**SURGICAL PREPARATION**
- Resect tumor
- Obtain hemostasis
- Confirm pathological diagnosis of grade III high-grade glioma or glioblastoma multiforme
- GLIADEL Wafer pouches should remain unopened until ready for implantation
- Communication between resection cavity and ventricular system should be avoided
  - Any communication larger than a wafer should be closed prior to implantation

**CAREFULLY OPEN PACKAGING**
- Handling with double-layer surgical gloves is recommended
- Remove non-sterile outer pouch (1)
  - Slowly pull corners outward
  - Grab crimped edge of inner pouch and pull upward
- Open sterile inner pouch
  - Gently hold the crimped edge
  - Cut inner pouch in an arc-like fashion around the wafer
- Remove wafer (2)
  - A dedicated surgical instrument should be used for wafer handling
  - Gently grasp wafer with forceps
  - Place onto a designated sterile field

**ADMINISTER GLIADEL WAFER**
- Up to 8 wafers may be placed to cover as much of the resection cavity as possible (3)
- Slight overlapping of wafers is acceptable
- Wafers broken in 2 may be used, but wafers broken in more than 2 pieces should be discarded
- Surgicel® may be placed over the wafers to secure them against the cavity surface (4)

**ENSURE CAVITY INTEGRITY**
- After wafer placement, irrigate cavity
- Close dura in a watertight fashion to minimize the risk of cerebrospinal fluid leak

**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 pregnant women.

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

Surgicel is a registered trademark of Johnson & Johnson.
INDICATIONS
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GLIadel Wafer is also indicated in patients with recurrent glioblastoma multiforme as an adjunct to surgery.

IMPORTANT SAFETY INFORMATION
GLIadel Wafer 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: Seizures occurred in 37% of patients treated with GLIadel Wafers in the recurrent disease trial. New or worsening (treatment emergent) seizures occurred in 20% of patients; 54% of treatment-emergent seizures occurred within the first 5 post-operative days. The median time to onset of the first new or worsened post-operative seizure was 4 days. Institute optimal 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 full Prescribing Information.
GLIADEL® WAFER (carmustine implant), for intracranial use

Use of this highlights only does not include all the information needed to use GLIADEL® WAFER. See full prescribing information for GLIADEL® WAFER. GLIADEL® WAFER (carmustine implant), for intracranial use

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

12.1 Mechanism of Action

11. DESCRIPTION

8.5 Geriatric Use

6.1 Clinical Trials Experience

5.5 Wafer Migration

5.4 Meningitis

5.3 Impaired Neurovascular Wound Healing

5.2 Neurosurgery

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5.  WARNINGS AND PRECAUTIONS

4. CONTRAINDICATIONS

3.  DOSAGE FORMS AND STRENGTHS

2.1 Recommended Dose

2.  DOSAGE AND ADMINISTRATION

1. Indications and Usage

1.  USE IN SPECIFIC POPULATIONS

1.1 Pregnancy

1.2 Lactation

1.3 Females and Males of Reproductive Potential

1.4 Pediatric Use

10. CONTRAINDICATIONS

9. Nature of the Clinical Studies

8. GENERAL ADVERSE REACTIONS

7. PATIENT COUNSELING INFORMATION

6. ADVERSE REACTIONS

5. Local Adverse Reactions

4. ADVERSE REACTIONS

3. Administration and Dosage

2. Wafers and Wafer Pouches

1. Introduction

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

Local Adverse Reaction

GLIADEL Wafer

Placebo

N=120

N=112

N=110

N=112

Urinary tract infections 21 17

Constipation 19 12

Back pain 7 3

Brain abscess 6 4

 tổ n=1) and acute coronary event (n=1). Deaths on the placebo arm resulted from

Cerebral edema 23 19

Brain cyst 2 3

Brain abscess 6 4

Brain edema 23% in patients with newly diagnosed gliomas treated with GLIADEL Wafers. Adverse reactions in GLIADEL Wafers-treated patients are shown in Table 2. The incidence of local adverse reactions is shown in Table 2.

Back pain7 3

Premature death 10

Generalized tonic-clonic seizure 4

Seizures occurred in 37% of patients treated with GLIADEL Wafers for recurrent gliomas. In Study 2, no new or worsening treatment emergent seizures occurred in 20% of patients. Prophylaxis for treatment emergent seizures occurred within the first 5 post-operative days [see Adverse Reactions (6.1)]. The median time to onset of the first new or worsened post-operative seizure was 6 days. Instruct patients on sodium valproate therapy prior to surgery. Monitor patients for seizures postoperatively. Use of this highlights only does not include all the information needed to use GLIADEL® WAFER. GLIADEL® WAFER (carmustine implant), for intracranial use

In Study 1, 38% of patients received 8 wafers and 78% received ≥ 6 wafers. Thirty-eight percent of patients had a histologic subtype of glioblastoma as determined by central pathology review. Eighty-one percent had only one prior surgery, and 46% had prior treatment with nitrosourea. Eighty-one percent of patients received ≥ 6 wafers. Eighty-one percent of patients with recurrent glioma receiving GLIADEL Wafers or matched placebo experienced an increased size of their recurrent tumor as determined by post-treatment imaging for at least 6 months based on ROI. Sixty-two percent of patients had ≥ 6 wafers. Eighty-one percent of patients with recurrent glioma receiving GLIADEL Wafers or matched placebo experienced an increased size of their recurrent tumor as determined by post-treatment imaging for at least 6 months based on ROI. Eighty-one percent of patients received ≥ 6 wafers. Eighty-one percent of patients with recurrent glioma receiving GLIADEL Wafers or matched placebo experienced an increased size of their recurrent tumor as determined by post-treatment imaging for at least 6 months based on ROI.

In Study 2, the population was 64% male, 92% White, and the median age was 59 years. Eighty-one percent of patients had a histologic subtype of glioblastoma as determined by central pathology review. Eighty-one percent of patients received ≥ 6 wafers. Eighty-one percent of patients with recurrent glioma receiving GLIADEL Wafers or matched placebo experienced an increased size of their recurrent tumor as determined by post-treatment imaging for at least 6 months based on ROI.

In Study 1, the population was 67% male and 97% White, and the median age was 55 years. Eighty-seven percent had a Karnofsky performance status ≥ 70 and 71% had a Karnofsky performance status ≥ 80. Eighty-seven percent had at least one subgaleal abscess of subdural empyema as determined by post-treatment paraventricular review. Thirty-eight percent of patients received ≥ 6 wafers and 79% received ≥ 6 wafers. Eighty-one percent of patients with recurrent glioma receiving GLIADEL Wafers or matched placebo experienced an increased size of their recurrent tumor as determined by post-treatment imaging for at least 6 months based on ROI.

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Meningitis occurred in 4% of patients with recurrent glioma receiving GLIADEL Wafers. Adverse reactions in GLIADEL Wafers-treated patients are shown in Table 2. The incidence of local adverse reactions is shown in Table 2.

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The incidence of seizures is shown in Table 4. The incidence of hydrocephalus, central venous catheterization, and meningitis are also shown in Table 4.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

GLIADEL Wafer can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. GLIADEL Wafer is not recommended in women who are known to be pregnant. It should be used in women of childbearing potential only when the potential benefit justifies the potential risk to the fetus.

**Warnings and Precautions**

Advise females of reproductive potential to use effective contraception for 6 months following implantation with GLIADEL Wafer.

**Nonclinical Toxicology**

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

**Patient Counseling Information**

Advise patients to report any new or change in their seizure activity [see Warnings and Precautions (5.1)]

**Nonclinical Pharmacology**

Carmustine concentrations delivered by GLIADEL Wafer in human brain tissue have been determined. Following wafer insertion, the mean whole brain concentration (Cmax) was 2.9 ± 1.2 ng/ml at 4 days after insertion.

**Pharmacokinetics**

Metabolism

Carmustine is metabolized both byaminolytically and metabolically.

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

The activity of GLIADEL Wafer is due to release of cytotoxic concentrates of carmustine, a DNA and RNA alkylating agent, into the tumor resection cavity. On exposure to the aqueous environment of the resection cavity, the amphoteric base of the carmustine alcohols, carmustine, carboxyphenoxypropane, and scissile side of the carmustine alcohols is formed.

#### 12.2 Pharmacodynamics

Carmustine concentrations delivered by GLIADEL Wafer in human brain tissue have been determined. Following wafer insertion, the mean whole brain Cmax (Cmax) was 2.9 ± 1.2 ng/ml at 4 days after insertion.

**Absorption**

Time from implantation to start of first new or worsening seizure.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenicity, Mutagenicity, Impairment of Fertility

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with GLIADEL Wafer. Carmustine, carboxyphenoxypropane, and monomeric components of the copolymer have been studied in specific test systems to evaluate certain biological effects.

### 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 Wafer or matched placebo wafers over the course of their tumor resection. Patients received post-operative radiation therapy (55 Gy delivered in 26 to 30 fractions over six weeks) starting three weeks after surgery. The primary endpoint was a reduction in the recurrence-free survival rate for patients with newly-diagnosed high-grade glioma, a secondary outcome measure, was the proportional reduction in the primary outcome measure, was the proportional reduction in the rate of progression.

**Efficacy Results**

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 improved in the GLIADEL arm, overall survival in the subset of patients with glioblastoma, where the outcome was more significant, was not significantly prolonging.

**Endpoints**

Endpoints include overall survival (OS), 6-month survival, and median survival.

### 15 REFERENCES


### 16 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 a flexible aluminum foil laminated pouch. The inner pouch is sterile and is designed to maintain product stability and protect the product from moisture. The outer pouch is a peelable overwrap. The outer surface of the outer pouch is not sterile.

**NDC for single dose treatment box:** 04512-23430-06

Store GLIADEL at or below 2°C to 8°C (40°F to 46°F).

### 20 PATIENT COUNSELING INFORMATION

**Drug Interactions**

Avoid drugs that may impair the liver.

**Nonclinical Pharmacology**

Carmustine was carcinogenic in rats and mice when delivered by GLIADEL Wafer. Carmustine was mutagenic in vitro (microsome assay), human lymphoid H9 assay, and dihydroethidium dihydrobioassay in vivo and in viva (Helen rat liver tumor assay, mouse mammary tumor assay). In rats, male rats, carmustine caused testicular atrophy at dosages of 8 mg/kg/day for eight weeks above 1.3 times the recommended human dose based on body surface area.

**Lactation**

No adequate and well-controlled studies in women who are breastfeeding have been conducted with GLIADEL Wafer. GLIADEL Wafer is a cytotoxic drug and special handling and disposal procedures should be considered.

**Informed Consent**

Special handling and disposal procedures should be considered.

**Nonclinical Pharmacology**

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