

Analysis of Reported Adverse Events for Carmustine Delivered Systematically versus Locally by Gliadel for Malignant Brain Tumors

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AUTHOR BIO

David Hu is a ninth grader at Acton-Boxborough Regional High School in Massachusetts. Outside of school, he enjoys working on research projects, as well as learning more about biology, chemistry, and medicine. He is an active Boy Scout in his local area, and he loves playing piano and tennis. Besides all of this, he is motivated in volunteer work in his community, and is working toward the Congressional Award. His long-term goal is to pursue a career in medicine or biomedical research, where he can contribute to developing improved treatments and advancing patient care.

ABSTRACT

Carmustine and Carmustine-loaded Gliadel wafers are two chemotherapeutic treatments commonly used in the management of malignant brain tumors, differing primarily in their methods of drug delivery. These two treatment methods use the same chemotherapeutic agent. However, while systemic Carmustine involves widespread distribution, Gliadel wafers provide localized treatment directly at the tumor site, potentially reducing systemic toxicity. This study aims to compare the adverse effect profiles of Carmustine and Gliadel to evaluate differences in safety and clinical risk. The data were primarily taken from the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database. Several important findings were identified, such as the significant difference between the adverse effects of the two drugs. For example, Carmustine displayed a significantly lower percentage of neurologically related adverse effects than Gliadel, but a significantly higher percentage for systemic adverse effects. These systemic effects include bone marrow, hematologic and lymphatic abnormalities. These findings support the conclusion that Carmustine can lead to severe systemic toxicity, while Gliadel is more frequently associated with localized infections and swelling in the brain region.

Keywords: *Adverse Events, Brain Tumor, Cancer, Carmustine, Chemotherapy, Drug Delivery, Gliadel, Infection, Malignancy*

INTRODUCTION

Malignant brain tumors are highly aggressive and are hard to treat. Chemotherapy is a commonly used treatment. However, the blood–brain barrier limits drug delivery, so treatments must balance effectiveness with toxicity; this is because systemic chemotherapy is often administered at a high dose to achieve efficacy, but also results in systemic side effects. Traditional chemotherapeutics block cell proliferation, which is meant to halt tumor growth, but this activity can also adversely affect healthy cells. The anti-proliferative effects of chemotherapeutics are the direct cause of their side effects.

Carmustine is a powerful alkylating agent that causes DNA cross-linking and DNA breakage, thereby inhibiting proper DNA replication and blocking cell division. This drug is administered via systemic injection. However, this can result in systemic distribution and off-target effects on healthy cells. In an attempt to prevent these systemic effects, Gliadel wafers have been developed as an alternative treatment option. These wafers are primarily composed of Carmustine embedded in a degradable polymer matrix; instead of Carmustine being administered via injection, the Gliadel wafer is surgically implanted and releases Carmustine in a controlled manner directly where it is needed. Gliadel is implanted into the tumor recession cavity after tumor removal, and releases the chemotherapeutic over the course of 2-3 weeks. This approach has both benefits and drawbacks, which this paper seeks to explore.

Increasing survival time alone, without stopping tumor progression or preventing adverse effects, is not sufficient; quality of life after treatment matters. Adverse effects influence treatment choice, patient compliance, patient outcomes, and long-term survival. However, there is limited direct comparison of real-world outcomes using large adverse event databases like FAERS (U.S. Food and Drug Administration, 2023; U.S. Food and Drug Administration, 2026). The FAERS is a web-based, searchable, comprehensive database of all adverse events reported to FDA for over-the-counter and prescription pharmaceuticals in the United States. Adverse events are reported to the FAERS database by the pharmaceutical industry, healthcare providers, and consumers; the pharmaceutical industry is a mandatory reporter, while healthcare providers and consumers can also make voluntary reports. FAERS is unique in that it provides insight into how drugs behave in real-world use, and it allows public participation and transparency. The objective of this research study is to examine trends in adverse event reporting for Carmustine injections and Gliadel wafers using the FAERS database, supplemented by reports on other public medical databases.

METHODS

Data and definitions were collected from five public medical databases: FAERS (U.S. Food and Drug Administration, 2026); DailyMed (National Library of Medicine, 2021); Drugs@FDA (U.S. Food and Drug Administration, 2009); American Hospital Formulary Service (American Society for Health System Pharmacists, 2025a; American Society for Health System Pharmacists, 2025b); and WHO Vigibase (World Health Organization, 2026). Specifically, the databases were searched using keywords of “Carmustine” and “Gliadel”, in order to find adverse effects on both treatments and possible comparisons between the two treatments. FAERS was used primarily for data gathering, although medicine reviews and other databases were consulted, because these additional sources provided valuable background information.

After all the adverse effects for both types of treatments were compiled, the most common adverse effects were analyzed to determine the types and seriousness of reported side effects for Carmustine and Gliadel, as well as the benefits and consequences of using each treatment. The chi-square test was used to determine whether observed differences were significant; a cutoff of $p < 0.05$ was used to establish significance. The chi-square test is designed to determine whether any observed differences between groups are due to random chance or reflect a statistically significant association. Because the study aimed to assess whether there was a relationship between categorical variables (rather than measure means or averages), the chi-square test was the most suitable statistical method.

FINDINGS FROM FAERS

After examining the FAERS (FDA Adverse Event Reporting System), a few conclusions can be made. The FAERS database includes detailed records of adverse events, as well as the drugs that are known to cause them. When searched using the keywords of “Carmustine” and “Gliadel,” the FAERS database generated two data sets of the case count by each year (the number of reported adverse event cases per year), as well as the most common side effects of Carmustine and Gliadel (Figures 1-2).

Figure 1.

Percent reported cases involving each type of effect for Gliadel wafers.

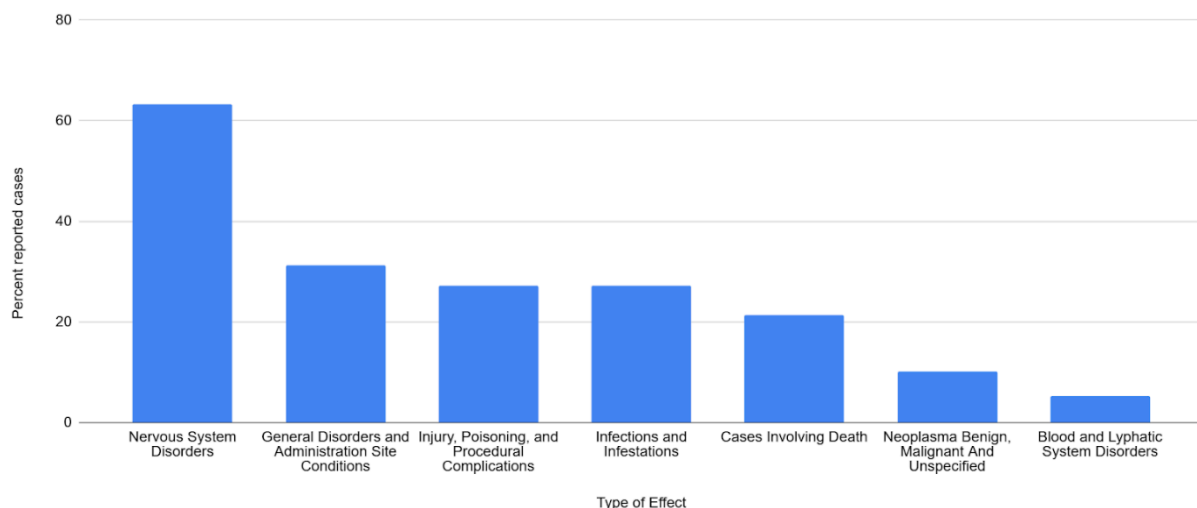
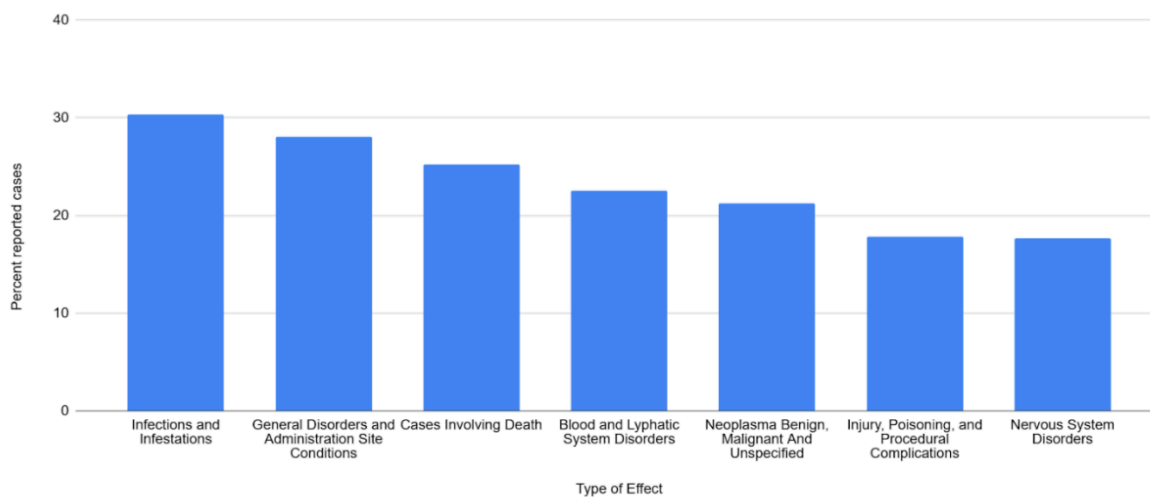


Figure 2.

Percent reported cases involving each type of effect for Carmustine



One particular difference between the graphs of Carmustine and Gliadel was that Carmustine had many more patients who reported adverse events; this likely reflects the fact that more patients had undergone treatment with Carmustine than with Gliadel. This is because Carmustine is more widely used and does not need to be surgically implanted. The database also reported total cases, serious cases, and death cases. One important thing to note is that the death reports do not necessarily mean that the usage of the drug caused the death, but the death occurred somewhere along that patient's life.

FAERS (U.S. Food and Drug Administration, 2023; U.S. Food and Drug Administration, 2026) contains voluntarily reported adverse events, so rare or localized treatments like Gliadel wafers often have little or no data specifically on patient counts and demographics. However, it did contain well-organized lists of adverse effects for both, as well as the specific numbers of patients that experienced those effects. Also, it was observed that adverse effects for Gliadel are less frequently reported compared to Carmustine. Carmustine is widely used systemically, so other medical websites were included. This study primarily focuses on the leading adverse effects that occurred in both types of treatments.

For example, when examining reported adverse events for the Gliadel wafer, systemic spread such as respiratory damage. The percent of adverse effects that involved respiratory damage was 10% lower for Gliadel than for Carmustine, which can distribute throughout the body. However, a far greater percentage of the adverse effects associated with Gliadel are nervous system disorders. The percentage of reported adverse events caused by respiratory disorders for Carmustine vs. Gliadel was calculated. In Carmustine, it was $1,021/5,765 = 17.7\%$, and Gliadel was $55/667 = 8.2\%$. So in conclusion, for respiratory disorders, a reported adverse event for Carmustine is twice as likely to be respiratory related as it is for Gliadel.

Then, the percentage of reported adverse events caused by blood disorders was calculated. Myelosuppression was also compared between Carmustine and Gliadel. Carmustine was $1,298/5,765 = 22.5\%$, but Gliadel was $35/667 = 5.2\%$. So, for blood disorders, a reported adverse event for Carmustine is four times as likely to be blood related as it is for Gliadel.

However, when the differences in infection rates were being calculated, the results were closer. Here, a tradeoff occurs. Gliadel is much more likely to cause infections in the brain, because the implantation of Gliadel involves opening up the brain. However, Carmustine is much more likely to cause infections throughout the body, because Carmustine suppresses the bone marrow's production of white blood cell..Carmustine was calculated to be $1,747/5,765 = 30.3\%$ and Gliadel was $181/667 = 27.1\%$.

Because these values were so similar, it was necessary to determine if Gliadel demonstrated a significantly better percentage than Carmustine or not. Using the chi-square test (Table 1), it was shown that this difference is statistically significant. The chi-square analysis was performed by comparing the actual number of infections reported for Gliadel to the expected number of infections if Gliadel and Carmustine had identical percentages of adverse events involving infections. If the two treatments were identical, it would be expected that 30.3% of reported adverse events for Gliadel would involve infection; this translates to $0.303 \times 667 = 202$ adverse events involving infection out of a total of 667 reported adverse events. This expected number was compared to the observed number of 181 adverse events involving infection out of a total of 667 reported adverse events. The calculated chi-square value was 5.691, which translates to a significance level of $p < 0.025$ at one degree of freedom. So, the difference between Carmustine and Gliadel in terms of percent adverse events leading to infection (30.3% for Carmustine versus 27.1% for Gliadel) was statistically significant.

Table 1.

Chi-square analysis of percent adverse events involving infection for Gliadel vs. Carmustine

Infection vs No Infection	Expected Number	Observed Number	$(\text{Observed} - \text{Expected})^2 / \text{Expected}$
Infection	202	181	2.183168
No Infection	445	486	3.777528
Total	667	667	5.960696

Lastly, the percentage of reported adverse events involving death for Carmustine vs. Gliadel was calculated. Carmustine was $1,453/5,765 = 25.2\%$, and Gliadel was $142/667 = 21.3\%$. Using the chi-square test (Table 2), it was found that these statistics are significantly different. The chi-square analysis was performed by comparing the actual number of deaths reported for Gliadel to the expected number of deaths if Gliadel and Carmustine had identical percentages of adverse events involving death. If the two treatments were identical, it would be expected that 25.2% of reported adverse events for Gliadel would involve death; this translates into $0.252 \times 667 = 168$ adverse events involving death out of 667 total adverse events. This expected number was compared to the observed number of 142 deaths out of 667 total adverse events. The calculated chi-square value was 5.378, which translates into a significance level of $p < 0.025$ for one degree of freedom. So, the difference between Carmustine and Gliadel in terms of

percent adverse events leading to death (25.2% for Carmustine versus 21.3% for Gliadel) was statistically significant.

Table 2.

Chi-square analysis of percent adverse events involving death for Gliadel vs. Carmustine

Death vs. No Death	Expected Number	Observed Number	(Observed-Expected)^2/Expected
Death	168	142	4.023809524
No Death	499	525	1.354709419
TOTAL	667	667	5.378518943

So, in all, the Gliadel wafer demonstrated, in general, a lower count of certain deadly adverse effects that were exhibited in Carmustine treatment, and had a statistically significant decrease as well, in blood disorders and death from adverse effects.

The most common adverse effect category for Gliadel wafers was Nervous System Disorders, but for Carmustine it was Infections and Infestations. Over 50% of adverse effects reported for Gliadel wafers were Nervous System Disorders, but less than 20% of adverse effects reported for Carmustine were Nervous System Disorders. Over 30% of adverse effects reported for Carmustine were Infections and Infestations, but less than 30% of adverse effects reported for Gliadel were Infections and Infestations.

FINDINGS FROM DAILYMED

DailyMed is a website primarily designed for drug review, packaging, and labeling, all documented in a formal database. An example from one medical package (National Library of Medicine, 2019) described adverse effects for both Carmustine and Gliadel wafer treatments. For Carmustine, the medical package described Myelosuppression and Pulmonary Toxicity. The drug delivered systemically may cause suppression of marrow function, which may cause or contribute to bleeding and infections. Also, Carmustine for injection causes dose related toxicity, and patients receiving greater than 1400 mg/m² cumulative dose are at significantly higher risk than those receiving a lower dose; this is typical of the increased risk of adverse events occurring with higher concentration of chemotherapeutic drugs.

Notably, DailyMed revealed adverse effects that were not immediately apparent from the FAERS database: according to DailyMed, delayed pulmonary toxicity can occur years after Carmustine treatment, and can result in death, particularly in patients treated in childhood. For Gliadel, the DailyMed database had a section on adverse effects on the description of the drug package. Seizures, Intracranial hypertension, Impaired neurosurgical wound healing, Meningitis, Wafer migration, and Embryo-fetal toxicity were documented for Gliadel wafers. These are clearly unique adverse effects to both Carmustine and Gliadel, but do not consider the possible benefits of both.

FINDINGS FROM DRUGS@FDA

Drugs@FDA (U.S. Food and Drug Administration, 2009) had entries for drug warnings for both chemotherapeutics as well. For example, a packaging insert for Gliadel (U.S. Food and Drug Administration, 2018) describes the adverse effects of the Gliadel wafer implant. Specifically, it described a few adverse effects such as Seizures, Intracranial Hypertension, Impaired Neurosurgical wound healing, Meningitis, Wafer migration, and Embryo-fetal toxicity; these findings are consistent with those reported in DailyMed. Drugs@FDA also had specific data about how many patients were inflicted with each adverse effect. 37% of patients got Seizures, 23% got Brain Edema, with common follow ups being Impaired Neurosurgical Wound Healing.

However, a packaging insert for Carmustine from Drugs@FDA (U.S. Food and Drug Administration, 2017) also described the adverse effects for Carmustine (in the normal injection form that does not need surgery to implant). Most adverse effects were not in the brain, but in the body, as expected. The main adverse effects were Pulmonary toxicity, Hematologic toxicity, Gastrointestinal Toxicity, Hepatotoxicity, and Nephrotoxicity. These different reported toxicities were expected, due to the Carmustine's tendency to spread all across the body during treatment. This shows the trade off between Carmustine and Gliadel. One offers targeted treatment but with increased risk of infection around the brain, while the other offers less infection around the brain, but damage from systemic distribution.

FINDINGS FROM AHFS DRUG INFORMATION

AHFS Drug Information had two articles describing Chlorambucil, which is an alkylating agent, as well as Carmustine, which is the drug being researched in this study. By consulting both sources, it is noted that the adverse effects in Chlorambucil are very similar to the ones found in Carmustine. The adverse effects are listed below, and even though bone marrow suppression is not on the list of adverse effects, the drug information site separately states that patients undergoing Chlorambucil and Carmustine treatment may experience a significantly lowered blood cell count in bone marrow (American System of Health-System Pharmacists, 2025a; American System of Health-System Pharmacists, 2025b). However, it is important to note that these two medicines are different, although they do belong to the same class of alkylating agents.

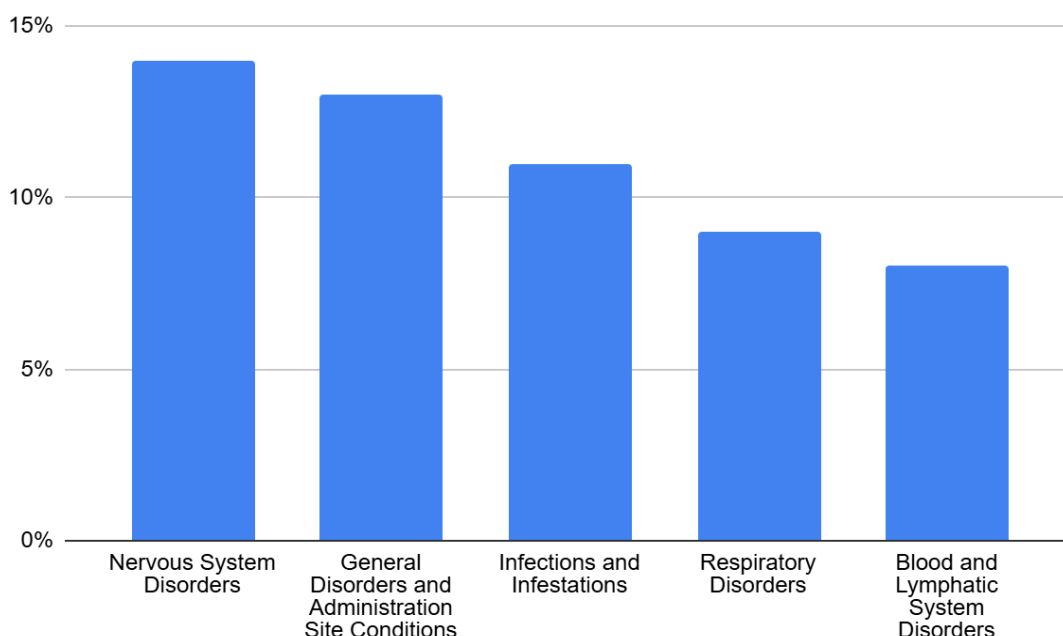
Common side effects for Chlorambucil (American System of Health-System Pharmacists, 2025b) included nausea, vomiting, sores in the mouth and throat, tiredness, and missed menstrual periods for girls and women. However, for Carmustine (American System of Health-System Pharmacists, 2025a), the adverse effects were similar. These included nausea, vomiting, headache, loss of balance or coordination, pale skin, fainting, dizziness, fast or irregular heartbeat, chest pain, and darkened skin.

FINDINGS FROM WHO VIGIBASE

WHO VigiBase (World Health Organization, 2015) is a global pharmacovigilance database, providing international adverse drug reaction reports for Carmustine. The most frequently reported categories based on percentages are shown below (Figure 3).

Figure 3.

Percent Reported Adverse Effects for Carmustine According to WHO Vigibase.



These findings support FAERS data indicating that systemic Carmustine exposure is associated with broader and more frequently reported adverse effects compared to localized Gliadel wafer therapy.

OVERALL REVIEW

Analysis of FAERS data demonstrated that Carmustine was associated with significantly higher percentages of adverse events from respiratory disorders (17.7% vs. 8.2%), blood disorders such as myelosuppression (22.5% vs. 5.2%), and reported deaths (25.2% vs. 21.3%) compared to Gliadel. Chi-square testing confirmed that several of these differences were statistically significant ($p < 0.05$). In contrast, Gliadel showed higher rates of nervous system–related complications, including seizures and intracranial hypertension, largely due to its surgical implantation and localized delivery. In all, it is shown by these results that Gliadel may decrease the risk of certain systemic effects, but precautions should be taken before deciding on a treatment in a clinical situation.

DISCUSSION

Based on data collected from FAERS and other public medical databases, it is clear that Carmustine and Gliadel wafers both have their respective advantages and disadvantages. Carmustine is injected, and has more systemic adverse effects throughout the body, creating respiratory and blood disorders. Individuals treated with Carmustine instead of Gliadel are at a higher risk of systemic

infections due to low white blood cell count. However, Gliadel has more localized effects in the nervous system, due to implantations in the brain. The surgical implantation procedure into the tumor cavity increases the risk of localized infection and postoperative complications, such as brain edema and other nervous system adverse effects. Despite the fact that Gliadel is a degradable wafer that releases its Carmustine load within 2-3 weeks, the adverse effects resulting from the invasive surgical placement can be long-lasting.

A consistent trend appeared across FAERS and all of the other public medical databases, which was that Carmustine and Gliadel had distinct side effect profiles. In FAERS (U.S. Food and Drug Administration, 2023; U.S. Food and Drug Administration, 2026), a significantly higher proportion of Gliadel patients experienced neurologic disorders compared to patients that took Carmustine by injection, but patients that took Carmustine were significantly more likely to develop blood and lymphatic system disorders, due to the immune system being temporarily disabled.

All of the databases reported differences in adverse effects between Gliadel and Carmustine. Gliadel wafers were primarily associated with Brain Edema, Cranial Hypertension, and Seizures. However, for Carmustine, the adverse effects that were mentioned were primarily associated with systemic infections and toxicities. These distinct adverse effect profiles can significantly affect treatment decisions. Gliadel wafers, because of their targeted nature, could be better for localized brain tumors with limited metastatic spread, where the priorities are to deliver targeted chemotherapeutic and reduce systemic side effects. However, Carmustine may be better for a broader exposure, but patients should consider the higher systemic risks. Carmustine may also be a better choice for patients with pre-existing neurological conditions, such as seizure disorders, intracranial hypertension, or neurodegenerative disease.

For FAERS specifically, it was necessary to determine if the differences between adverse effect profiles between Gliadel and Carmustine was statistically significant, with respect to death vs. no death, as well as systemic infection vs. no systemic infection. Chi-square testing determined that the differences were significant for both the death outcome and the systemic infection outcome. Carmustine had a greater percentage of reported adverse events leading to death, and Carmustine had a greater percentage of reported adverse events that were systemic infections. Even small clinical differences can make a large impact when choosing the proper treatment technique for certain diseases.

For future studies, more controlled clinical studies directly comparing Carmustine and Gliadel would be beneficial, in addition to observational data from databases such as FAERS. Such studies could provide a more comprehensive understanding of the benefits and risks of each treatment. Conclusions from a single study are limited. Also, it would be beneficial to aim toward documenting adverse effects not only in the short term, but also in the long term. Lastly, data could be collected from different countries (internationally), in order to increase the validity of these findings and provide a more comprehensive picture.

LIMITATIONS

There are a few limitations to this research paper. First, reporting to FAERS is voluntary for healthcare providers and consumers. Many times, important data will be left out, reducing the reliability. Also, the data might be distorted due to the much larger group of people that take Carmustine, as it is much easier than Gliadel to implant. Adverse effects could be influenced by other treatments or conditions, and databases could or could not have consistent formatting and reporting across all the different sources.

CONCLUSION

Overall, Carmustine was associated with higher rates of systemic adverse effects, while Gliadel demonstrated a greater frequency of nervous system–related and surgical adverse events. Despite these localized risks, Gliadel showed a lower reported incidence of certain severe systemic outcomes, including blood disorders and death, when compared to Carmustine.

In conclusion, treatment selection should consider not only therapeutic effectiveness but also the nature and severity of potential adverse effects. Understanding these differences may assist clinicians in optimizing treatment strategies for patients with malignant brain tumors.

REFERENCES

- American Society for Health-System Pharmacists. (2025a). *Carmustine*. SafeMedication. <https://www.safemedication.com/drug-library/a/6/8/2/0/a682060>
- American Society for Health-System Pharmacists. (2025b). *Chlorambucil*. SafeMedication. <https://www.safemedication.com/drug-library/a/6/8/2/8/a682899>
- National Library of Medicine. (2021). DailyMed. <https://dailymed.nlm.nih.gov/dailymed/>
- U.S. Food and Drug Administration. (2009). *Drugs@FDA: FDA approved drug products*. <https://www.accessdata.fda.gov/scripts/cder/daf/>
- U.S. Food and Drug Administration. (2017). *BiCNU (carmustine) for injection, for intravenous use* [Drug Label]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/017422s0551bl.pdf
- U.S. Food and Drug Administration. (2018). *GLIADEL® WAFER (carmustine implant), for intracranial use* [Drug Label]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020637s0291bl.pdf
- U.S. Food and Drug Administration. (2023). *FDA Adverse Event Reporting System (FAERS) public dashboard*. <https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard>
- U.S. Food and Drug Administration. (2026). *FDA Adverse Event Reporting System (FAERS) public dashboard for drugs and biologics*. <https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis>
- World Health Organization. (2026). *VigiAccess*. <https://www.vigiaccess.org/>