



Canada's Drug and  
Health Technology Agency

CADTH Reimbursement Recommendation

# Bevacizumab Solution for IV Infusion

**Reimbursement request:** In combination with lomustine, for the treatment of patients with glioblastoma multiforme after relapse or disease progression, following prior therapy

**Final recommendation:** Reimburse with conditions

## Why Did CADTH Make This Recommendation?

The CADTH Formulary Management Expert Committee (FMEC) acknowledged that recurrent glioblastoma multiforme is highly refractory and challenging to treat, with particularly low survival rates. There are only a limited number of therapeutic options, all of which have little impact on prognosis. FMEC concluded that the availability of additional therapies is required.

FMEC reviewed the European Organization for Research and Treatment of Cancer (EORTC) 26101 trial, which demonstrated the efficacy of bevacizumab, in combination with lomustine, to lengthen progression-free survival in patients with recurrent glioblastoma multiforme as compared to lomustine monotherapy. FMEC highlighted that the combination treatment was associated with greater adverse events than lomustine monotherapy.

The expected cost of bevacizumab represents an additional cost to lomustine monotherapy or temozolomide.

FMEC recommends that bevacizumab, in combination with lomustine, be reimbursed for patients with recurrent glioblastoma multiforme, if clinical conditions are met.

# Therapeutic Landscape

## What Is Recurrent Glioblastoma Multiforme?

Glioblastoma multiforme is a highly malignant and rapidly progressing brain tumour with poor prognosis. It is characterized by significant disability and dependence, with patients experiencing inexorable neurologic decline. The average annual incidence rate is 4.05 per 100,000 individuals, which means it is responsible for half of all malignant central nervous system tumours.

## Why Did CADTH Conduct This Review?

Publicly funded drug plans requested this nonsponsored reimbursement review, as it met the eligibility criteria outlined in the Non-Sponsored Reimbursement Review Procedures.



### Patient With Lived Experience

A patient with lived experience presented her journey living with glioblastoma after being diagnosed in 2018. Following the diagnosis, she underwent multiple treatments, including 2 craniotomies, radiation therapy, chemotherapy, and clinical trials. Living in an urban center allowed her to access diagnostic and treatment centers more easily and she underscored the need for better access for people who live outside of urban settings in Canada. She emphasized the challenges patients face in obtaining drug coverage, stressing the need for equal access in Canada, noting that the process is lengthy and often requires support from family and friends. She stressed that there are limited treatment options available, and that providing more options to patients should be a priority. She also emphasized that patients living with glioblastoma need individualized treatments and that reducing adverse effects are important.

# Stakeholder Feedback

## What Did We Hear From Patients?

CADTH did not receive written input during the open call for stakeholder feedback. FMEC heard directly from a patient and patient group (Brain Cancer Canada and the Brain Tumour Foundation of Canada) on their lived experiences. They highlighted a need for greater treatment options that slow disease progression, reduce corticosteroids reliance, and improve quality of life.

## What Did We Hear From Clinicians?

CADTH received feedback from 1 clinician group, which highlighted the current lack of treatment options. Improving survival in patients with cancer should remain the primary goal of therapy, but the clinical experts consulted by CADTH noted that progression-free survival was a more appropriate objective in the context of this review.

## What Did We Hear From the Pharmaceutical Industry?

Industry highlighted that most patients with glioblastoma multiforme experience progression and/or recurrence after initial therapy, which consists of maximal tumour resection followed by chemoradiotherapy. They also commented that administration of bevacizumab and related evaluations would not be abnormally burdensome or impede adoption.

## What Did We Hear From Public Drug Programs?

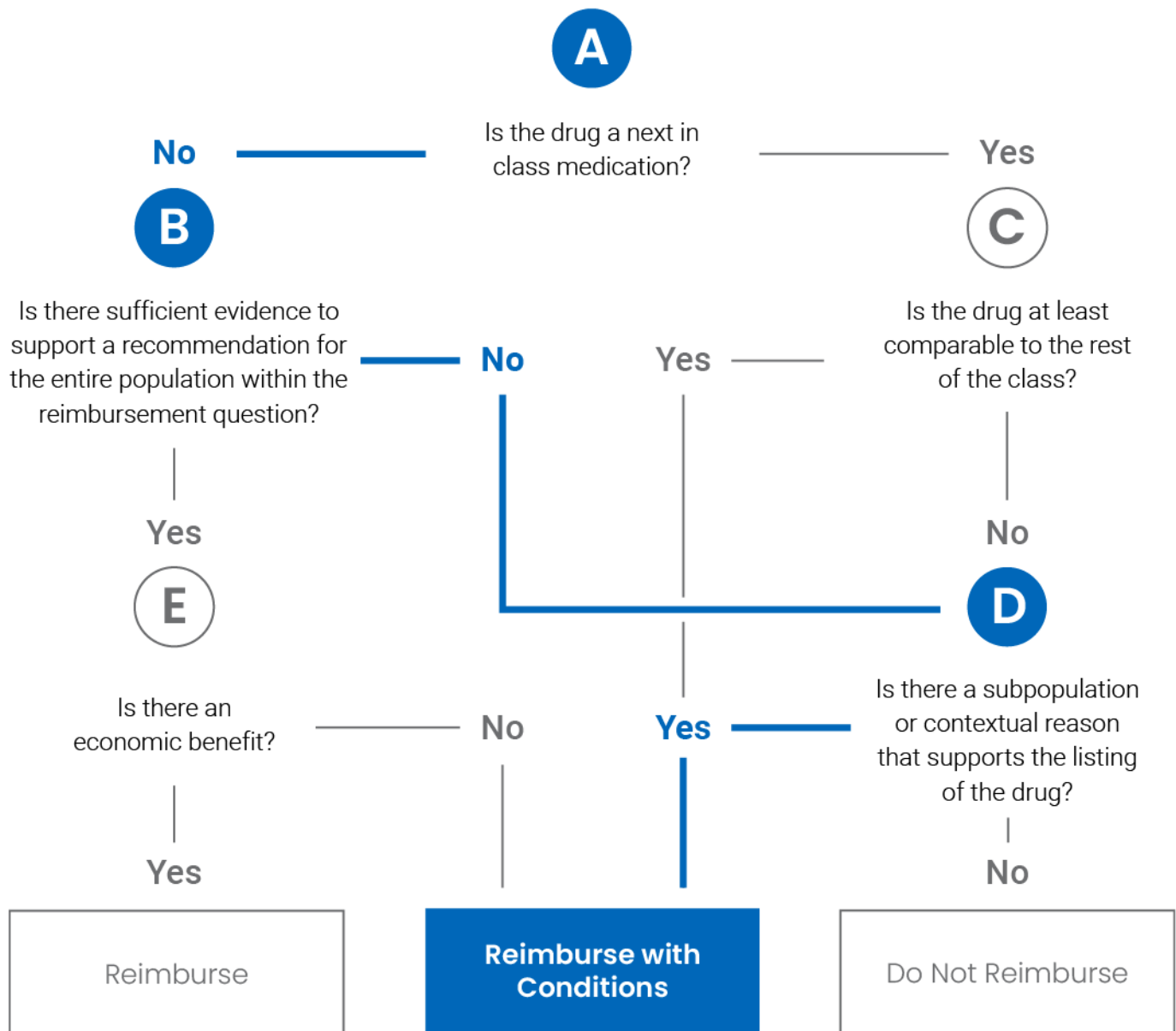
The public drug programs have requested this review as the availability of bevacizumab, in combination with lomustine, is a desirable alternative in the context of limited options in the management of a severe disease. Input was also provided on questions related to treatment implementation.



Refer to the [Stakeholder Input](#) section of the CADTH report.

# Deliberative Framework

Figure 1: Decision Path



# Decision Summary

**Table 1: Why Did FMEC Make This Recommendation?**

Decision Node	Vote	Reason
(A) Is the drug a next in class medication?	Yes (0)	—
	No (7)	<ul style="list-style-type: none"> <li>FMEC noted that bevacizumab, in combination with lomustine, is not a next in class medication.</li> <li>FMEC considered that there is a significant unmet need in the treatment of recurrent glioblastoma, considering the severity of the disease and the poor prognosis, as well as the lack of therapeutic options. This was noted from the literature and highlighted by clinicians and individuals with lived experience.</li> <li>FMEC acknowledged the evidence from the EORTC 26101 trial, which informs the efficacy of the combination of bevacizumab and lomustine in patients with recurrent glioblastoma compared to lomustine monotherapy.</li> <li>FMEC acknowledged that the combination of bevacizumab and lomustine did not improve overall survival, the primary end point of the EORTC 26101 trial. However, in this context, given the significant unmet need, the benefit of the combination treatment on progression-free survival (a secondary outcome) was deemed clinically important.</li> </ul>
(B) Is there sufficient evidence to support a recommendation for the entire population within the reimbursement question?  Population under consideration for reimbursement: Patients with glioblastoma after relapse or disease progression following prior therapy	Yes (0)	—
	No (7)	<ul style="list-style-type: none"> <li>FMEC noted that the EORTC 26101 trial was performed in a specific patient population (<math>\geq 3</math> months post treatment with radiotherapy, which is smaller than the broader Health Canada indication).</li> <li>FMEC also considered that patients in the EORTC 26101 trial were younger with better performance status than those typical of Canadian clinical practice.</li> <li>As such, treatment with bevacizumab, in combination with lomustine, should be reimbursed for patients whose disease characteristics are consistent with those of the patients included in the study.</li> </ul>
(D) Is there a subpopulation or contextual reason that supports the listing of the drug?	Yes (7)	<ul style="list-style-type: none"> <li>FMEC noted the disease severity and significant unmet need in patients with glioblastoma.</li> <li>FMEC acknowledged that the EORTC 26101 trial was performed in patients who had histologically confirmed glioblastoma multiforme with unequivocal first progression after chemoradiotherapy (at least 3 months after the end of radiotherapy), a WHO performance status <math>\leq 2</math>, as well as adequate hematologic, renal, and hepatic function.</li> <li>FMEC considered that bevacizumab combined with lomustine is associated with a higher number of adverse events compared to lomustine monotherapy, inconclusive benefits on health-related quality of life, and incremental cost to public drug programs.</li> </ul>

Decision Node	Vote	Reason
		<ul style="list-style-type: none"> <li>Given the significant unmet need, FMEC considered the evidence to be supportive of a positive reimbursement recommendation.</li> </ul>
	No (0)	—

EORTC = European Organization for Research and Treatment of Cancer; FMEC = CADTH Formulary Management Expert Committee.

## Full Recommendation

CADTH FMEC recommends that bevacizumab, in combination with lomustine, be reimbursed for patients with recurrent glioblastoma multiforme, if the conditions presented in [Table 2](#) are met.

**Table 2: Conditions, Reasons, and Guidance**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. Bevacizumab, in combination with lomustine, should be reimbursed for patients who meet all the following criteria: <ol style="list-style-type: none"> <li>1.1. histologically confirmed glioblastoma multiforme, and</li> <li>1.2. unequivocal first progression after chemoradiotherapy (at least 3 months after the end of radiotherapy), and</li> <li>1.3. WHO performance status <math>\leq 2</math>, and</li> <li>1.4. adequate hematologic, renal, and hepatic function.</li> </ol>	<p>Health Canada has approved the use of bevacizumab in combination with lomustine for any patient with recurrent, previously treated glioblastoma.</p> <p>The initiation criteria as per the EORTC 26101 study did not encompass the entire Health Canada indicated population due to the nature of conducting studies in patients with advanced forms of cancer. Treatment with bevacizumab, in combination with lomustine, should be reimbursed for patients whose disease characteristics are consistent with those of patients included in the study.</p>	<p>Consideration for reimbursement of bevacizumab, in combination with lomustine, could also be given to additional specific populations, such as patients who receive high doses of corticosteroids, patients with substantial peritumour edema, patients with confirmed tumour progression within less than 3 months after the end of chemoradiotherapy, and patients with a WHO performance status greater than 2. Based on clinical expertise, it is possible that patients within these subpopulations may benefit from treatment.</p>
<b>Discontinuation</b>		
2. Bevacizumab, in combination with lomustine, should be discontinued if the patient has any of the following: <ol style="list-style-type: none"> <li>2.1. disease progression as per the RANO criteria and clinical assessment, or</li> <li>2.2. significant intolerance to therapy.</li> </ol>	<p>The EORTC 26101 trial investigated the use of bevacizumab, in combination with lomustine, until disease progression occurred. The FMEC clinical experts also noted that this aligns with Canadian clinical practice.</p>	<p>FMEC noted that intolerance to, and discontinuation of, lomustine therapy should not automatically lead to the discontinuation of bevacizumab. Instead, the decision of whether to also discontinue bevacizumab should be made on a case-by-case basis.</p>

Reimbursement condition	Reason	Implementation guidance
Prescribing		
3. Bevacizumab, in combination with lomustine, must be initiated by a clinician with expertise in the treatment of recurrent glioblastoma multiforme.	Patients with recurrent glioblastoma are part of a specialized population who are expected to be under the care of an experienced treatment team. This aims to address the complexity of treating patients with recurrent glioblastoma and to maximize the potential benefits and mitigate adverse outcomes.	—

EORTC = European Organization for Research and Treatment of Cancer; FMEC = CADTH Formulary Management Expert Committee; RANO = Response Assessment in Neuro-Oncology.

## Feedback on Draft Recommendation

CADTH received feedback on the draft recommendation from the Ontario Health (Cancer Care Ontario) Central Nervous System Cancer Drug Advisory Committee, Amgen Canada Inc., Brain Cancer Canada, and CADTH's Provincial Advisory Group (PAG). This feedback was reviewed, and no revisions were made to the recommendation.

## FMEC Information

**Members of the committee:** Dr. Emily Reynen (Chair), Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, Dr. Sarah Ironside (guest clinical specialist)

**Meeting date:** October 17, 2023

**Conflicts of interest:** None

**Special thanks:** CADTH extends our special thanks to the individuals who presented directly to FMEC on behalf of patients with lived experience, patient organizations representing the community of those living with glioblastoma, Brain Cancer Canada, and the Brain Tumour Foundation of Canada, which include Anita Angelini, Rebecca Grundy, Shannon LaHay, Sarah Rogers, and Jessica Soares.



The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third-party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian Copyright Act and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

Confidential information in this document may be redacted at the request of the sponsor in accordance with the CADTH Drug Reimbursement Review Confidentiality Guidelines.



Canada's Drug and  
Health Technology Agency

CADTH was established by Canada's federal, provincial, and territorial governments to be a trusted source of independent information and advice for the country's publicly funded health care systems. Health administrators and policy experts rely on CADTH to help inform their decisions about the life cycle management of drugs, devices, and services used to prevent, diagnose, and treat medical conditions.

CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.