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Use of carmustine implants (GLIADEL wafer) in patients with malignant glioma at The McGill University Health Centre

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Invitation. This document was designed to assist decision-making in the McGill University Health Centre. Others are welcome to make use of it, preferably with acknowledgment. More important, to assist us in making our own evaluation, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way, and even if it has not, whether it has been helpful in informing decision makers.

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Outline

EXECUTIVE SUMMARY

The Carmustine implant (GLIADEL wafer) is a local drug delivery system, consisting of a biodegradable polymer wafer impregnated with carmustine (1,3-bis (2-chloroety1) – 1 – nitrosourea; BCNU). It is indicated for use as a treatment of patients with malignant glioma undergoing primary and /or recurrent surgical resection.

The overall safety profile for this treatment appears adequate. However, significant adverse effects may not be fully documented due to the small study sizes. There are limited data concerning the efficacy of the carmustine implantable wafers for these indications as only three randomized trials with a total 494 patients have been published. Moreover, there are obvious shortcomings in these trials including small sample sizes, somewhat diverse initial pathology, a lack of control of subsequent therapies and a lack of comparative studies of competing adjunctive therapies.

Nevertheless there is fairly consistent evidence of a median survival benefit of approximately **6 - 8 weeks** compared to placebo whether the implants were used at the time of a recurrent surgery or administered at the time of initial resection. Regulatory authorities have also concluded that this therapy is efficacious when used with both primary and recurrent surgical resection.

While this health benefit may appear marginal, it must be interpreted in the context of a disease with a uniformly poor prognosis. The benefit of other treatment modalities is equally small. A meta-analysis of 12 RCTs of accepted chemotherapeutic strategies for gliomas has shown a similar survival benefit (2 months, 95% CI 1-3).

Thus although the clinical benefit is limited, it is comparable to current therapies. No formal cost-effectiveness studies have been performed. However, approximate calculations suggest a cost-effective ratio of approximately $100,000 per life year, a

value higher than most currently funded activities, including the standard benchmark of hemodialysis ($85,000/life year).

However, this cost-effectiveness is comparable to other current chemotherapeutic regimes (temozolomide) offered to patients with malignant gliomas at the MUHC. Based on these observations and the fact that regulatory authorities accept its efficacy, it would be difficult to justify total refusal of this agent.

Furthermore, such decisions must be consistent with societal values and there is a recognized preference for society to give support, even relatively minimal support, to individuals who are severely ill before those who are less ill. Thus the critical issue turns on the economic impact. While a consensus would approve of supporting a limited number of such terminally ill patients at relatively high cost, few would condone such support for a large number, with the associated high opportunity costs and consequent reduction in other hospital services.

In the event of patients transferred to the MUHC from other provinces for resection of malignant gliomas and where this therapy may be judged appropriate, authorization from the referring province to cover the costs of the carmustine wafers should be procured before surgery.

Recommendations:

Based on the above considerations, the TAU recommends that the use of carmustine implantable wafers at the MUHC, be restricted to a limited number of selected Quebec patients undergoing recurrent resection for malignant glioma and who have had an unsuccessful response to previous standard chemotherapy. The number so supported should not exceed <u>10 cases</u> per year. Recognizing that the evidence for this therapy is less than ideal, it is recommended that a registry be kept of all patients receiving this therapy so this assessment may be revised in light of accumulating data.

Foreword

On July 20, 2003 Mr. Andre Bonnici, on behalf of the Pharmacology and Therapeutics Committee and the Administration of the MUHC, requested that the Technology Assessment Unit (TAU) give its opinion/expertise on the use of GLIADEL wafers during surgery for patients with malignant glioma.

1. Objectives

The objective of this report is to review the effect of GLIADEL wafer on survival and quality of life of patients following primary or recurrent resection of malignant gliomas, to assess the complications of this technology, and to estimate the cost effectiveness and potential budgetary impact of the use of GLIADEL at the MUHC.

A recommendation to the MUHC regarding the use of GLIADEL as adjunctive treatment to surgery for high-grade malignant glioma is formulated, in light of the evidence presented here.

2. Brain Cancer Background

2.1. Epidemiology

Brain tumors represent one of the most rapidly progressive and universally fatal of all cancers. Males are more often affected than females. It is estimated that in 2003, 2450 people (1350 males and 1000 females) developed new primary brain cancers in Canada, causing 900 deaths in men and 700 deaths in women. In Quebec, 670 cases were diagnosed in 2003 (350 males and 320 females)[7]. Approximately 44% of these primary brain tumors are malignant gliomas[3]. About 60 patients with newly diagnosed malignant gliomas are treated annually at the MUHC (Dr. Rolando Del Maestro, personal

communication). Brain tumors may occur at any age, but rates decline after a small peak in childhood, increase after age 25, and level off after age 75 [4].

2.2. Grading severity

There are nearly 100 different types of brain tumors, generally named after the type of cell from which they developed or the area of growth. More than half of all primary brain tumors are gliomas, which developed from the glial cells that support the structure for the neurons or nerve cells of the brain. Four main types of gliomas are astrocytoma, ependymoma, oligodendroglioma, and mixed glioma - a mixture of the other types [2;6;24].

Four grades of gliomas are recognized according to their malignancy. Low-grade gliomas (Grade 1 and Grade 2) are relatively slower growing and unlikely to spread to other parts of the brain, presenting a better prognosis. However, a slow growing tumor can also cause serious symptoms and can be life threatening as well if it is in a crucial part of the brain like brain stem. Grade 3 and 4 tumors are very malignant and are often difficult to treat [2;4].

The most common and malignant histopathologic subtypes of high-grade gliomas are Grade 4 astrocytomas, also called Glioblastoma multiforme or GBM, accounting for approximately 75% of primary malignant gliomas. These malignant gliomas grow very rapidly and invade surrounding tissues, but they rarely spread beyond the central nervous system. The prognosis of high-grade brain tumors with current treatments is generally grim. The median survival in patients harboring this neoplasm is 10-12 months, irrespective of therapy [4;23].

2.3 Treatment

There have been no significant new developments in the treatment of malignant gliomas for over 20 years. The standard treatment for patients with malignant glioma is palliative in nature and typically consists of surgical resection followed by radiotherapy and sometimes followed by systemic chemotherapy [2;24].

Due to the diffuse nature of these tumors, complete surgical resection of high-grade tumors is difficult. After surgery, tumors are likely to recur and grow more rapidly, usually at a site within 2 cm of the original tumor. The majority of patients with malignant glioma experience more than one re-operation.

The first chemotherapy treatment for brain tumors was Carmustine (BCNU), approved by the US FDA in 1977 [9]. This chemotherapeutic agent is administered intravenously. Other chemotherapeutic agents more recently approved by the FDA for clinical use include Temodal, oral etopodise (VP-16) PCB, and procarbaxine (PCV).

3. Biodegradable delivery systems of chemotherapeutic agents

3.1. Rationale

Systemic chemotherapy has been used for brain cancer for over 20 years; however, chemotherapeutic agents in general lack the ability to cross the blood-brain barrier and decompose rapidly in the bloodstream. Thus, they often fail to achieve efficacious concentrations at the tumor site in the brain. Moreover, increasing the dose of these anti-cancer agents may result in significant systemic toxicity. Also, chemotherapy agents administered intravenously are cleared rapidly from tissue, with the subsequent limitation of lack of bioavailability at the tumor site [1;22;27]. To overcome all above mentioned limitations of systemic chemotherapies, a different means of supplying the drug more directly to the tumor site was sought to maximize drug effect and minimize systemic toxicity. In this regard, advances in biocompatible polymer technology, which allows controlled, predictable and localized administration of drugs, makes this new method of drug delivery possible.

3.2. Description of GLIADEL wafer

GLIADEL wafers were developed as a suitable vehicle for incorporating chemotherapeutic agents and delivering them directly to the tumor site. They are biodegradable polymer wafers that are implanted in the cavity created when a brain tumor is surgically removed. They are small, dime-sized wafers incorporating 7.7 mg of the cancer chemotherapeutic drug carmustine (BCNU) [11]. As the wafer slowly dissolves in the brain, it releases carmustine directly to the tumor site in high concentrations over an extended period of time. As a result, GLIADEL provides brain concentrations of BCNU that are 100-1000 times higher than the potential concentrations offered with conventional intravenous administration [10]. The duration of drug delivery by GLIADEL is 2-3 weeks. The number of GLIADEL wafers that will be used during surgery depends on the size of the tumor resection cavity, with a maximum of eight being used at any one time[11].

3.3. GLIADEL wafer approval

The Food and Drug Administration (FDA) in the United States first approved GLIADEL on September 23, 1996 for use as an adjunctive therapy to surgery to prolong survival in patients with **recurrent GBM** for whom surgical resection is indicated. More recently, on February 26, 2003, the FDA extended the use of GLIADEL to **newly diagnosed patients** with high-grade malignant glioma as an adjunct to the surgery and radiation therapy [9].

It received approval in Canada for both first and recurrent surgical intervention for GBM in December 1998[12] and was added to the Québec provincial formulary in February 2003[15] but has as yet not been added to any other provincial formularies. Since it must be administered in the hospital the cost of this product is attributable to the hospital budget.

As of December 2000, GLIADEL has received marketing approval for patients with recurrent malignant gliomas or GBM in 24 countries. As of 2002, the product was licensed in the European Union but not yet launched. According to the company website, GLIADEL wafers have been used for 6000 patients worldwide [12].

4. Evidence of efficacy and safety.

4.1. Methods of literature review

A detailed description of our literature search strategy is provided in Appendix A. Regarding the *efficacy* of GLIADEL wafers, only results from randomized controlled trials were abstracted, due to the possibility of bias when using uncontrolled studies for assessing treatment effects. The quality of each trial was acceptable as evaluated by the Jadad Scale [18] (Appendix B). Evidence for the *safety* of GLIADEL wafer included data not only from randomized controlled trials but also non-experimental clinical studies.

4.2. Evidence of efficacy and safety

4.2.1. Use with recurrent tumor resection

The first phase III, multi-center, randomized, placebo-controlled, double blind trial was reported in 1995 [5]. It evaluated the efficacy and safety of GLIADEL wafers in a study involving 222 patients with recurrent malignant glioma, enrolled at 27 centers in the U.S. and Canada. Patients were randomly assigned to receive surgically implanted GLIADEL (3.85% BCNU) or placebo wafers. The primary endpoint was survival from the time of polymer implant. Secondary outcomes included complications and quality of life measurements.

Survival benefit: The study found that median survival was 31 weeks in the GLIADEL group of 110 patients and 23 weeks in the placebo group of 112 patients. The unadjusted six-month survival rate after surgery was 47% (53/112) in patients receiving placebo and 60% (66/110) in patients treated with GLIADEL (p=0.061, Fisher's Exact Test); The overall treatment effect did not reach statistical significance in an univariate proportional hazard model [hazard ratio (HR)=0.83, P=0.19, log rank test]. After adjusting for all significant predicators of outcome, including age, KPS, interval from previous surgery, race, and previous nitrosourea chemotherapy, GLIADEL showed a significant decrease of 33% in risk of overall death (HR = 0.67, 95% CI: 0.51-0.90, P=0.006). However, this effect was not sustained at 12 months, as 93% of all patients were dead.

In the subgroup of patients with GMB (145 patients), both survival analysis and proportional hazard model produced favorable results for GLIADEL treatment, with an unadjusted six-month survival rate of 36% (26/73) in GLIADEL compared to 56% (40/72) in placebo, (p=0.02, Fisher's Exact Test), and a significant decrease of 33% in risk (HR=0.67, 95% CI: 0.48-0.95, P=0.02) after adjusting for prognostic factors.

In patients with pathologic diagnoses other than GBM, the treatment with GLIADEL wafers did not show any statistically significant survival benefit (HR= 0.46, 95%: 0.20 - 1.07), although this may be partially explained by low power.

Quality of life measurements: In this study two measures, the Karnofsky Performance Status (KPS) and the Mini-Mental State Examinations (MMSE), which quantify the physical and cognitive functional status of tumor patients, were used as surrogates of quality-of-life assessments. The authors observed that the KPS and the MMSE score declined over time in both GLIADEL and placebo groups, but the difference between the two treatment groups was not statistically significant.

Safety: During postoperative follow-up, few serious side effects were identified and no increase in clinically important adverse events was attributable to GLIADEL.

Comments: This study was sponsored and funded by Guilford Pharmaceuticals Inc, a manufacturer of GLIADEL. It appears to have been an adequately designed and well-controlled study. The difference in the primary outcome, an average survival after implant of 23 weeks versus 31 weeks on placebo, was not statistically significant, (p=0.19). By 12 months almost all patients in both groups has succumbed to their disease. As randomization was performed there is no justification for the subsequent data manipulation of adjusted results. This modeling exercise may have introduced more noise than precision into the analysis.

4.2.2. Use with primary tumor resection

Two phase III, randomized, double-blind, placebo-controlled studies have been conducted to confirm the efficacy and safety of GLIADEL (3.85% BNCU) for the use in newly diagnosed malignant glioma patients.

The first study[26] involved only 32 patients undergoing initial surgical resection followed by standard radiation therapy for malignant glioma (grade III or IV). The study was planned to include 100 patients. However, due to a shortage of GLIADEL, it had to be terminated prematurely.

Survival benefit: Using intent-to treated (ITT) analysis, after 2 years of follow-up, median survival was 58 weeks for GLIADEL and 40 weeks for the placebo (p=0.012). For 27 patients with GBM, median survival was 53 weeks for GLIADEL and 40 weeks for the placebo (p=0.008).

Quality of life measurements: No cancer specific quality of life measurement instruments were used. Patients were evaluated periodically for up to two years by neurological examination, KPS score, and MMSE evaluation. Both KPS and MMSE scores declined during the study [-27 in GLIADEL vs. -40 in Placebo, and -6.1 in GLIADEL vs. -4.9 in Placebo, respectively). However, changes from baseline to the final visit were not statistically significant in between-treatment-group comparisons.

Safety: The total number of patients with adverse events during the two years of the study period was 56% (9/16) in the placebo group and 75% (12/16) in the GLIADEL group. The most frequently documented treatment-emergent adverse events included hemiparesis (38% in GLIADEL vs. 25% in Placebo), convulsions (19% in GLIADEL vs. 13% in Placebo), aphasia (13%) and visual field defect (13%) in the group receiving GLIADEL only. The small sample size limits conclusions that can be made regarding safety.

Comments. The study was also supported by Guilford Pharmaceuticals Inc. Although patients were randomized, the small sample size is a serious limitation.

A larger trial[28]enrolling 240 newly diagnosed patients with single supratentorial malignant tumors, randomized to GLIADEL or placebo wafers at the time of initial surgical resection has been performed. Patients with prior cytoreductive therapy, multifocal disease, prior radiotherapy to the brain, hypersensitivity to nitrosoureas and clinically significant laboratory abnormalities were excluded. Both groups were treated with external beam radiation postoperatively, but no additional systemic chemotherapy was allowed until documented recurrence of disease progression. The primary outcome was the 12-month survival rate, assessed on the basis of intention to treat. Progression free survival was also estimated.

Survival benefit: Median survival in the treated group was 13.9 months for the GLIADEL and 11.6 months for the placebo group, with a 1-year unadjusted survival rate of 59.2% and 49.6%, respectively. The treatment effect of GLIADEL was positive with a risk reduction of 29% (HR=0.71, 95% CI: 0.52-0.96, p=0.03 log rank statistic stratified by country) compared to placebo. The treatment effect remained significant after adjusting for prognostic factors including KPS, age, number of wafers implanted, with 28% (HR= 0.72, 95%CI: 0.53-0.98, P=0.03) reduction in risk of death. In the subgroup of patients with GBM, the median survival was similarly improved (GLIADEL 13.5 months versus placebo 11.4 months), but the Kaplan-Meier estimates using a stratified logrank test did not reach statistical significance (P=0.10). The progression-free survival was the same in both treatment groups[1]

Quality of life measurements: Two tumor specific quality of life instruments - the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Brain Cancer Module (BCM-20) - which were designed to assess problems specific to brain tumor patients were employed in this study. However, noncompliance in the completion of questionnaires and missing data due

to death reduced the amount of data available for analysis and thus limited any conclusions.

However, the study suggested that the survival benefits of GLIADEL treatment are accompanied by maintenance of overall function with significantly better Time-to- KPS decline (HR=0.74, 95% CI: 0.55-1.0) and significantly longer time to neurological progression in 10 of 11 measures of neurological function for GLIADEL treatment group.

Safety: There are similar adverse event profiles in the GLIADEL and placebo groups, except for cerebrospinal fluid (CSF) leak (5% in GLIADEL vs. 0.8% in Placebo) and intracranial hypertension (9.1% in GLIADEL vs. 1.7% in Placebo). However, in 9 of the 11 patients who received GLIADEL intracranial hypertension occurred after 6 months of implantation. It cannot be determined with certainty if these adverse events were caused by GLIADEL or whether they were related to recurrence of the primary tumor. The most common symptoms of CSF leakage include postural headache, nausea, vomiting and diplopia[21]. Most cases heal spontaneously with no lasting symptoms. However, CSF leak due to brain surgery might be the cause of serious complications such as infection and cerebral edema[16].

Other adverse events included convulsions, intracranial infections, and healing abnormalities, which were comparable between two treatment groups.

Comments:

This industry-sponsored study was a generally well-conducted, double-blind, randomized trial. However, other unspecified treatment modalities, including reoperation, chemotherapy, or radiation therapy, were used for patients when the diagnosis of tumor progression was made, and since it is unlikely that these and all other post-study treatments are perfectly evenly distributed in the two treatment groups, the attributed treatment effect may have been confounded.

4.2.3 Previous Technology Assessments and Observational Studies

Only one other technology assessment has been published on this drug. This was a new and emerging technology brief published by the National Horizon Scanning Center at the University of Birmingham [13]. Conclusions in this brief are restricted as the authors observed the same limitations in available evidence that we encountered. In assessing the clinical impact, they conclude that this therapy offers hope for patients with an otherwise poor prognosis.

Several case reports have identified cerebral cyst formation as a potential complication associated with the carmustine wafer[14].

4.3. Summary of benefits and risks of GLIADEL used in malignant glioma

There is limited data concerning the efficacy of the carmustine implantable wafers for the treatment of newly diagnosed or recurrent GBM. There are 2 medium sized clinical trials that have demonstrated improved survival with the use of this technology[5;28]. There are shortcomings in both these trials including small sample sizes, somewhat diverse initial pathology and a lack of control of subsequent therapies. Nevertheless there is a somewhat consistent median survival benefit of approximately 8 weeks compared to placebo whether the implants were administered at the time of initial resection[26;28] or when used only at the time of a recurrent surgery[5], there is a tendency for improvement of surrogate quality of life measures with the carmustine wafer in one of three studies[28]. Unfortunately the medium term prognosis remains grim irrespective of the treatment options chosen. The same lack of data limits conclusions regarding the overall safety of this technology.

There are no head to head comparisons between carmustine wafers and standard systemic chemotherapy. A meta-analysis of 12 randomized controlled trials (RCTs) of chemotherapy for glioma shows that mean-survival time increases by 2 months (95% CI: 1-3 months)[23], which is consistent with the size of benefit predicted with the implanted wafers.

5. Budget impact of the use of GLIADEL on the MUHC

5.1. Patient Demand at the MUHC

To date, only three patients have received GW at the MUHC (Dr. Del Maestro) and all satisfied the following conditions: Recurrent malignant glioma , possibility of complete resection of localized brain tumor, previous full course of radiotherapy, and failed treatment with temozolomide. (Chart review reveals that one of these patients died two months later, and in the other two there is evidence of continued tumor growth).

According to Dr. Del Maestro there are approximately 30 recurrent malignant gliomas at the MUHC each year, only 5-10 of whom would be suitable surgical candidates for carmustine implants.

5.2. Cost analysis:

There is insufficient evidence to assess the comparative efficacy of carmustine implants to standard chemotherapy[17]. Implants are used at the time of surgery, and surgery is never carried out with the objective of inserting an implant. The cost-effectiveness can only be compared to supportive care in patients having previously failed standard chemotherapy.

Assuming that implantation of carmustine wafers does not prolong surgery time or increase equipment needs (beyond drug acquisition costs) means that these hospital costs may be ignored. Although only 3 patients have been treated at the MUHC, their hospital stay was 4.5 days longer than the average stay for 9 patients undergoing the same operation without receiving Gliadel implants. It is unclear from this small sample size, if implantation of carmustine wafers will be systematically associated with prolonged hospitalizations. The collection of more prospective data is required to answer this question. Hospital stay at the MUHC for this type of care is presently estimated at $442/day (Mr G Gaudet.Finance Dept. MUHC).

Budget impact.

Acquisition cost of a pack of 8 wafers equals $14,844.30 (Pharmacy, MUHC). (Unlike other chemotherapeutic agents such as temozolamide, the costs of Gliadel wafers must be paid by the hospital)

Between 6 and 8 implants are used per procedure. Assume on average,
7 wafers per patient = $12,988.76
Assume increased hospital stay of 4.5 days at $442 per day = $1,989.
Total cost per patient = $14,977
Economic impact on the MUHC for 10 treatments a year = $149,770

Cost-effectiveness

Assuming an estimated direct cost to the healthcare system of this treatment of $15,000 ($14,977) per patient and an average extension to life of 8 weeks, the cost-effectiveness without discounting, would be approximately $100,000 ($97,350).

The technology assessment briefing by National Horizon Scanning Center[13] describes a US pharmacoeconomic study of the cost-effectiveness of GW implants and reports an incremental cost of carmustine wafer implant was £45,000 or Ca$ 103,500 per life-year saved. No other published estimates are available.

6. Conclusion & Recommendation

There is limited data concerning the efficacy of the carmustine implantable wafers for the treatment of newly diagnosed or recurrent GBM as only a total of three randomized trials with 494 patients have been published. Moreover, there are obvious shortcomings in these trials including small sample size, somewhat diverse initial pathology and a lack of control of subsequent therapies. Studies of competing therapies such as temozolomide versus carmustine implants and formal cost-effectiveness studies have not been performed.

Nevertheless there is a somewhat consistent median survival benefit of approximately 8 weeks compared to placebo, whether the implants were administered at the time of initial resection or when used only at the time of a recurrent surgery. Regulatory authorities have also concluded that this therapy is efficacious, whether for primary or recurrent surgical resection. Although the overall safety profile for this treatment appears adequate, it must be stressed that significant adverse effects may be present and not fully documented due to the small sample sizes.

In considering whether Gliadel wafers should become accepted treatment at the MUHC the following points were considered:

- While this health benefit may appear marginal, it must be interpreted in the context of a disease with a uniformly poor prognosis where other treatment modalities are virtually non-existent.

- Although this clinical benefit is very limited, it is comparable to current therapies that have already been approved, on the basis of equally scant evidence. For example, temozolomide was approved for recurrent glioma management at the MUHC on the basis of only one randomized trial of 225 patients which showed a median survival advantage of only six weeks. The National Institute for Clinical Excellence (NICE) has also accepted temozolomide for patients with recurrent malignant glioma who have failed conventional chemotherapy on the basis of these data[19].

- While formal economic analyses are not available, approximate calculations suggest that the direct costs of the use of Gliadel wafers to the healthcare system would be in the order of $100,000 per year of life saved ignoring any discounting. This is a high cost in comparison with most currently funded activities, including the standard benchmark of hemodialysis ($85,000 per year of life [8]).

- The cost-effectiveness of carmustine implants is comparable to other current chemotherapeutic regimes (e.g. temozolomide) offered to patients with malignant gliomas at the MUHC. Based on these observations and the fact that it's efficacy is accepted by regulatory authorities, it would be difficult to justify total refusal of this agent.

- In terms of human values, however, it is clear that not all life years are equal. Thus Eric Nord concluded from a series of studies on this issue that "small improvements in severely ill patients were seen as being more important than larger improvements (in quality adjusted life years (QALYs)) for less severely disabled patients"[20]. Similarly, Peter Ubell concluded that "when given a choice between helping two groups of patients who stand to gain equal QALYs, people almost always prefer to help those with the more severe illness"[25].

- Thus, the deciding issue in this difficult question is the budget impact which is determined by the *number* of applications anticipated each year. While a consensus might agree to give this slight therapeutic support to a small number of such seriously affected individuals, few would consider the opportunity cost associated with supporting many such patients would be justifiable in the light of the present MUHC budgetary status. Thus to administer wafers to 100 patients per year would cost the MUHC approximately $1.5 million, and would result in a significant reduction in services elsewhere in the institution.

RECOMMENDATION

For these reasons the TAU recommends that the MUHC should approve only very limited use of the Gliadel wafer. Use should be restricted to highly selected cases with a reasonable quality of life who are undergoing a second surgical intervention for a single lesion and who have already received chemotherapy. Specifically such cases should not exceed <u>10 per year</u>. Recognizing that the evidence for this therapy

is slender, it is recommended that a registry be kept of all patients receiving this therapy so this assessment may be revised in light of accumulating data.

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Appendix A

Literature Search strategies

The database or websites were searched using the following keywords individually or combined, without language restriction, between January 1990 and November 2003.

The keywords:

1. Brain tumor
2. Malignant Glioma
3. GBM
4. GLIADEL wafer
5. carmustine
6. BCNU
7. Quality-of-life
8. Temozolomide
9. Cost-effectiveness
10. Cost

Databases

The Cochrane Library

EMBASE

MEDLINE

PubMed

DARE (http://www.york.ac.uk/inst/crd/)

DEC reports (http://www.doh.gov.uk/)

Trip database (http://www.tripdatabase.com/)

Medscape (http://www.medscape.com/px/urlinfo)

NHS – National Horizon Scanning Center

N.I.C.E. – National Institute for Clinical Excellence

Health Technology Assessment (HTA) websites:

CHSPR – Centre for Health Services and Policy Research (UBC) British Columbia

HSURC – Health Services Utilization and Research Commission (Saskatchewan)

ICES – Institute for Clinical Evaluative Sciences

MCHP – Manitoba Centre for Health Policy

INAHTA database – International Network of Agencies for Health Technology Assessment

AÉTMIS - Agence d'évaluation des technologies et des modes d'intervention en santé

AHFMR - Alberta Heritage Foundation for Medical Research

ASERNIP-S– Australian Safety & Efficacy Register of New Interventional Procedures - Surgery

ANAES - L'agence nationale d'accréditation et d'évaluation en santé

CAHTA - Catalan Agency for Health Technology Assessment and Research

CCOHTA – Canadian Coordinating Office for Health Technology Assessment

CÉDIT – Comité d'évaluation et de diffusion des innovation technologiques

CMT – Center for Medical Technology Assessment (Sweden)

DACEHTA – Danish Centre for Evaluation and Health Technology Assessment

DIMDI – German Institute of Medical Documentation and Information

DSI – Danish Institute for Health Services Research

FinOHTA – Finnish Office for Health Care Technology Assessment

ITA – Institute of Technology Assessment ((Austria)

MSAC – Medical Services Advisory Committee (Australia)

NCCHTA - National Coordinating Centre for Health Technology Assessment

NHS QIS - NHS Quality Improvement Scotland

SBU – The Swedish Council on Technology Assessment in Health Care

SNHTA – Swiss Network for Health Technology Assessment

TA-SWISS – Center for Technology Assessment

Other websites

American brain tumor association (http://www.abta.org/library.htm)

Canadian cancer society. (www.cancer.ca/ccs/internet/cancer/)

The brain tumor society. (www.tbts.org)

Doctor's guide (www.pslgroup.com)

Guilford Pharmaceuticals Inc. (www.gliadel.com)

FDA (www.fda.gov)

Clinical trial results (www.clinicaltrialresults.com)

Appendix B

Phase III RCT studies on GLIADEL wafer used for patients with malignant glioma

	Study I (#T-301)	Study III (#0190)	Study I (#8802)
Trial Design	Phase 3 RCT, randomized, placebo-controlled, double-blind, multicenter	Randomized, double-blind placebo-controlled multicenter	Randomized, double-blind placebo-controlled multicenter.
Sample size	240	32	222
Study period	Dec.19,1997-Jun.30,1999	Mar.23,1992 – Mar.19, 1993	Mar.1989-Jan.1992
Patient selection	Newly diagnosed malignant glioma	Newly diagnosed malignant glioma	Recurrent malignant gliomas
Eligibility criteria	-18-65 yrs, - KPS ≥ 60, -Cranial MRI of a single, contrast-enhancing, unilateral ,supratentorial, cerebral tumor, -be treated within 2 weeks of the baseline MRI, -tumor confirmed by frozen section	-18-65 yrs, -KPS ≥ 60, -Witnessed informed consent, -Unilateral, unifocal tumor of ≥ 1 cm, by brain imaging. -Tumor must not cross midline, -Confirmation of high grade glioma by frozen or squash preparation surgery	-Age: no restriction -KPS ≥ 60, -Unilateral single focus of tumor of ≥ 1cm. By computed tomography scan or magnetic resonance imaging, -completion of external beam radiation therapy, -no nitrosoureas for 6 weeks -no other systemic chemotherapeutic agent for 4 weeks.

Exclusion criteria	-with prior cytoreductive therapy, -multifocal tumor or a tumor crossing the midline, -prior radiotherapy or chemotherapy, -Known hypersensitivity to nitrosoureas, -clinically significant laboratory abnormalities -Pregnancy	-Significant renal or hepatic disease, -Concomitant life-threatening disease that would limit lifespan to within 6 months of study entry, -Platelets <100,000/ml or leukocytes <4,000/ml, -Pregnancy, -Hypersensitivity to contrast material	No information
Follow-up time	12 months	Up to 2 years	12 months
Treatment	-GW vs. placebo wafer - implants plus surgery and limited field radiation therapy, -No additional systemic chemotherapy allowed until documented recurrence of disease progression.	-Following maximal tumour resection, up to eight wafers (3.85% BCNU) were to be placed in the cavity. -Standard radiotherapy, -No systemic chemotherapy w as allowed.	Maximum resection of tumor
Primary Endpoints	12 month survival rate, Median survival duration	12 months survival Overall survival rate, Median survival duration	Median survival duration Six-month survival
Secondary outcome	-Time-to-clinical decline measured by KPS -neuroperformance score and time-to-disease progression -Quality of life evaluation	Time-to treatment failure Change in KPS, MMSE score and neurological examination changes.	Change in KPS, MMSE score and neurological examination changes.

Appendix C

Product labeling of GLIADEL wafer on possible adverse events [11]

Four categories of adverse events which are possibly related to treatment with GW, based on evidence obtained from randomized studies, are listed in the approved product labeling of GLIADEL:

Seizure: The median time to onset of the first new or worsened post-operative seizure was 3.5 days in patients treated with GW and 61 days in placebo patients. The majority of seizures in the placebo and GW groups were mild or moderate in severity.

Brain edema: it was observed in 4% of patients treated with GW and in 1% of patients with placebo.

Healing abnormalities: These events included cerebrospinal fluid (CSF) leaks, subdural fluid collections, subgaleal or wound effusions, and wound breakdown. The majority of these events were mild to moderate in severity. They occurred in 14% of patients with GW compared to 0 5% of placebo recipients.

Intracranial infection: Intracranial infection (meningitis or abscess) occurred in 4% of patients treated with GW and 1% of patients receiving placebo.