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CADTH Health Technology Review Recommendation

Optune (NovoTTF-200A)

Sponsor: Novocure Canada, Inc.
Therapeutic area: Supratentorial glioblastoma multiforme
Recommendation: Reimburse with conditions

Summary

What Is the Indication Under Review?

The indication under review is for the treatment of adults with newly diagnosed glioblastoma multiforme (ndGBM) following maximal debulking surgery and completion of radiotherapy (RT) together with and after standard of care maintenance chemotherapy using temozolomide.

What Is Optune?

Optune is a portable medical device that produces alternating electrical fields called tumour-treating fields (TTFields) to target growth of cancerous cells.

How Did CADTH Evaluate This Device?

To examine the value of Optune for the treatment of ndGBM, CADTH reviewed and critically appraised evidence submitted by the sponsor, reviewed the literature, sought input from patient and clinician groups, and consulted an expert panel.

What Is the CADTH Reimbursement Recommendation for Optune?

The CADTH Health Technology Expert Review Panel (HTERP) recommends that Optune **be reimbursed with conditions** for the treatment of adults with ndGBM following maximal debulking surgery and completion of RT together with and after standard of care maintenance chemotherapy.

Who Is Eligible for Coverage?

Optune should be covered with conditions to treat adults with ndGBM following maximal debulking surgery and completion of RT.

What Are the Conditions for Reimbursement?

Optune should be reimbursed only if prescribed by a clinician certified by Novocure Canada Inc. who specializes in oncology and the use of anticancer treatments, if the patient has good performance status, if it is feasible to adopt Optune and temozolomide based on the implementation considerations identified by HTERP, if the cost of Optune is reduced by 97%, and if any patient who does not have caregiver support can be accommodated.

Why Did CADTH Make This Recommendation?

- One multicentre, open-label, randomized controlled trial that compared the efficacy and safety of Optune with temozolomide in adults with ndGBM following maximal debulking surgery and completion of RT

Summary

together with and after standard of care maintenance chemotherapy was assessed. Optune may increase overall survival (OS) rates (at 24 months) and likely increases progression-free survival (PFS) rates (at 6 months) when compared to temozolomide alone.

- Optune may meet some important patient needs as it is an additional treatment option that may maintain a patient's health-related quality of life (HRQoL) (i.e., no differences in HRQoL) and does not add safety concerns when compared to temozolomide alone.
- Based on CADTH's assessment of the health economic evidence, Optune does not represent good value to the health care system at the submitted monthly fee. A reduction in the monthly fee is therefore required.
- At the submitted price, Optune is estimated to cost the public payer approximately $76 million for 232 patients over the initial 3 years of funding.

Additional Information

Unmet Needs in Glioblastoma

There have been no new treatment options that have been demonstrated to improve survival of patients with glioblastoma (GBM) since the early 2000s. None of the currently available treatments are curative and the disease has a poor prognosis. Thus, several patient needs are not being met by the current standard of care for ndGBM.

How Much Does Optune Cost?

The submitted fee for Optune is $27,000 per month, which includes the treatment kit and support features. This fee is in addition to the cost of temozolomide.

What Is the Indication Under Review?

The indication under review is for the treatment of adults with ndGBM following maximal debulking surgery and completion of RT together with and after standard of care maintenance chemotherapy with temozolomide. GBM is the development of cancer among glial cells in the central nervous system and is the most common form of brain cancer in Canada. There are approximately 1,850 patients with GBM in Canada (data from 2010 to 2017).[1]

What Is Optune?

Optune is a portable medical device that produces alternating electrical fields called TTFields to target the growth of cancerous cells in addition to chemotherapy. Current treatment for GBM consists of a combination of surgery, RT, and chemotherapy.

How Did CADTH Evaluate Optune?

To examine the value of Optune for the treatment of ndGBM, CADTH:

- reviewed and critically appraised the evidence submitted by the sponsor, including clinical evidence on Optune's efficacy and safety and economic evidence on its cost-effectiveness and budget impact
- reviewed the literature to assess the validity of the sponsor's modelling approaches, assumptions, and estimates regarding Optune, and to identify and describe ethical considerations relevant to the use of Optune for the treatment of ndGBM in Canada
- solicited and sought input from patient and clinician groups through an open call, and established and consulted an expert panel to identify unmet needs, and place in therapy and implementation considerations for Optune.

CADTH's Health Technology Expert Review Panel

HTERP is an advisory body to CADTH that develops guidance and/or recommendations on nondrug health technologies to inform a range of decision-makers within the Canadian health care system.

HTERP comprises 7 core members to serve for all topics under consideration during their term of office: chair, ethicist, health economist, patient member, 2 health care practitioners, and a health technology assessment specialist. In addition to the core members, HTERP comprises up to 5 expert members appointed to provide their expertise on a specific topic. For this reimbursement review, 1 member with expertise in neuro-oncology, 1 member with expertise in medical oncology, 1 member with expertise in radiation oncology, and 1 member with lived experience of GBM as a caregiver were appointed.

To make its recommendation, HTERP considered the following information:

- CADTH's review of:
  - 1 multicentre, randomized, open-label trial in adults with ndGBM following maximal debulking surgery and completion of RT together with and after standard of care maintenance chemotherapy
  - the pharmacoeconomic model and report submitted by the sponsor
  - ethical issues related to Optune from published literature and patient and clinician group and expert panel input
- input received from an open call that included:
  - patients' perspectives gathered by a patient group, the Brain Tumour Foundation of Canada
  - clinician input from a group of 20 oncologists in Canada who treat patients with ndGBM.

Reimbursement Recommendation

HTERP recommends that Optune **be reimbursed with conditions** for the treatment of adults with ndGBM following maximal debulking surgery and completion of radiotherapy together with and after standard of care maintenance chemotherapy.

Rationale for the Recommendation

HTERP recognized the unmet needs of patients with GBM, for which there have been no new treatment options that improve survival since 2005.

One multicentre, open-label, randomized controlled trial (EF-14) that compared the efficacy and safety of Optune with temozolomide in adults with ndGBM following maximal debulking surgery and completion of RT together with and after standard of care maintenance chemotherapy resulted in the following benefits.

- Optune with temozolomide resulted in likely increases of PFS rates at 6 months of treatment (absolute difference = 19.1%; 95% confidence interval [CI], 10.6% to 27.4%). Delaying disease progression is another important goal of treatment for ndGBM that is important to patients and clinicians. HTERP concluded that Optune with temozolomide meets the need to delay disease progression at 6 months as the findings indicated a clinically meaningful benefit for PFS at this time point.
- Optune with temozolomide may increase OS rates at 24 months of treatment (absolute difference = 12.5%; 95% CI, 4.7% to 20.2%) compared to temozolomide alone. The main goal of treatment of ndGBM is prolonging life and HTERP concluded that Optune meets this need at this time point.
- In addition to extending life and delaying disease progression, patients identified the need for treatments that can maintain their quality of life and reduce side effects. Optune with temozolomide

may result in little to no difference in HRQoL when compared to temozolomide alone, and the evidence suggests there is little to no difference in serious adverse events between Optune plus temozolomide and temozolomide alone. Optune treatment did not clearly add safety concerns to temozolomide alone.

However, HTERP acknowledged the limitations of the EF-14 study with concerns regarding possible selection bias that may affect the internal validity of the results with potential overestimation of the efficacy findings and low generalizability to real-world settings.

HTERP noted that, based on the economic evidence at the submitted monthly fee for Optune and public list price for temozolomide, the incremental cost-effectiveness ratio (ICER) for Optune plus temozolomide versus temozolomide alone was $899,470 per quality-adjusted life-year (QALY) gained (incremental costs = $336,902; incremental QALYs = 0.37). At this ICER, Optune plus temozolomide was not considered cost-effective relative to temozolomide alone at conventional willingness-to-pay thresholds (e.g., $50,000 per QALY gained or $100,000 per QALY gained). The budget impact of reimbursing Optune through the federal, provincial, and territorial public drug plans (excluding Quebec) is estimated to be $75,795,323 over 3 years.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults with all of the following: 1.1. newly diagnosed, supratentorial GBM 1.2. received maximal debulking surgery and RT concomitant with temozolomide (45 Gy to 70 Gy) 1.3. completion of RT.	Evidence from the EF-14 trial demonstrated a clinical benefit in adults with newly diagnosed, supratentorial GBM following maximal debulking surgery and completion of RT.	—
2. Patients should have good performance status.	KPS is a measure of overall health status with scores ranging from 0 to 100. Higher KPS scores postoperatively are associated with better survival. Patients in the EF-14 trial were included if they had a KPS score of 70% or higher.	Treating patients with a KPS score of 60 and below could be at the discretion of the treating clinician.
Discontinuation		
3. Reimbursement of Optune and temozolomide should be discontinued upon any of the following: 3.1. clinical disease deterioration 3.2. unacceptable device-related serious adverse events 3.3. intolerance to treatment with Optune.	Patients from the EF-14 trial did not continue treatment upon clinical disease deterioration or after 24 months or second progression, whichever occurred first; unacceptable device-related serious adverse events; or intolerance to treatment with Optune.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
4. Optune with temozolomide should be initiated and supervised by a clinician certified by Novocure Canada Inc. who specializes in oncology and the use of anticancer treatment.	Optune can only be prescribed by a clinician who has completed the required certification training provided by Novocure Canada Inc.	—
Pricing		
5. A reduction in price of 97%	The ICER for Optune + temozolomide vs. temozolomide alone was $899,470 per QALY gained. A price reduction of between 91% and 97% is required for Optune + temozolomide to be considered cost-effective at a willingness-to-pay threshold between $50,000 and $100,000 per QALY gained.	—
Feasibility of adoption		
6. The feasibility of adoption of Optune and temozolomide must be addressed.	HTERP noted that, at the submitted price, the uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate. HTERP noted uncertainties with identifying the appropriate public health care payer for Optune and whether the monthly fee structure is implementable.	Implementation considerations should be addressed meaningfully, including providing more clarity as to who the appropriate payer would be for Optune, whether the subscription model and full set of included services indicated by the sponsor is implementable by the payer, ensuring sufficient support to facilitate device uptake to increase the ability to adhere to treatment, and ensuring the privacy, confidentiality, and security of patient data.
7. Patients who lack caregiver support must be accommodated.	Ensuring equitable access to, and effective use of, Optune for eligible patients may require offering additional resources for people who require support with the use of Optune but lack a caregiver.	Formal, funded supportive resources should be offered for patients who require help to use Optune (e.g., with product placement and/or head shaving). Supportive resources should be reliable (to ensure continuity of treatment) and accessible (e.g., to avoid exacerbating inequities for those with limited mobility).

GBM = glioblastoma; HTERP = Health Technology Expert Review Panel; ICER = incremental cost-effectiveness ratio; KPS = Karnofsky performance status; QALY = quality-adjusted life-year; RT = radiotherapy; vs. = versus.

Considerations

- **Need**:
  - None of the available treatments (including Optune) are curative and the disease has a poor prognosis.

- There have been no new treatment options that demonstrate improved survival of people with GBM since the early 2000s.
- The current standard of care for adults with ndGBM in Canada is maximal surgical resection, followed by RT plus the chemotherapeutic drug temozolomide. However, temozolomide is considerably less effective in patients with *MGMT* unmethylated tumours, which constitutes up to 60% of people with ndGBM.

- **Quality of clinical evidence**: HTERP noted the potential sources of bias impacting the interpretation of findings, including possible selection bias from enrolling patients with a better prognosis and deviation from the intended intervention (crossover). Additionally, only those patients who survived (without progression) from diagnosis to randomization were included in the study, which further affects the internal validity of the results. Because of these issues, the selection bias may result in higher survival outcomes in both treatment groups. HTERP acknowledged that in comparison to the average person with ndGBM presenting in real-world settings, the study participants were slightly younger, with better health status and degree of independent functioning. A higher proportion of patients in the trial underwent complete resection than what might be typically seen in Canadian practice. These factors lowered the generalizability of the trial results.
- **HRQoL:**
  - The efficacy analyses suggest that the benefit of Optune + temozolomide increases with the number of hours wearing the device, with perhaps at least 18 hours as an important threshold. How this will affect HRQoL and how the level of adherence and suggested stable HRQoL during the progression-free period will translate to real-world clinical settings is unknown based on the existing evidence.
  - An earlier version of the device (NovoTTF-100A) was used in the EF-14 trial. While it had the same functionality, the NovoTTF-100A was heavier (around 2.7 kg). The newer generation Optune (NovoTTF-200A) includes a redesigned electric field generator and smaller battery, which makes the device lighter (around 1.2 kg) and more user friendly, according to the manufacturer.[2] The lighter weight and reduced noise of the NovoTTF-200A could impact HRQoL; though, the degree of the impact is unknown.
- **Patients' experiences:** Patients using Optune need to manage lifestyle adjustments, such as wearing it for 18 hours daily, maintaining regular head shaving, and applying the arrays to the head, which may require caregiver assistance.
- **Economic impact:**
  - HTERP discussed the ICER for Optune plus temozolomide, and noted that Optune plus temozolomide was not cost-effective relative to temozolomide alone at conventional willingness-to-pay thresholds.
  - HTERP noted that a price reduction of between 91% and 97% is required for Optune plus temozolomide to be considered cost-effective at a willingness-to-pay threshold between $50,000 and $100,000 per QALY gained.

- HTERP discussed the key areas of uncertainty that impacted the economic evaluation and noted that there are wide ranges in time on treatment for patients using Optune in the EF-14 trial and differences in median and mean time on treatment. It is unclear whether time on treatment data from the EF-14 trial will align with time on treatment if Optune were funded in Canadian clinical practice.
- HTERP discussed that, at the submitted monthly fee of $27,000, Optune is estimated to cost the payer $75,795,323 over 3 years. HTERP discussed the sponsor's approach of considering the federal, provincial, and territorial public drug plans (excluding Quebec) to be appropriate, and noted that there was uncertainty as to who the appropriate payer would be for Optune.

- **Implementation considerations:**
  - HTERP noted there was uncertainty whether the subscription model and full set of included services indicated by the sponsor will be implementable by the health care system.
  - The effectiveness of Optune appears to be dependent on treatment adherence (i.e., time wearing the device); thus, patient motivation may be important in determining device uptake. Family and/or caregiver support may be important in increasing the ability to adhere to treatment.
  - The lifespan of Optune and its components is uncertain. The sponsor assumed that the device's monthly rental fee would cover the repairs, replacement, maintenance, technical support, and clinical support associated with the device; however, the responsiveness of the sponsor to deliver the suggested services within the monthly fee is unknown. Furthermore, it is unclear if new versions of Optune will be covered under the submitted agreement or associated with changes to the sponsor's fee structure.
  - To ensure the privacy, confidentiality, and security of the patient data collected by the device and sponsor, sound measures need to be considered and implemented to adhere to all applicable provincial and national privacy laws. Patient-provider consent conversations should cover privacy considerations before initiating treatment with Optune as use of the device requires transmitting patient data to the sponsor.
- **Ethical considerations:**
  - The acceptability of Optune, and the extent to which it meets people's needs for effective, accessible, and easily usable treatment, will likely depend on an individual patient's values (e.g., whether they see Optune as offering hope and an opportunity to regain a sense of control over the disease or as burdensome or a visible reminder of the condition), motivation, and caregiver support network.
  - As patients with ndGBM can be described as "vulnerable," owing to their incurable and progressive condition and reliance on clinician recommendations and referrals as well as caregiver support, careful attention must be paid to the quality of consent conversations and shared decision-making. This includes ascertaining what is important for an individual patient, with consideration of their poor prognosis. and which treatment(s) and care are most likely to support achieving their goals of care and vision of a good life. Eliciting a patient's values with

respect to treatment is also important as disease progression may impair capacity to consent and require the involvement of a substitute decision-maker.
    - For implementation, it is important to consider and mitigate potential barriers to equitable access and effective use of Optune (e.g., due to geography, socioeconomic status, provincial funding of temozolomide, lack of caregiver support, language barriers).
    - Implementation of Optune raises ethical considerations for publicly funded health care systems related to fair allocation of scarce resources. This includes determining how to weigh providing access to a therapy with potential benefit for a small population that has a high unmet need with the opportunity costs of reimbursing a highly expensive treatment in the context of limited health care budgets and other significant needs.
- **Future research:** HTERP is aware of ongoing research assessing the efficacy of Optune among people with ndGBM.[3] Once available, the findings of this study should be considered along with the EF-14 trial findings to further assess the clinical efficacy and safety of Optune.

Patients', Caregivers', and Clinicians' Perspectives

A call for patient, caregiver, and clinician input opened on July 13, 2023, and closed on September 1, 2023. A total of 2 responses were received.

Patient input was received from the Brain Tumour Foundation of Canada, which gathered information via online surveys and videoconference interviews conducted in 2023. In total, 339 respondents were received for the online surveys (259 caregivers and 80 patients) and 10 interviews were conducted (6 patients and 4 caregivers, all of whom had experience with Optune). The majority of the survey respondents were from Canada (> 94%). Patients with GBM reported experiencing a wide range of symptoms, including headaches, cognitive changes, changes in behaviour, weakness or problems with arms and legs, seizures, nausea, and problem seeing; all of which have significant impact on their emotional and psychological well-being. In total, 88% and 93% of respondents indicated that they or their loved ones had undergone surgery or RT for GBT, respectively. It was noted in the submission that while these interventions have helped decrease tumour size or slow progression, the effects were often short-term and associated with side effects. Input from the 10 individuals who had experience with Optune (plus temozolomide) indicated that Optune resulted in clear MRI results and increased survival, and helped them resume several daily activities. Scalp irritation and dermatitis were the primarily reported negative side effects associated with Optune treatment, with a few mentions of low blood platelet count, nausea, constipation, and tiredness. Overall, most individuals with Optune experience noted that they would recommend the treatment be made accessible to people living with GBM.

Clinician input was received from a group of 20 oncologists who treat patients with ndGBM in Canada. The input noted that current treatment of GBM requires a multidisciplinary approach where surgery is generally followed by postoperative RT with concurrent temozolomide, after which maintenance temozolomide is given for a minimum of 6 months. The primary goal of therapy is to prolong life and PFS with minimal adverse events while maximizing the patient's quality of life. Clinician input further stated that no new

treatment options for ndGBM have been introduced since 2005 and currently available treatments continue to be associated with poor prognosis. Based on the EF-14 trial, clinicians indicated that outcomes used to assess treatment response would align with those in the EF-14 trial (e.g., PFS and OS). Factors including HRQoL, neurocognitive functioning, and treatment-related cytotoxicity should be used to determine treatment discontinuation. Finally, clinician input indicated that TTFields treatment requires no additional outpatient services, such as infusion sites.

The call for input was open to drug plan input; however, none was received for this review.

What Did CADTH Find?

A summary of key findings and uncertainties from the CADTH review of clinician, economic, and ethics considerations can be found in Table 2.

Clinical Evidence

This review included the EF-14 trial, the pivotal, multicentre, open-label randomized controlled trial that assessed the efficacy and safety of Optune plus temozolomide in adults with ndGBM following maximal debulking surgery and completion of RT together with and after standard of care maintenance chemotherapy.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessments included an evaluation of the main outcomes considered important by clinician and patient groups. The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups.

Based on the single trial, there is evidence of low to moderate certainty that Optune plus temozolomide likely increases PFS at 6 months of treatment and OS at 24 months of treatment compared to temozolomide alone. The treatment effect of Optune plus temozolomide on PFS and OS may be dose-dependent, with at least 18 hours of daily use required for the most benefit.

Optune plus temozolomide may result in little to no difference in HRQoL (very low certainty) when compared to temozolomide alone. There was little to no difference in serious adverse events between Optune plus temozolomide and temozolomide alone, which suggests that the addition of Optune did not add safety concerns to temozolomide alone. More than half of the patients who received Optune reported skin irritation (2% severe), likely due to the transducer arrays placed on the scalp.

Overall, the evidence was of very low to moderate certainty due to concerns regarding selection bias and low generalizability of the results to real-world settings. No longer-term studies or indirect comparisons were identified by the sponsor for the review.

Economic Evidence

Cost and Cost-Effectiveness

The submitted fee for Optune is $27,000 per month, which is added to the cost of temozolomide based on its public list price. Using this pricing information, the available clinical evidence, and input from clinicians, patients, and caregivers who have experience with GBM, the ICER for Optune plus temozolomide versus temozolomide alone was $899,470 per QALY gained (incremental costs = $336,902; incremental QALYs = 0.37). Optune plus temozolomide was not considered cost-effective relative to temozolomide alone at conventional willingness-to-pay thresholds (e.g., $50,000 per QALY gained and $100,000 per QALY gained). Consequently, a price reduction of between 91% and 97% would be required for Optune plus temozolomide to be considered cost-effective at a willingness-to-pay threshold between $50,000 and $100,000 per QALY gained.

Budget Impact

The budget impact of reimbursing Optune through the federal, provincial, and territorial public drug plans (excluding Quebec) is estimated to be $75,795,323 to cover 232 patients over the initial 3 years of funding.

Ethical Considerations

GBM is physically, psychosocially, and economically burdensome for patients and their caregivers. The extent to which Optune meets patients' needs for an effective, accessible, and easily usable treatment may depend on an individual patient's values and caregiver support network, especially as Optune requires managing an additional treatment modality and may require additional caregiver support. Due to generalizability limitations with the pivotal trial data, further study on how, or if, factors such as functional status, race, sex, age, socioeconomic status, and availability of caregiver support have implications for device uptake and ability to adhere to treatment would be helpful to inform patient-centred and equitable use given the diverse patient population in Canada. Careful attention must be paid to the quality of clinical consent conversations, including as disease progression may impair capacity to consent and require a substitute decision-maker. Consent conversations require ensuring that patients and caregivers understand that Optune is not curative and is proposed as an addition to standard of care maintenance chemotherapy, so that Optune is considered within a full range of therapeutic and care options. Equity-enhancing strategies for implementation will need to be explored if Optune is to be accessible in a fair and effective manner for eligible patients in Canada, including those who do not fit the profile of participants enrolled in the pivotal trial or who are otherwise underserved.

Key Findings and Uncertainties

Table 2: Summary of Key Findings and Uncertainties

Domains	Key findings	Uncertainties
Need	• GBM is a high-grade brain tumour with poor	• There have been no new treatment options that

Domains	Key findings	Uncertainties
	prognosis and no curative treatment. It is the most common primary malignant tumour of the CNS. • There are approximately 1,850 patients with GBM in Canada (data from 2010 to 2017).[1] • The current treatment strategy is the Stupp regimen, which includes surgical resection followed by chemoradiation and adjuvant chemotherapy with temozolomide. • GBM is physically, psychosocially, and economically burdensome for patients and their caregivers. • Optune (NovoTTF-200A) is a portable and noninvasive device that treats GBM by providing continuous, locoregional treatment with TTFields.	improve survival of patients with GBM since the early 2000s. • The current chemotherapeutic drug temozolomide is considerably less effective in patients with *MGMT* unmethylated tumours,[4] which constitutes up to 60% of patients with ndGBM.[5] • None of the available treatments (including Optune) are curative and the disease has a poor prognosis.
Clinical benefits	• CADTH reviewed evidence from a multicentre, open-label RCT that compared the efficacy and safety of Optune with temozolomide in adult patients with ndGBM following maximal debulking surgery and completion of RT, together with and after standard of care maintenance chemotherapy. • Optune plus temozolomide likely increases PFS at 6 months of treatment and OS at 24 months of treatment compared to temozolomide alone (moderate to low certainty). • The treatment effect of Optune plus temozolomide on PFS and OS may be dose-dependent, with at least 18 hours of daily Optune use required for the most benefit. • Optune plus temozolomide may result in little to no difference in HRQoL (very low certainty) when compared to temozolomide alone.	• CADTH identified weaknesses of the study that could affect the internal validity of the results. • The patient inclusion criteria were skewed toward enrolling patients with a better functional and disease status, and better prognosis at baseline. Only those patients who survived (without progression) from diagnosis to randomization were included in the study. • The open-label design of the trial created uncertainty in interpreting the patient-reported outcomes. • There were concerns regarding the crossover of some patients from the temozolomide-alone arm. • The study participants were slightly younger and had better health status and degree of independent functioning than what is typically observed in clinical practice. These factors lowered the generalizability of the results. • Overall, evidence was of moderate to very low certainty due to concerns regarding selection bias and low generalizability of results to real-world settings. • No longer-term studies or indirect comparisons were identified by the sponsor for the review.
Clinical harms	• CADTH found little to no difference in serious adverse events between Optune plus temozolomide and temozolomide alone (moderate certainty). • Optune treatment did not clearly add safety concerns to temozolomide alone.	There were some adverse events related to the device, such as skin irritation or itching from the transducer arrays, but they were mostly not severe.

Domains	Key findings	Uncertainties
Patient preferences	• Patients receiving Optune with temozolomide may benefit from clear MRI results, prolonged survival, and some resumption of daily activities. Nonetheless, they may also experience side effects, particularly scalp irritation and dermatitis. • Most patients with lived experience using Optune recommended making the treatment more accessible to people living with GBM.	• Patients using Optune need to manage lifestyle adjustments, such as wearing it for 18 hours daily, maintaining regular head shaving, and applying the transducer arrays to the head, which may require caregiver assistance.
Economic impact	• The submitted fee for Optune is $27,000 per month, which includes the treatment kit and support features. This cost is added to the cost of temozolomide. • At the submitted monthly fee for Optune and public list price for temozolomide, the ICER for Optune plus temozolomide vs. temozolomide alone was $899,470 per QALY gained (incremental costs = $336,902; incremental QALYs = 0.37). At this ICER, Optune plus temozolomide was not considered cost-effective relative to temozolomide alone at conventional willingness-to-pay thresholds (i.e., $50,000 per QALY gained or $100,000 per QALY gained). • A price reduction of between 91% and 97% is required for Optune plus temozolomide to be considered cost-effective at a willingness-to-pay threshold between $50,000 and $100,000 per QALY gained. • The budget impact of reimbursing Optune through the federal, provincial, and territorial public drug plans (excluding Quebec) is estimated to be $75,795,323 over 3 years. • Optune is estimated to be used by 232 patients over 3 years.	• The long-term efficacy of Optune is uncertain and may be dependent on the frequency and duration of the use of Optune by patients. • The sponsor assumed that patients would be functionally cured after 15 years. There is no robust evidence to support the validity of this assumption. • Time on treatment for Optune plus temozolomide and temozolomide alone were based on data from the EF-14 trial. There were wide ranges in time on treatment in the trial and differences in median and mean time on treatment. It is unclear how time on treatment data from the EF-14 trial will translate to Canadian clinical practice. • Health state utility values did not meet face validity.
Implementation	• Following surgical resection and RT with concomitant temozolomide, patients would receive Optune during the adjuvant temozolomide treatment phase. • The sponsor assumed the payer for Optune would be drug plans. • The sponsor assumed that the monthly rental fee would cover repair, replacement, maintenance, technical support, and clinical support. • A clinician must undergo a training course provided by the sponsor and obtain certification to prescribe Optune. • It is suggested that there are no additional	• It is unclear whether the CADTH participating drug plans, as suggested by the sponsor, are the appropriate payer for Optune. • It is unclear whether the subscription model and full set of included services indicated by the sponsor will be implementable by the payer. • The lifespan of Optune and its components is uncertain. The responsiveness of the sponsor to deliver the suggested services within the monthly fee cost is unclear. It is also unclear whether any new versions will be associated with changes to the sponsor's fee structure. • It is unclear whether the same standard of device repair and maintenance support

Domains	Key findings	Uncertainties
	costs to the health care payer associated with training physicians, patients, and caregivers to be familiar with the technology. • Clinical experts consulted by CADTH commented that it may be reasonable for patients to continue treatment beyond initial disease progression.	observed in clinical trials could be maintained as the customer base of Optune expands in the real-world health system environment. • Effectiveness of Optune appears to be dependent on treatment adherence (e.g., time wearing the device); thus, patient motivation may be important in determining device uptake. Family and caregiver support may be important in increasing the treatment adherence. • It is unclear whether any suggested discontinuation criteria can be implemented.
Ethics	• The balance of benefits, risks, and burdens associated with Optune is understood within the context of an individual patients' values and situation. Some patients may consider Optune as providing hope and an opportunity to gain a sense of control over the disease, while others may consider it as burdensome or a visible reminder of the disease. • To mitigate false hope, clinicians will need to covey that burdens experienced with maintenance chemotherapy will not be lifted with the addition of Optune, and instead, patients and caregivers will be required to manage an additional treatment modality. • As patients with ndGBM can be described as "vulnerable," careful attention must be paid to the quality of consent conversations to support informed decision-making and respect for patient autonomy. Eliciting a patient's values with respect to treatment is also important as disease progression may impair capacity to consent and require the involvement of a substitute decision-maker. • Consent conversations require ensuring that patients and caregivers understand that Optune is not curative and is proposed as an addition to maintenance chemotherapy, and that Optune is considered within a full range of treatment and care options, including available palliative care supports. Consent should also cover privacy considerations as the use of Optune requires transmitting patient data to the sponsor. • Equity- enhancing strategies will need to be explored if Optune is to be accessible in a fair and effective manner for patients in Canada. Special attention is required to address barriers to accessing Optune due to geography, socioeconomic status, language barriers, requirements for additional caregiver support,	• Acceptability of the device, and the extent to which Optune meets patients' needs for effective, accessible, and easily usable treatment remain uncertain and will likely depend on an individual patient's values and caregiver support network. • Limitations in HRQoL data and the generalizability of the trial findings have implications for consent conversations and the ability to adhere to and benefit from treatment in a diverse patient population in the real-world. • Further study on how, or if, factors such as functional status, race, sex, age, socioeconomic status, and availability of caregiver support have implications for acceptability and ability to adhere to treatment would be helpful to support patient-centred care and equitable access given the diversity of the population in Canada. • There are no data for pregnant patients and neither Optune nor temozolomide are recommended for use in this population. Patient or substitute decision-maker preferences may prompt reconsideration as risk tolerance and individual circumstances vary.

Domains	Key findings	Uncertainties
	and barriers to accessing oral temozolomide in jurisdictions where it is not reimbursed.	

CNS = central nervous system; GBM = glioblastoma multiforme; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; ndGBM = newly diagnosed glioblastoma multiforme; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RCT = randomized controlled trial; RT = radiotherapy; TTFields = tumour-treating fields; vs. = versus.

HTERP Core Members

Leslie Anne Campbell — Chair, Nova Scotia

Louise Bird — Patient member, Saskatchewan

Sandor Demeter — Health care practitioner, Manitoba

Lawrence Mbuagbaw — Health technology assessment specialist, Ontario

Brian Chan — Health economist, Ontario

Duncan Steele — Ethicist, Alberta

Note: As of January 2024, there is currently a committee seat vacancy for 1 health care practitioner.

Meeting date: January 12, 2024

Regrets: None

Conflicts of interest: None

References

1. Walker EV, Zhou Y, Wu Y, et al. The Incidence and Prevalence of Primary Central Nervous System (CNS) Tumours in Canada (2010-2017), and the Survival of Patients Diagnosed with CNS Tumours (2008-2017). *Curr Oncol.* 2023;30(4):4311-4328. PubMed
2. Kinzel A, Ambrogi M, Varshaver M, Kirson ED. Tumor Treating Fields for Glioblastoma Treatment: Patient Satisfaction and Compliance With the Second-Generation Optune((R)) System. *Clin Med Insights Oncol.* 2019;13:1179554918825449. PubMed
3. Novocure Canada Inc. TRIDENT – Glioblastoma Clinical Trial. [2024]; https://novocuretrials.com/cancer-clinical-trials/glioblastoma-clinical-trial-trident/. Accessed 2024 Jan 23.
4. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352(10):997-1003. PubMed
5. Iorgulescu JB, Sun C, Neff C, et al. Molecular biomarker-defined brain tumors: Epidemiology, validity, and completeness in the United States. *Neuro Oncol.* 2022;24(11):1989-2000. PubMed

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