PACKAGE LEAFLET

Package leaflet: Information for the user

GLIADEL 7.7 mg Implant
Carmustine

Read all of this leaflet carefully before you receive GLIADEL Implants because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What GLIADEL Implants are and what they are used for
2. What you need to know before you receive GLIADEL Implants
3. How GLIADEL Implants are used
4. Possible side effects
5. How to store GLIADEL Implants
6. Contents of the pack and other information

1. What GLIADEL Implants are and what they are used for

GLIADEL Implants are a way to deliver the anti-cancer substance carmustine directly to the site of the brain tumour after the tumour has been removed by surgery. Carmustine belongs to a group of anticancer substances that act by slowing the growth of cancer cells in brain.

GLIADEL Implants can be used in combination with radiation for the treatment of brain tumours.

GLIADEL Implants have been shown to prolong survival in patients with brain tumours.

2. What you need to know before you receive GLIADEL Implants

Do not use GLIADEL Implants if you are allergic to carmustine or Polifeprosan 20.

Warnings and precautions

Following surgery to remove the brain tumour and insert the GLIADEL Implants, your doctor or surgeon will monitor you closely for known complications. In some cases your surgeon may need to re-operate (due to complications or recurrence of the tumour). Complications include:

- Convulsions (seizures)
- Infections in the brain (infections within the skull)
- Swelling of the brain due to accumulation of fluid
- Brain fluid leak
- Wound healing problems

Your doctor will monitor you closely in case you are taking steroids due to swelling or high fluid pressure in the brain.

Prior to inserting the implants your surgeon may need to close a canal in your brain to avoid the implants passing through it which could cause an accumulation of fluids within the skull.

After insertion of Gliadel Implants, medical imaging may detect swelling of the brain due to accumulation of fluid and inflammation caused by Gliadel Implants or tumour progression.

Other medicines and GLIADEL Implants
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine. GLIADEL Implants have not been studied in pregnant women. The active ingredient, carmustine, has been shown to adversely affect the development of unborn babies. GLIADEL Implants should not be used if you are pregnant or breast-feeding. Women of childbearing potential are advised to use effective contraception for 6 months after receiving GLIADEL implants. Men who have a female partner of childbearing potential should use contraception for 90 days after receiving GLIADEL implants.

Driving and using machines
Driving is not advisable after treatment. You must check with your doctor before driving or operating any tools or machines.

3. How GLIADEL Implants are used

GLIADEL Implants are for use in adults only

Your surgeon or pharmacist will ensure that the product is available for your surgery. After the surgeon removes your brain tumour, he or she inserts up to eight implants into the space the tumour once occupied. Your surgeon will decide how many implants to place into the cavity created by the removal of your brain tumour. The implants are placed in such a manner that they cover as much of the cavity as possible. After your surgery, the implants slowly dissolve over a 2 to 3 week period releasing carmustine directly to the surrounding cells.

If you have any further questions on the use of this product, ask your surgeon.

4. Possible side effects

Like all medicines, GLIADEL Implants can cause side effects, although not everybody gets them.

If you experience any of the following side effects as a **new event**, or if a side effect that you have **worsens**, tell your doctor immediately or go to the casualty department at your nearest hospital.

The most common adverse events observed during trials in either newly-diagnosed malignant glioma (brain tumour) (120 patients) or recurrent diagnosed malignant glioma (110 patients) are presented below.

The following four categories of side effects are possibly related to treatment with GLIADEL Implants.

1. Seizures were very common. Most of them had a mild to moderate intensity and occurred within 5 days of the surgical treatment.

2. Brain swelling was very common. The development of brain swelling could necessitate a new surgical intervention either to remove the implants or the remnants of the implants.

3. Mild to severe **wound healing problems** were very common.

4. Infections in the brain (infections within the skull) such as meningitis and abscess(es) (localised collections of pus) were common.

The following side effects were seen in the patients during the trials. They were similar to those encountered by patients who have surgery for their brain cancer without the insertion of GLIADEL Implants.

Very common: may affect more than 1 in 10 people

- Psychiatric disorders
Depression

- Nervous system disorders
Weakness, especially on one side of the body; convulsion (fits); confusion; headache; swelling of the brain; somnolence (drowsiness); problems with speech

- **Vascular disorders**
Vein inflammation

- Gastrointestinal disorders (stomach and intestinal related disorders)
Nausea (feeling sick); vomiting; constipation

- Skin and subcutaneous (tissue under the skin) disorders
Rash; hair loss

- Renal (kidney) and urinary disorders
Infection of the urinary tract

- General disorders and administration site conditions
A worsening of your condition; infection; headache; feeling of weakness; fever or pain; abnormal (slow) healing of the surgical wound

Common: may affect up to 1 in 10 people

- Blood and lymphatic (immune) system disorders

Reduction in red blood cells which can make the skin pale and cause weakness and breathlessness; reduction in blood platelets which increases the risk of bleeding; increase in white blood cells

- Endocrine disorders (hormonal disorders)

Diabetes mellitus (abnormally high sugar level in blood)

- Metabolism and nutrition disorders

Peripheral oedema (excess fluid in the arms and legs); low blood levels of sodium which can cause tiredness and confusion; muscle twitching, fits or coma; high blood sugar levels; low blood levels of potassium which can cause muscle weakness, twitching or abnormal heart rhythm

- Psychiatric disorders

Changes in your personality; excessive anxiety; abnormal thinking; hallucinations; insomnia (little or poor sleep)

- Nervous system disorders

Amnesia (loss of memory); an increase in the blood pressure in the skull due to abnormal build up of fluid; paralysis of the face; lack of coordination; diminished sensitivity to stimulation; abnormal burning or prickling sensation; problems with walking; dizziness; epileptic seizures (fits); tremor (small shaking movements); meningitis (inflammation of the brain); abscess (localised collection of pus); loss of consciousness

- Eye disorders

Blurred or abnormal vision; swelling of the eye lining; eye pain

- Vascular disorders

Bleeding; high or low blood pressure

- Respiratory disorders (lung related disorders)

Lung infection or pneumonia which causes breathlessness, cough and raised temperature

- Gastrointestinal disorders (stomach and intestinal related disorders)

Yeast infection of the mouth; diarrhoea; constipation; faecal incontinence (uncontrolled bowel movements); difficulty in swallowing; bleeding in the stomach or in bowels

- Skin and subcutaneous (tissue under the skin) disorders

Rash

- Muscle, skeletal and soft tissue related disorders

General infection

- Renal (kidney) and urinary disorders
Urinary infections; urinary incontinence

- General disorders and administration site conditions
Abdominal, back and chest pain; swelling of the face; abscess (localised collection of pus); accidental injury; allergic reaction; neck pain and infection in the blood stream

Uncommon side effects (between 1 and 10 patients in every 1000)

Injury, poisoning and procedural complications
Pneumocephalus (air accumulation at the implant site)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet.
You can also report side effects directly via the HPRA Pharmacovigilance Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store GLIADEL Implants

Keep this medicine out of the sight and reach of children.

Store in a freezer at or below -20°C.

Unopened outer sachets may be kept at a temperature of not more than 22°C for a maximum of six hours.

The product may be refrozen only once if the sachets have been unopened and kept for a maximum of 6 hours at a temperature of not more than 22°C. After the refreezing, the product should be used within 30 days.

Do not use GLIADEL Implants after the expiry date which is stated on the outer carton and/or the sachet. The expiry date refers to the last day of that month. Your surgeon or hospital pharmacist will check the expiry date before implants are used.

6. Contents of the pack and other information

What GLIADEL Implants contain

- The active substance is carmustine. Each implant contains 7.7 mg of carmustine.
- The other ingredient is polifeprosan 20.

What GLIADEL Implants look like and contents of the pack

GLIADEL Implants are available in boxes containing eight implantable wafers. These wafers are off-white to pale yellow flat discoid implants. Each wafer is individually packaged in an aluminium foil laminate sachet.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
CLINIGEN HEALTHCARE B.V.
Schiphol Boulevard 359
WTC Schiphol Airport, D Tower 11th floor
1118BJ Schiphol
The Netherlands

Manufacturer 1 (Importer)
ALMAC PHARMA SERVICES (IRELAND) LIMITED
Finnabair Industrial Estate,
Dundalk,
Co. Louth, A91 P9KD
Ireland
Tel: +353 42 932 0718
Fax: +353 42 932 0718

Manufacturer 2 (Importer)
ALMAC PHARMA SERVICES LIMITED
Seagoe Industrial Estate, Portadown
Craigavon, Northern Ireland, BT63 5UA
United Kingdom
Tel: +44 (0)28 3836 3363
Fax: +44 (0)28 3836 3300

Manufacturer 3 (Importer)
Clinigen Clinical Supplies Management GmbH
Am Kronberger Hang 3
65824 Schwalbach am Taunus
Germany

This leaflet was last revised in xx/2025

The following information is intended for medical or healthcare professionals only

PROFESSIONAL INFORMATION LEAFLET

1. NAME OF THE MEDICINAL PRODUCT

GLIADEL 7.7 MG IMPLANT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each implant contains 7.7 mg of carmustine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Implant
Off-white to pale yellow flat discoid implant.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GLIADEL Implant is indicated for the treatment of adult patients with newly-diagnosed high-grade malignant glioma as an adjunct to surgery and radiation.

GLIADEL Implant is indicated as an adjunct to surgery for the treatment of adult patients with recurrent histologically proved glioblastoma multiforme and for whom surgical resection is indicated.

4.2 Posology and method of administration

Posology

For intralesional use only.

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.

Paediatric population

The safety and efficacy of GLIADEL Implant in children under 18 years of age have not been established. No data are available.

Method of administration

It is recommended that a maximum of eight implants be placed if the size and shape of the resection cavity allows it. Implants broken in half may be used, but implants broken in more than two pieces should be discarded in the dedicated biohazard waste containers (see section 6.6).

It is recommended that the placement of the implants should be directly from the product's inner sterile packaging into the resection cavity. Oxidised regenerated cellulose may be placed over the implants to secure them to the cavity surface (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance carmustine or to any of the excipients of GLIADEL Implant.

4.4 Special warnings and precautions for use

Patients undergoing craniotomy for glioblastoma and implantation of GLIADEL Implant should be monitored closely in view of known complications of craniotomy which includes convulsions, intracranial infections, abnormal wound healing, and brain oedema and pneumocephalus (see section 4.8). Cases of intracerebral mass effect unresponsive to corticosteroids have been described in patients treated with GLIADEL Implant, including one case leading to brain herniation. Careful monitoring of GLIADEL Implant-treated patients for cerebral oedema/intracranial hypertension with consequent steroid use is warranted (see section 4.8). CSF leak was more common in GLIADEL Implant-treated patients. Attention to a water-tight dural closure and local wound care is indicated (see section 4.8).
Changes of wall of cerebral blood vessels located close to Gliadel wafer, including cases of aneurysms leading to cerebral bleeding several months after Gliadel wafer implantation, have been described. Gliadel wafers implantation adjacent to large cerebral vessels should be avoided.

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 Implant or its remnants.

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

Computed tomography and magnetic resonance imaging 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 Implants or tumour progression.

Women of child-bearing potential should use effective contraception for at least 6 months after receiving GLIADEL Implant.

Male patients with female partners of child-bearing potential should be advised to use effective contraception for at least 90 days after receiving GLIADEL Implant.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no studies of GLIADEL Implant in pregnant women and no studies assessing the reproductive toxicity of GLIADEL Implant.

Carmustine, the active component of GLIADEL Implant, when administered systemically, can have genotoxic effects and can adversely affect foetal development (see section 5.3). GLIADEL Implant, therefore, is not recommended during pregnancy and in women of childbearing potential not using contraception. Women of child-bearing potential should use effective contraception for at least 6 months after receiving GLIADEL Implant.

Male patients with female partners of child-bearing potential should be advised to use effective contraception for at least 90 days after receiving GLIADEL Implant. If the use of GLIADEL Implant during

pregnancy is still considered necessary, the patient should be informed of the potential risk to the foetus. In case of patients getting pregnant after receiving GLIADEL Implant, genetic advice should be sought.

Breastfeeding:

It is not known if GLIADEL Implant components are excreted in human milk. Since some drugs are excreted in human milk and because of the potential risk of serious adverse reactions of carmustine in nursing infants, breast-feeding is contra-indicated.

Fertility:

No impairment of fertility studies have been conducted with GLIADEL Implants.

4.7 Effects on ability to drive and use machines

GLIADEL Implant has no influence on the ability to drive and use machines. However, craniotomy and GLIADEL Implant may cause nervous system and vision abnormalities. Therefore patient should be warned of the potential effect of these events on the ability to drive or to use machines.

4.8 Undesirable effects

The spectrum of undesirable effects observed in patients with newly-diagnosed high-grade malignant glioma and recurrent malignant gliomas was generally consistent with that encountered in patients undergoing craniotomy for malignant gliomas.

Very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100) adverse reactions reported in patients receiving GLIADEL Implant during the clinical trials are listed below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Primary Surgery
The following data are the most frequently occurring adverse reactions observed in 5% or more of the 120 newly-diagnosed malignant glioma patients receiving GLIADEL Implant during the trial.

Common Adverse Reactions Observed in ≥ 5% of Patients Receiving GLIADEL Implant at Initial Surgery

System Organ Class		Adverse Reactions
Endocrine disorders	common	Diabetes mellitus
Psychiatric disorders	very common	Depression
	common	Personality disorder, anxiety, thinking abnormal, hallucinations, insomnia
Nervous system disorders	very common	Hemiplegia, convulsion, confusion, brain oedema, aphasia, somnolence, speech disorder

System Organ Class		Adverse Reactions
	common	Amnesia, intracranial pressure increased, personality disorder, anxiety, facial paralysis, neuropathy, ataxia, hypoesthesia, paresthesia, thinking abnormal, abnormal gait, dizziness, grand mal convulsion, hallucinations, insomnia, tremor
Eye disorders	common	Conjunctival oedema, abnormal vision, visual field defect
Vascular disorders	very common	Thrombophlebitis
	common	Haemorrhage
Respiratory, thoracic and mediastinal disorders	common	Pulmonary embolism
Infections and infestations	common	Pneumonia
Gastrointestinal disorders	very common	Nausea, vomiting, constipation
	common	Diarrhoea
Skin and subcutaneous tissue disorders	very common	Rash, alopecia
Renal and urinary disorders	common	Urinary tract infection, urinary incontinence
General disorders and administration site conditions	very common	Aggravation reaction, headache, asthenia, infection, fever, pain, healing abnormal
	common	Abdominal pain, back pain, face oedema, chest pain, abscess, accidental injury, peripheral oedema

Intracranial hypertension was present in more GLIADEL Implant-treated patients than in placebo patients (9.2% vs. 1.7%). It was typically observed late, at the time of tumour recurrence, and was unlikely to be associated with GLIADEL Implant use (see section 4.4).

CSF leak was more common in GLIADEL Implant-treated patients than in placebo patients. However intracranial infections and other healing abnormalities were not increased (see section 4.4).

Surgery for Recurrent Disease

The following post-operative adverse reactions were observed in 4% or more of the 110 patients receiving GLIADEL Implant at recurrent surgery in a controlled clinical trial. Except for nervous system effects, where there is a possibility that the placebo implants could have been responsible, only reactions more common in the GLIADEL Implant group are listed. These adverse reactions 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 Reactions in ≥4% of Patients Receiving GLIADEL Implant at Recurrent Surgery

System Organ Class		Adverse Reactions
Blood and lymphatic system disorders	common	Anaemia
Metabolism and nutrition disorders	common	Hyponatraemia

System Organ Class		Adverse Reactions
Nervous system disorders	very common	Convulsion, hemiplegia, headache, somnolence, confusion
	common	Aphasia, stupor, brain oedema, intracranial pressure increased, meningitis or abscess
Vascular disorders	common	Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	common	Pulmonary embolism
Infections and infestations	common	Pneumonia, oral candidiasis
Gastrointestinal disorders	common	Nausea, vomiting
Skin and subcutaneous tissue disorders	common	Rash
Renal and urinary disorders	very common	Urinary tract infection
General disorders and administration site conditions	very common	Fever, healing abnormal
	common	Infection, pain

The following adverse reactions, not listed in the table above, were reported in patients treated with GLIADEL Implant in all studies. The reactions listed were either not present pre-operatively or worsened post-operatively. Whether GLIADEL Implant caused these events cannot be determined.

Adverse Reactions in Patients Receiving GLIADEL Implant

System Organ Class		Adverse Reactions
Blood and lymphatic system disorders	common	Thrombocytopenia, leukocytosis
Metabolism and nutrition disorders	common	Hyponatraemia, hyperglycaemia, hypokalaemia
Nervous system disorders	common	Hydrocephalus, ataxia, dizziness, hemiplegia, coma, amnesia, diplopia
	uncommon	Cerebral haemorrhage, cerebral infarct
Psychiatric disorders	common	Depression, abnormal thinking, insomnia, paranoid reaction
Eye Disorders	common	Visual defect, eye pain
Cardiac and vascular Disorders	common	Hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	common	Infection, aspiration pneumonia
Gastrointestinal disorders	common	Diarrhoea, constipation, dysphagia, gastrointestinal haemorrhage, faecal incontinence
Skin and subcutaneous tissue disorders	common	Rash
Musculoskeletal and connective tissue disorders	common	Infection
Renal and urinary disorders	common	Urinary incontinence
General disorders and administration site conditions	common	Peripheral oedema, neck pain, accidental injury, back pain, allergic reaction, asthenia, chest pain, sepsis
Injury, poisoning and procedural complications	uncommon	Pneumocephalus

Cases of air accumulation at the implant site, sometimes associated with neurological symptoms (hemiplegia, aphasia, seizures) have been reported with Gliadel.

The following four categories of adverse reactions are possibly related to treatment with GLIADEL Implant.

Seizures:

In the initial surgery trial, the incidence of seizures within the first 5 days after implantation was 2.5% in the GLIADEL Implant group.

In the surgery for recurrent disease trial, the incidence of post-operative seizures was 19% in patients receiving GLIADEL Implant. 12/22 (54%) of patients treated with GLIADEL Implant 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 Implant.

Brain Oedema:

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 Implant or its remnants (see section 4.4).

Healing Abnormalities:

The following healing abnormalities have been reported in clinical trials of GLIADEL Implant: wound dehiscence, delayed wound healing, subdural, subgaleal or wound effusions, and cerebrospinal fluid leak.

In the initial surgery trial, cerebrospinal fluid leaks occurred in 5% of GLIADEL Implant recipients. During surgery, a water-tight dural closure should be obtained to minimise the risk of cerebrospinal fluid leak (see section 4.4)

Intracranial Infection:

In the initial surgery trial, the incidence of brain abscess or meningitis was 5% in patients treated with GLIADEL Implant.

In the recurrent setting, the incidence of brain abscess or meningitis was 4% in patients treated with GLIADEL Implant.

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 cysts is possible after resection of a malignant glioma.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, ATC Code: L01AD01

Preclinical data

GLIADEL Implant delivers carmustine directly into the surgical cavity created after tumoural 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 Implant diffuses into the surrounding brain tissue and produces an antineoplastic effect by alkylating DNA and RNA.

Carmustine is spontaneously both degraded and metabolised. The alkylating moiety thus produced and presumed to be chloroethyl carbonium ion, leads to the formation of irreversible DNA cross-links.

The tumourcidal activity of GLIADEL Implant is dependent on release of carmustine into 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_2 in animals.

Clinical data

Primary surgery
In a randomised, double-blind, placebo-controlled clinical trial in 240 adults with newly-diagnosed high grade malignant glioma undergoing initial craniotomy for tumour resection median survival increased from 11.6 months with placebo to 13.9 months with GLIADEL Implant (p-value 0.079, unstratified log-rank test) in the original study phase. 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). The hazard ratio for GLIADEL Implant was 0.77 (95% CI: 0.57 to 1.03). In the long term follow-up phase, patients still alive at the completion of the original phase were followed for up to at least three years or until death. Median survival increased from 11.6 months with placebo to 13.9 months with GLIADEL Implant (p-value <0.05, log-rank test). The hazard ratio for GLIADEL Implant treatment was 0.73 (95% CI: 0.56 to 0.95).

Surgery for Recurrent Disease
In a randomised, double-blind, placebo-controlled clinical trial in 145 adults with recurrent glioblastoma (GBM), GLIADEL Implant prolonged survival in these patients. Ninety-five percent of the patients treated with GLIADEL Implant received 7 to 8 implants.

The six-month survival rate was 36% (26/73) with placebo compared to 56% (40/72) with GLIADEL Implant treatment. Median survival of GBM patients is 20 weeks with placebo versus 28 weeks with GLIADEL Implant treatment.

5.2 Pharmacokinetic properties

The absorption, distribution, metabolism, and excretion of the copolymer in humans is unknown. Carmustine concentrations delivered by GLIADEL Implant in human brain tissue have not been determined. Plasma levels of carmustine after GLIADEL Implant implantation cannot be assayed. In rabbits that had implants containing 3.85% carmustine placed, carmustine is not detected in the blood or cerebrospinal fluid.

Following an intravenous infusion of carmustine at doses ranging from 30 to 170mg/m^2, the average terminal half-life, clearance, and steady-state volume of distribution are 22 minutes, 56mL/min/kg, and 3.25L/kg, respectively. Approximately 60% of the intravenous 200mg/m^2 dose of ^{14}C-carmustine is excreted in the urine over 96 hours and 6% is expired as CO_2.

GLIADEL Implants are biodegradable in 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.

5.3 Preclinical safety data

No carcinogenicity, mutagenicity, embryo-foetal toxicity, pre- and post-natal toxicity and impairment of fertility studies have been conducted with GLIADEL Implants.

Carmustine, the active component of GLIADEL Implant, when administered systemically, has embryotoxic, teratogenic, genotoxic and carcinogenic effects and can cause testicular degeneration in several animal models.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Polifeprosan 20

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

4 years

6.4 Special precautions for storage

Store in a freezer at or below -20°C.

Unopened outer sachets may be kept at a temperature of not more than 22°C for a maximum of six hours.

The product may be refrozen only once if the sachets have been unopened and kept for a maximum of 6 hours at a temperature of not more than 22°C. After refreezing, the product should be used within 30 days.

6.5 Nature and contents of container

GLIADEL Implant is available in a box containing eight implants. Each implant is individually packaged in two aluminium foil laminate sachets.

6.6 Special precautions for disposal and other 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 indicated, any implant or implant remnant should be handled as a potentially cytotoxic agent. Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

GLIADEL Implants should be handled with care. The sachets containing GLIADEL Implants should be delivered to the operating room and remain unopened until ready to place the implants in the resection cavity. Only the outside surface of the outer sachet is not sterile. In any case, if an implant is dropped, it should be discarded accordingly.

<u>Instructions for opening sachets containing the implant</u>:

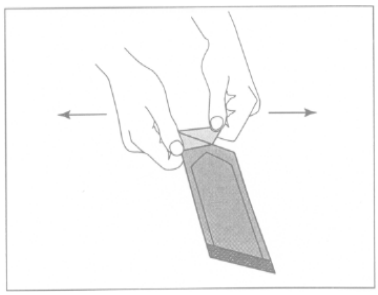

Illustration 1: To open the outer sachet, locate the folded corner and slowly pull in an outward motion.

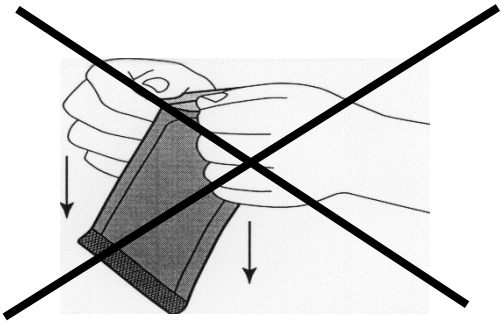

Illustration 2: Do not pull in a downward motion rolling knuckles over the sachet. This may exert pressure on the implant and cause it to break.

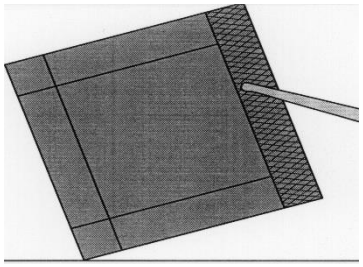

Illustration 3: The implant and the inner sachet should be handled with surgical gloves. Remove the inner sachet by grabbing with the aid of forceps and pulling upward.

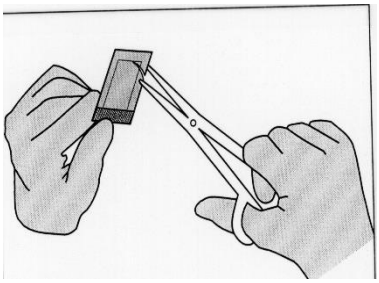

Illustration 4: To open the inner sachet, gently hold it and cut in an arc-like fashion around the implant.

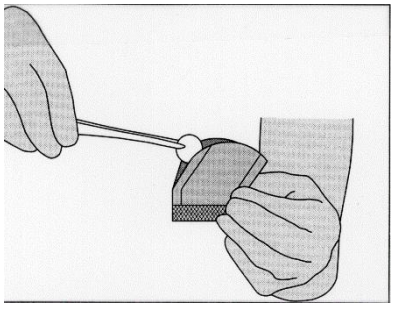

Illustration 5: To remove the implant, gently grasp the implant with the aid of forceps and place it directly into the resection cavity. The forceps must be kept for the manipulation of the implants only.

In any case, if an implant is dropped, it should be discarded accordingly.

Once the tumour is resected, tumour pathology is confirmed and haemostasis is obtained, up to eight 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 the dedicated biohazard waste containers.

Oxidised regenerated cellulose may be placed over the implants to secure them to the cavity surface. After placement of the implants, the resection cavity should be irrigated and the dura closed in a watertight fashion.

Any unused product or waste material should be disposed of in accordance with local requirements for biohazardous waste.

7. MARKETING AUTHORISATION HOLDER

CLINIGEN HEALTHCARE B.V.
Schiphol Boulevard 359
WTC Schiphol Airport, D Tower 11th floor
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8. MARKETING AUTHORISATION NUMBER

PA 22701/003/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 07/07/1999
Date of last renewal: 10/12/2008

10. DATE OF REVISION OF THE TEXT

November 2025