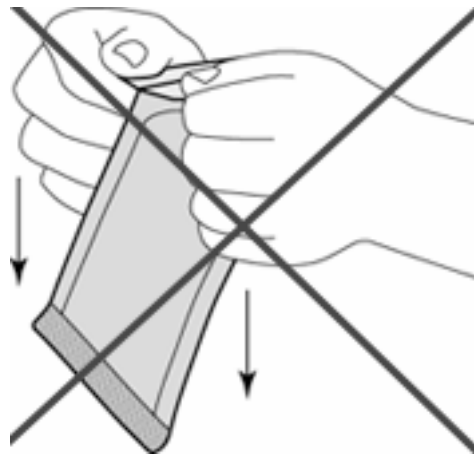
The sachets containing GLIADEL should be delivered to the operating room and remain unopened until ready to place the implants into the resection cavity. **The outside surface of the outer foil pouch is not sterile and must be removed under sterile conditions from the sterile inner pouch prior to implantation.**

### Instructions for Opening Pouch Containing GLIADEL Implant

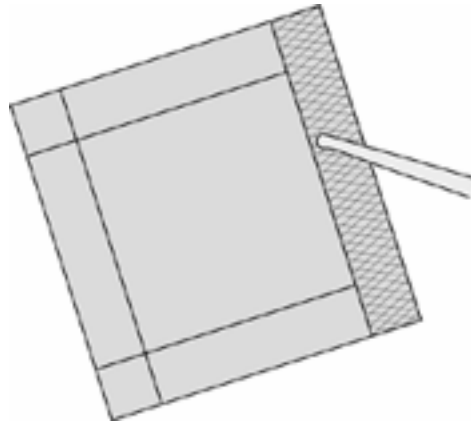
**Figure 1:** To remove the sterile inner pouch from the outer pouch, locate the folded corner and slowly pull in an outward motion.



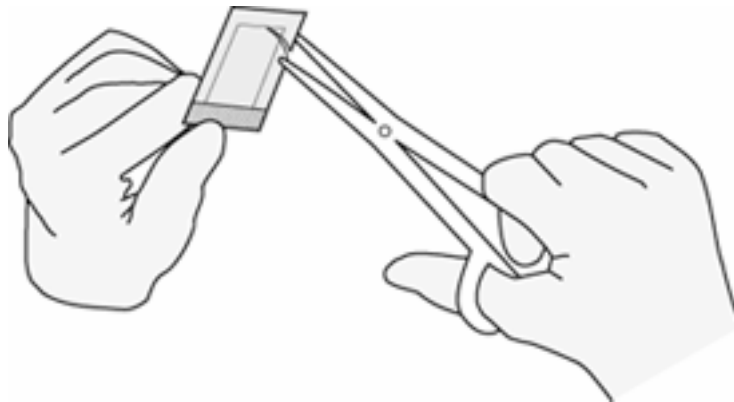
**Figure 2:** Do NOT pull in a downward motion rolling knuckles over the pouch. This may exert pressure on the implant and cause it to break.



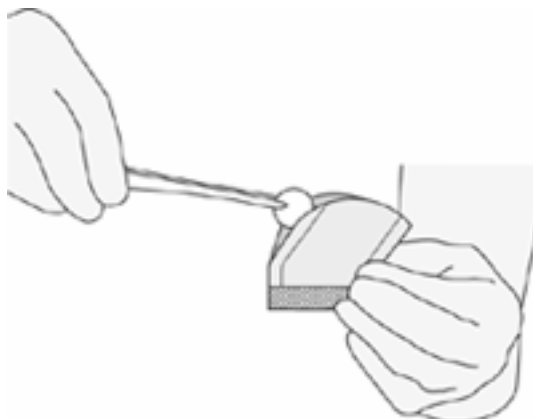
**Figure 3:** Remove the inner pouch by grabbing hold of the **crimped** edge and pulling upward.



**Figure 4:** To open the inner pouch, gently hold the crimped edge and cut in an arc-like fashion around the implant.



**Figure 5:** To remove the GLIADEL implant, gently grasp the implant with the aid of forceps and place it onto a designated sterile field.



Once the tumour is resected, tumour pathology is confirmed, and haemostasis is obtained, up to eight GLIADEL Implants may be placed to cover as much of the resection cavity as possible. Slight overlapping of the implants is acceptable. Implants broken in half may be used, but implants broken in more than two pieces should be discarded in a biohazard container.

Oxidised regenerated cellulose (Surgicel®) may be placed over the implants to secure them against the cavity surface. After placement of the implants, 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 implants per surgical procedure.

## STORAGE

GLIADEL must be stored at or below -20°C (Deep Freeze). GLIADEL implants have been demonstrated to be stable at either -18°C or -20°C.

Unopened outer sachets may be kept at a temperature of not more than 22°C for a maximum of six hours. Refreezing of sachets is allowed if they have not been opened and have been kept for a maximum of 6 hours at a temperature of not more than 22°C. GLIADEL Implants should be used within 30 days when refrozen.

## PRESENTATION

Each box of GLIADEL contains eight implants representing a single dose.

Each implant contains 7.7 mg of carmustine and is packaged in two aluminium 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.**

## SPONSOR

Orphan Australia Pty Ltd  
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Australia

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Revised Text Approved by TGA: 27 October 2004

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