Draft Reimbursement Recommendation

Dabrafenib-Trametinib

Reimbursement request: For the treatment of pediatric and young adult patients for first line or greater therapy of low-grade gliomas with residual disease and with known BRAF V600 mutations.

Requester: Public drug programs

Draft recommendation: Reimburse with conditions

Summary

What is the Reimbursement Recommendation for Dabrafenib-Trametinib?

The Formulary Management Expert Committee (FMEC) recommends that dabrafenib and trametinib, be reimbursed in patients with low grade gliomas and V600 mutation, provided certain conditions are met.

What Are the Conditions for Reimbursement?

Dabrafenib-trametinib should only be reimbursed in patients 1 year of age and older with low grade gliomas and V600 mutation for first or later lines in therapy, for those with inoperable and residual disease after surgery. Note that a reduction in the prices of dabrafenib-trametinib may be required.

Why did CDA-AMC Make This Recommendation?

FMEC reviewed 1 randomized controlled trial (Bouffet et al) and 1 single arm cohort within a basket trial (ROAR trial), identified by CDA-AMC's systematic review of literature. FMEC also considered input received from 1 patient group from Advocacy for Canadian Childhood Oncology Research Network (Ac2orn) and input from public drug programs.

FMEC concluded that there was uncertainty in the clinical value demonstrated by dabrafenib-trametinib, however given the significant morbidities associated with pediatric low grade gliomas, considerations was given to dabrafenib-trametinib based on the significant unmet clinical need despite available treatments. The reimbursement conditions were further developed based on distinct social and ethical considerations, economic considerations and impacts on health systems.

The reimbursement of dabrafenib plus trametinib for the treatment of patients 1 year of age and older as first-line or greater therapy in low-grade gliomas with residual disease and with known BRAF V600 mutations is expected to increase drug acquisition costs.

Therapeutic Landscape

What Is Low Grade Glioma?

Low-grade gliomas (LGGs) are the most common type of central nervous system (CNS) tumours found in children, adolescents and young adults, accounting for about one-third of all CNS tumours. LGGs are a diverse group of tumours that differ in terms of location in the CNS, histology type, and molecular profile. The incidence of LGGs in Canada was reported as 1.41 cases per 100,000 person years in children aged 0 to 14 from 2001 to 2015.

What Are The Current Treatment Options?

The preferred first-line treatment for LGGs is complete surgical removal (resection) of the tumour. Where complete resection is not possible, chemotherapy with vinblastine monotherapy or carboplatin plus vincristine is currently first-line treatment. Where cancer has progressed or relapsed, second-line therapy currently includes targeted therapies with dabrafenib monotherapy, dabrafenib-trametinib combination for patients identified to have BRAF V600 mutations. Radiation therapy is generally avoided in children and younger people due to the risk of significant long-term neurologic and cognitive damage.

What Is the Treatment Under Review?

Dabrafenib is a *BRAF*-kinase inhibitor and trametinib is a protein kinase inhibitor against the enzymes of MEK-1 and MEK-2. Dabrafenib-trametinib is approved by Health Canada for the treatment of pediatric patients 1 year of age and older with LGGs with a BRAF V600E mutation who require systemic therapy. It is also approved for other indications including those with BRAF V600E mutations in adjuvant or metastatic melanoma and non-small cell lung cancers.

Why Did We Conduct This Review?

Patients with low grade gliomas often face significant morbidities and long term sequalae from their tumours. Currently, the treatment options include surgery, radiation therapy and cytotoxic chemotherapy with significant risks and adverse effects and limited efficacy. Given the slow growing nature of these tumours, the treatment strategy may adapt over time, resulting in the need for multiple lines of therapy over the years. The use of oral targeted agents is preferred by many patients and families as it potentially offers benefits in quality of life and allows pediatric patients to attend school and achieve important developmental milestones.

Given the data protection for dabrafenib-trametinib has ended in 2021, this treatment is eligible for a non-sponsored reimbursement review as per the procedures for reimbursement reviews. At the request of the participating public drug programs, we reviewed the combination dabrafenib and trametinib to inform a recommendation on whether it should be reimbursed for pediatric and young adult patients for first line or greater therapy in low grade gliomas with residual disease and with known BRAF V600 mutations.

Input From Community Partners

- **Advocacy for Canadian Childhood Oncology Research Network (Ac2orn)** highlighted that pediatric low-grade gliomas has profound long-term physical, emotional and financial impacts on the child and their families.

- **Public Drug Programs** inquired about the evidence for dabrafenib-trametinib to inform a reimbursement recommendation in the setting of low-grade gliomas. The public drug programs outlined implementation questions related to treatment eligibility and potential costs.

- We did not receive input from clinician groups.

► **Refer to the main report and the supplemental material document for this review.**

Person With Lived Experience

A mother shared her experience as a caregiver to a vibrant young child with an aggressive form of glioma and few treatment options. Maximizing her child's quality of life and prolonging survival were the main treatment goals for her and her family. Her child underwent palliative radiation therapy and developed multiple debilitating, treatable side effects. She passed away peacefully eight months after diagnosis. Her family incurred high out-of-pocket costs obtaining medication from Europe that was unavailable in Canada. Restrictive hospital protocols, drug shortages, and reduced access to clinical trials due to the global pandemic made treatment more challenging. The stress and mental health toll her family endured were significant and lasting, and she underscored the importance of Canadian patients having more glioma treatment options from the time of diagnosis.

Disclaimer: The perspectives shared by people with lived experience who present to the committee reflect their individual experiences and are not necessarily representative of all people with the same condition or course of treatment. Their insights provide valuable context about what a patient, support person or caregiver might go through when facing this condition or treatment, helping to inform the committee's deliberations. These narratives complement other forms of evidence and input and should be considered as part of a broader understanding of the condition and treatment under review.

Summary of Deliberation

FMEC deliberated on all domains of value of the deliberative framework prior to developing their recommendation: clinical value, unmet clinical need, distinct social and ethical considerations, economic considerations, and impacts on health systems.. For further information on the domains of value, please refer to the Expert Committee Deliberation at Canada's Drug Agency document.

FMEC considered the following key discussion points, organized by the five domains of value.

Clinical Value

- **FMEC concluded that it is uncertain whether dabrafenib-trametinib demonstrates acceptable clinical value versus appropriate comparators in the Canadian setting.**
- Through reflection on the input from patient groups and insights shared by people with lived experience, FMEC members noted the following important patient values or perspectives:
    - Patients and families affected by low grade gliomas want access to, treatments that can offer improved outcomes and tolerability. It is important to also consider the impacts of the disease on mental health of patients and families. These impacts are not captured through clinical evidence. Additionally, school absenteeism related to treatment administration may impact on academic performance and social functioning for pediatric patients.
- **FMEC** members highlighted the following points:
    - FMEC discussed the clinical evidence from the included studies. The first study by Bouffet et al. was a phase II randomized trial in 110 pediatric patients. The second study was the ROAR trial which was a phase II single arm trial (as part of a basket trial) and enrolled 13 young adults. Based on the trial by Bouffet et al., there was improved progression-free survival with dabrafenib plus trametinib compared with chemotherapy. The Kaplan-Meier estimated probabilities for PFS as determined by the independent review at 6 months and 12 months, respectively, were higher in the dabrafenib-trametinib group (87% and 67%) than in the chemotherapy group (58% and 26%). The median PFS was 20.1 months (95% CI 12.8 to NE) and 7.4 months (95% CI 3.6 to 11.8) in the dabrafenib and trametinib group as compared with the chemotherapy group, respectively. The hazard ratio for PFS favoured dabrafenib-trametinib over chemotherapy (HR 0.31, 95% CI, 0.17 to 0.55). FMEC discussed that the treatment discontinuations due to adverse events occurred at a lower rate with dabrafenib-trametinib group than with chemotherapy (4% vs. 18%) in the Bouffet et al. trial. FMEC discussed there was no planned statistical assessment of the difference between the PFS in both arms, although it was noted that the confidence intervals did not overlap.
    - FMEC highlighted that the HRQoL data were incomplete and based on small patient numbers.

Unmet Clinical Need

- **FMEC concluded that there is significant unmet clinical need arising from low grade gliomas despite available treatments.**
- Through reflection on the input from patient groups and insights shared by people with lived experience, FMEC members noted the following important patient values or perspectives:
    - There is a need for more effective and better tolerated treatments, such that patients can avoid or postpone the use of other intensive treatments such as radiation or chemotherapy. Even when treatment may not be curative, patients greatly appreciate therapeutic options that can extend survival and improve quality of life. Orally administered treatments can reduce burden on patients, caregivers and families. Despite the high survival rates for low grade gliomas, there may be significant long-term physical, social and emotional impacts on the patients and families.
- **FMEC** members highlighted the following points:
    - FMEC discussed that the current treatment options for unresectable low-grade gliomas include conventional chemotherapies. As reported in the main report, the risk of progression and progression-free survival after treatment with conventional chemotherapy range around 40-50%. Hence, there is a need for more effective treatment options.
    - FMEC discussed dabrafenib-trametinib offers an oral option with manageable safety profile. The oral option allows patients to receive treatment at home, if the cost of treatment is funded by public or private payers. FMEC also discussed that access to BRAF V600 testing is required for patient selection.

Distinct Social and Ethical Considerations

- **FMEC concluded that dabrafenib-trametinib would potentially address a significant nonclinical need arising from low grade gliomas despite available treatments. FMEC concluded that there are important measures that should be implemented to ensure that the use of dabrafenib-trametinib addresses relevant social and ethical implications.**
- **FMEC** members highlighted the following points:
    - FMEC discussed that access to the oral combination treatment could lessen the burden on the patient and family caregivers, especially for the pediatric population.
    - FMEC also discussed that access to rapid BRAF V600 testing needs to be available to all patients

with low grade glioma. FMEC heard from the guest clinical experts that BRAF testing is widely available. In addition, the patient should have access to specialist neurologists or pediatricians.

- FMEC also noted that the cost of oral medications is variable across jurisdictions and presents a concern for inequity. These treatments should be available for all patients regardless of where they reside within Canada.

Economic Considerations

- **FMEC concluded that there are economic considerations that are important to address when implementing dabrafenib-trametinib.**
- **FMEC** members highlighted the following discussion points:
  - The reimbursement of dabrafenib plus trametinib for the treatment of adult and pediatric patients as first-line or greater therapy in low-grade gliomas with residual disease and with known BRAF V600 mutations is currently expected to increase overall drug acquisition costs.
  - No evidence was identified regarding the cost-effectiveness of dabrafenib plus trametinib relative to carboplatin plus vincristine, vinblastine, or dabrafenib monotherapy as first-line or greater therapy in low-grade gliomas with residual disease and known BRAF V600 mutations in Canada, and therefore, estimates of cost-effectiveness were not available to the committee. FMEC discussed that a cost-effectiveness analysis would be valuable to fully inform the reimbursement recommendation.
  - FMEC noted that dabrafenib plus trametinib likely demonstrates a clinical benefit compared to carboplatin plus vincristine, while its benefit relative to vinblastine monotherapy remains unknown. Given this uncertainty, FMEC recommended price reductions.
  - FMEC noted that BRAF V600 mutation testing is routinely available across jurisdictions; therefore, its associated costs are unlikely to represent an incremental expense.
  - FMEC noted that both drugs are approaching the end of their market exclusivity, which may lead to the availability of generic products and exert downward pressure on market prices. The patent for trametinib is set to expire in mid-2025, while the patent for dabrafenib is expected to expire in 2029.

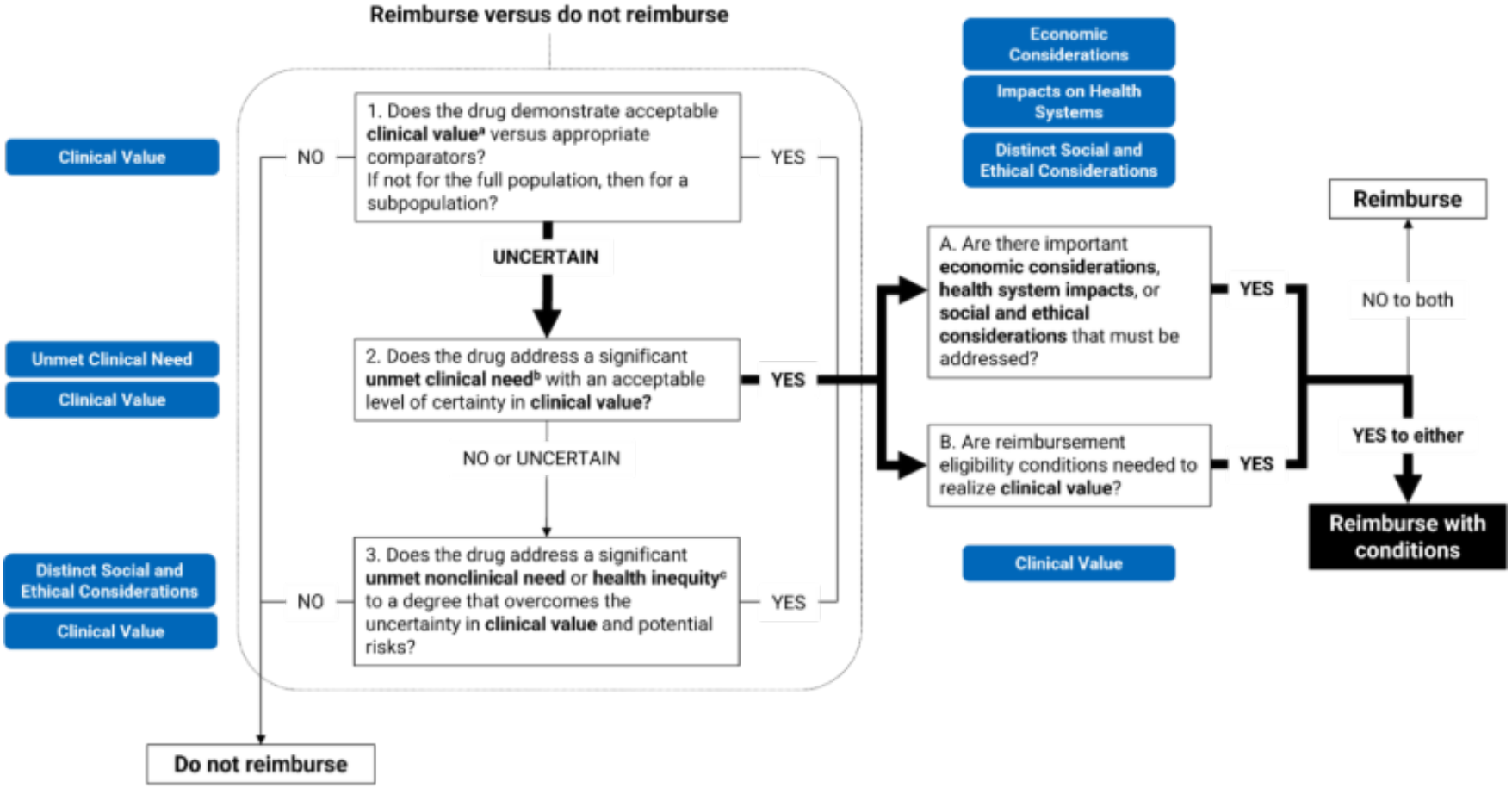
Impacts on Health Systems

- **FMEC concluded that there are impacts on health systems that are important to address when implementing dabrafenib-trametinib.**
- **FMEC** members highlighted the following points:

- FMEC discussed that access to dabrafenib-trametinib will likely decrease resources required for nursing administration and monitoring of intravenous chemotherapies and the pharmacy preparation time. In addition, it may reduce complications related to chemotherapy administration (e.g., hospital admission for febrile neutropenia or central line complications). However, there may be increased drug costs. The guest specialist also shared that, given this treatment is administered at home, there is less demand on the patients and families to travel into the clinics for in-person monitoring. In rural communities and for some age groups (4-5 years of age), the travel time saving is substantial.
- FMEC also discussed that this treatment has been available for use in other settings. As such, no special training or implementation would be needed.

Figure 1: Recommendation Pathway

Alt-text: Flow chart indicating the steps used by the committee for this recommendation. The committee determined that it was uncertain whether the drug demonstrated acceptable clinical value versus relevant comparators. However, the committee also determined that the drug addresses a significant unmet clinical need with an acceptable level of certainty in clinical value. Therefore, the committee recommended reimbursement of the drug for the patient population under consideration. After deliberating on economic considerations, impacts on health systems, distinct social and ethical considerations, and whether reimbursement conditions are needed to realize clinical value, the committee determined that reimbursement of the drug should be contingent upon 1 or more conditions being satisfied.



a Acceptable clinical value refers to at least comparable clinical value (if the drug is expected to be substitutive treatment) or added clinical value (if the drug is expected to be additive treatment) versus appropriate comparators.

b Significant unmet clinical need depends on all of the following: severity of the condition, availability of effective treatments, and challenges in evidence generation due to rarity of the condition or ethical issues.

c Unmet nonclinical need and health inequity are key components within the distinct and social ethical considerations domain of value.

Full Recommendation

With a vote of 8 to 0 FMEC recommends that dabrafenib-trametinib, for the treatment of patients 1 year of age and older with low grade gliomas and known BRAF V600 mutations, be reimbursed if the conditions presented in Table 1 are met.

Table 1: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Dabrafenib-trametinib may be initiated in patients 1 year of age and older with low grade gliomas and V600 mutation for first or later lines of therapy in those with inoperable or residual disease after surgery.	There is evidence from 1 RCT (Bouffet et al.) comparing dabrafenib-trametinib to carboplatin plus vincristine as first line therapy in pediatric patients with BRAF V600 mutated LGG. In this RCT, there was improved progression-free survival, overall response rate and clinical benefit with dabrafenib-trametinib compared with chemotherapy. In addition, there is evidence from a single arm cohort within a basket trial (ROAR trial), suggesting that greater than half of adult patients with relapsed or refractory BRAF V600E mutated LGG achieved overall response.	BRAF V600 testing is required to determine if patients are eligible for treatment with dabrafenib-trametinib. The guest specialists noted that dabrafenib-trametinib may also be used in patients with other rare BRAF V600 mutations. Bouffet et al. included a small portion of patients with other BRAF V600 mutations. While low grade glioma primarily affects the pediatric population, many patients may have disease progression to occur later during adulthood (e.g., 18 years or older). As such, the age eligibility is kept broad to include any patients 1 year of age and older, as long as they meet the initiation conditions.
Discontinuation and renewal		
2. Dabrafenib-trametinib should be discontinued if there is disease progression or significant toxicity.	Consistent with clinical practice, patients in the RCT by Bouffet et al. and ROAR study discontinued treatment upon disease progression or significant toxicity.	Treatment response should be monitored with imaging (e.g., MRI) and clinical exam as per standard of care.
Prescribing		
3. Prescribing should be limited to clinicians with expertise in the diagnosis and management of low-grade gliomas.	This will ensure that appropriate treatment is prescribed for patients and adverse events are optimally managed.	The dosage prescribed should be as per the Bouffet trial for pediatric patients and the usual dosing for adult patients.

Reimbursement condition	Reason	Implementation guidance
Pricing		
4. A reduction in the prices of dabrafenib and trametinib may be required.	The reimbursement of dabrafenib plus trametinib for the treatment of adult and pediatric patients as first-line or greater therapy in low-grade gliomas with residual disease and with known BRAF V600 mutations is expected to increase overall drug acquisition costs. No evidence was identified regarding the cost-effectiveness of dabrafenib plus trametinib relative to carboplatin plus vincristine and vinblastine monotherapy for first-line or greater therapy in low-grade gliomas with residual disease and with known BRAF V600 mutations in Canada. Therefore, estimates of cost-effectiveness were not available to the committee. A cost-effectiveness analysis would be needed to determine whether dabrafenib plus trametinib is cost-effective. Given that dabrafenib plus trametinib is associated with increased drug acquisition costs and likely clinical benefit relative to carboplatin plus vincristine —and its benefit relative to vinblastine monotherapy remains unknown— price reductions may be required.	

Abbreviation: LGG = low grade gliomas; MRI = magnetic resonance imaging; RCT = randomized controlled trial

Feedback on Draft Recommendation

<to be updated after the feedback period>

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and two guest specialists from Alberta and Nova Scotia.

Meeting date: March 20, 2025

Conflicts of interest: None

Special thanks: Canada's Drug Agency (CDA-AMC) extends our special thanks to the individuals who presented directly to FMEC and to patient organizations representing the community of those living with gliomas, including Brain Cancer Canada, Anita Angelini, and Jackie Borkowski. A very special thank you to Isabelle Borkowski.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.