Canada's Drug Agency
L'Agence des médicaments du Canada

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Drugs Health Technologies Health Systems

Reimbursement Review

# Dabrafenib Plus Trametinib: Supplemental Material

Requester: Public drug programs
Therapeutic area: Low-grade gliomas with *BRAF* V600 mutations

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# Abbreviations

| | |
|---|---|
| **AE** | adverse event |
| **AESI** | adverse event of special interest |
| **CBR** | clinical benefit rate |
| **CI** | confidence interval |
| **CNS** | central nervous system |
| **CR** | complete response |
| **D+T** | dabrafenib plus trametinib |
| **ECOG** | Eastern Cooperative Oncology Group |
| **HR** | hazard ratio |
| **HRQoL** | health-related quality of life |
| **ITT** | intention to treat |
| **LGG** | low-grade glioma |
| **OR** | odds ratio |
| **ORR** | overall response rate or objective response rate |
| **OS** | overall survival |
| **PFS** | progression-free survival |
| **PLGG** | pediatric low-grade glioma |
| **PR** | partial response |
| **RAF** | rapidly accelerated fibrosarcoma |
| **RCT** | randomized controlled trial |
| **RR** | risk ratio |
| **SAE** | serious adverse event |
| **SD** | standard deviation |

# Background Appendices

## Appendix 1: Drug Program Input and Treatment Characteristics

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized and provided to the expert committee in a separate document.

### Table 1: Key Characteristics of Dabrafenib Plus Trametinib and Comparators

| Treatment | Mechanism of action | Indication[a] | Recommended dosage and route of administration | Serious adverse effects or safety issues |
|---|---|---|---|---|
| Dabrafenib | Inhibits RAF kinases, including BRAF, which results in blocking the MAPK pathway that regulates the proliferation and survival of tumour cells in different cancers. | Treatment of pediatric patients 1 year of age and older with LGG with a BRAF V600E mutation who require systemic therapy<br>Confirmation of BRAF V600 mutation using a validated test is required to select patients appropriate for treatment with dabrafenib or trametinib as monotherapies or in combination | Pediatric patients,<br>Recommended dosing based on Health-Canada approved dosing[b]<br>Adult patients, Dabrafenib: 150 mg oral, twice daily | Secondary malignancies<br>Non-infectious febrile events<br>Venous Thromboembolism<br>Major hemorrhagic events |
| Trametinib | Inhibitor of MEK1 and MEK2 proteins, which are components of the MAPK pathway, causing tumour cell growth inhibition and cell death. | | Pediatric patients,<br>Recommended dosing based on Health-Canada approved dosing[b]<br>Adult patients<br>Trametinib: 2 mg oral, once daily | Left ventricular dysfunction<br>Retinal pigment epithelial detachment, Retinal vein occlusion<br>Interstitial lung disease<br>Skin toxicity<br>Non-infectious febrile events<br>Venous Thromboembolism<br>Major hemorrhagic events |
| **Comparators[c]** | | | | |
| Carboplatin | Interferes with DNA in cells exposed to the drug. | Off-label use<br>(No HC indication for LGG in pediatrics and young adults) | IV injection; 10 weeks of induction therapy, followed by 8 cycles of consolidation therapy[d] | Serious and fatal infections after receiving live or live-attenuated vaccines<br>Hypersensitivity reactions<br>Allergic reactions<br>Myelosupression |

| Treatment | Mechanism of action | Indication[a] | Recommended dosage and route of administration | Serious adverse effects or safety issues |
|---|---|---|---|---|
| | | | | Fatal hemolytic anemia<br>Fatal hemolytic uraemic syndrome<br>Fatal veno-occlusive disease |
| Vincristine[c] | Irreversible binding of drug to microtubules of cells and interferes with RNA synthesis | Off-label use<br>(No HC indication for LGG in pediatrics and adults) | | Hair loss<br>Sensorimotor dysfunction,<br>paresthesia, difficulty in walking, slapping gait, loss of deep tendon reflexes and muscle wasting |
| Vinblastine[c] | Inhibiting mitosis at metaphase and RNA synthesis in tumour cells | Off-label use<br>(No HC indication for LGG in pediatrics and adults) | IV injection; Incremental approach to dosage at weekly intervals | Leukopenia<br>Epilation<br>Gastrointestinal effects |

LGG = low-grade glioma; MAPK = mitogen-activated protein kinase; RAF = rapidly accelerated fibrosarcoma; RAS = rat sarcoma.

[a]Health Canada–approved indication.

[b]Recommended dosage for dabrafenib and trametinib for pediatric patients according to the product monographs are outlined in Tables 2, 3, 4 and 5.

[c]Information obtained from product monograph for respective comparator treatments, except otherwise stated.

[d]Carboplatin and vincristine for pediatrics in the Bouffet et al (2023) was dosed according to dosing schedule used in the Children's Oncology Group trial.[1]

## Table 2: Recommended Dosage for Dabrafenib Capsules in Pediatric Patients

| Body weight (kg) | Recommended starting dosage |
|---|---|
| 26 to 37 kg | 75 mg orally twice daily |
| 38 to 50 kg | 100 mg orally twice daily |
| ≥ 51 kg | 150 mg orally twice daily |

Source: Dabrafenib product monograph[2]. 

## Table 3: Recommended Dosage for Dabrafenib Tablets for Suspension in Pediatric Patients

| Body weight (kg) | Recommended starting dosage | |
|---|---|---|
| | Daily Dose | Number of 10 mg tablets twice daily |
| 8 to 9 kg | 20 mg twice daily | 2 |
| 10 to 13 kg | 30 mg twice daily | 3 |
| 14 to 17 kg | 40 mg twice daily | 4 |
| 18 to 21 kg | 50 mg twice daily | 5 |
| 22 to 25 kg | 60 mg twice daily | 6 |
| 26 to 29 kg | 70 mg twice daily | 7 |
| 30 to 33 kg | 80 mg twice daily | 8 |
| 34 to 37 kg | 90 mg twice daily | 9 |

| Body weight (kg) | Recommended starting dosage | |
|---|---|---|
| | Daily Dose | Number of 10 mg tablets twice daily |
| 38 to 41 kg | 100 mg twice daily | 10 |
| 42 to 45 kg | 110 mg twice daily | 11 |
| 46 to 50 kg | 130 mg twice daily | 13 |
| ≥ 51 kg | 150 mg twice daily | 15 |

Source: Dabrafenib product monograph[2] © His Majesty the King in Right of Canada, as represented by the Minister of Health, 2024.

## Table 4: Recommended Dosage for Trametinib Tablets in Pediatric Patients

| Body weight | Recommended starting dosage |
|---|---|
| 26 to 37 kg | 1 mg orally once daily |
| 38 to 50 kg | 1.5 mg orally once daily |
| ≥ 51 kg | 2 mg orally once daily |

Source: Trametinib product monograph[3] © His Majesty the King in Right of Canada, as represented by the Minister of Health, 2024.

## Table 5: Recommended Dosage for Reconstituted Trametinib Powder for Oral Solution

| Body weight (kg) | Recommended dose: Total volume of oral solution once daily (trametinib content) |
|---|---|
| 8 kg | 6 mL (0.3 mg) |
| 9 to 10 kg | 7 mL (0.35 mg) |
| 11 kg | 8 mL (0.4 mg) |
| 12 to 13 kg | 9 mL (0.45 mg) |
| 14 to 17 kg | 11 mL (0.55 mg) |
| 18 to 21 kg | 14 mL (0.7 mg) |
| 22 to 25 kg | 17 mL (0.85 mg) |
| 26 to 29 kg | 18 mL (0.9 mg) |
| 30 to 33 kg | 20 mL (1 mg) |
| 34 to 37 kg | 23 mL (1.15 mg) |
| 38 to 41 kg | 25 mL (1.25 mg) |
| 42 to 45 kg | 28 mL (1.4 mg) |
| 46 to 50 kg | 32 mL (1.6 mg) |
| ≥ 51 kg | 40 mL (2 mg) |

Source: Trametinib product monograph[3] © His Majesty the King in Right of Canada, as represented by the Minister of Health, 2024.

# Clinical Review Appendices

## Appendix 2: Methods of the Clinical Review

For the systematic review, we included studies that adhered to the a priori eligibility criteria detailed in Table 2 of the main report.

### Search Strategy

#### Strategy for Primary Studies (Systematic Review)

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist.[4]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were dabrafenib, trametinib, and gliomas. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results.

The initial searches were completed on October 30, 2024. Regular alerts updated the searches until the meeting of the Formulary Management Expert Committee meeting on March 20, 2025.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts.

#### Strategy for Indirect Treatment Comparisons

A focused literature search for indirect treatment comparisons (ITCs) dealing with dabrafenib and trametinib or gliomas was run in MEDLINE on October 30, 2024. Retrieval was not limited by publication date or by language.

## Clinical Literature Search

### Overview

**Interface:** Ovid

**Databases:**

- MEDLINE All (1946 to present)
- Embase (1974 to present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

**Date of search:** October 30, 2024

**Alerts:** Biweekly search updates until project completion

**Search filters applied**: No filters were applied to limit the retrieval by study type.

**Limits:**

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

### Table 6: Syntax Guide

| Syntax | Description |
|---|---|
| **/** | At the end of a phrase, searches the phrase as a subject heading |
| **exp** | Explode a subject heading |
| ***** | Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings |
| **.ti** | Title |
| **.ot** | Original title |
| **.ab** | Abstract |
| **.hw** | Heading word; usually includes subject headings and controlled vocabulary |
| **.kf** | Keyword heading word |
| **.dq** | Candidate term word (Embase) |
| **.pt** | Publication type |
| **.rn** | Registry number |
| **.nm** | Name of substance word (MEDLINE) |
| **medall** | Ovid database code: MEDLINE All, 1946 to present, updated daily |
| **oemezd** | Ovid database code; Embase, 1974 to present, updated daily |

## Warning

To conduct a comprehensive search, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, *Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches*.

## Multi-Database Strategy

1. (dabrafenib* or Tafinlar* or Taffiner* or Tafinra* or Finlee* or drb436 or drb-436 or gsk-2118436* or gsk2118436* or QGP4HA4G1B).ti,ab,kf,ot,hw,rn,nm.
2. (trametinib* or Mekinist* or Megsel* or Mekinst* or Spexotras* or gsk-1120212* or gsk1120212* or jtp-74057 or jtp74057 or snr-1611 or snr1611 or tmt-212 or tmt212 or 33E86K87QN).ti,ab,kf,ot,hw,rn,nm.
3. 1 and 2
4. exp Glioma/
5. (glioma* or astrocytoma* or ependymoma* or medulloblastoma* or oligodendroglioma* or ganglioglioma* or oligoastrocytoma* or xanthoastrocytoma* or astroblastoma* or neurogliocytoma* or neuroglioma* or neurospongioma* or gliosarcoma* or gliobastoma*).ti,ab,kf.
6. ((glia* or CNS or central nervous system* or brain or spinal cord) adj3 (tumor* or tumour*)).ti,ab,kf.
7. or/4-6
8. 3 and 7
9. 8 use medall
10. *dabrafenib/
11. (dabrafenib* or Tafinlar* or Taffiner* or Tafinra* or Finlee* or drb436 or drb-436 or gsk-2118436* or gsk2118436* or QGP4HA4G1B).ti,ab,kf,dq.
12. 10 or 11
13. *trametinib/
14. (trametinib* or Mekinist* or Megsel* or Mekinst* or Spexotras* or gsk-1120212* or gsk1120212* or jtp-74057 or jtp74057 or snr-1611 or snr1611 or tmt-212 or tmt212 or 33E86K87QN).ti,ab,kf,dq.
15. 13 or 14
16. 12 and 15
17. exp glioma/ or brain tumor/ or central nervous system neoplasms/ or central nervous system cancer/
18. (glioma* or astrocytoma* or ependymoma* or medulloblastoma* or oligodendroglioma* or ganglioglioma* or oligoastrocytoma* or xanthoastrocytoma* or astroblastoma* or neurogliocytoma* or neuroglioma* or neurospongioma* or gliosarcoma* or glioblastoma*).ti,ab,kf.
19. ((glia* or CNS or central nervous system* or brain or spinal cord) adj3 (tumor* or tumour*)).ti,ab,kf.

20. or/17-19
21. 16 and 20
22. 21 use oemezd
23. (conference abstract or conference review).pt.
24. 22 not 23
25. 9 or 24
26. remove duplicates from 25

### Clinical Trials Registries

#### *ClinicalTrials.gov*

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- (dabrafenib OR tafinlar OR finlee OR rafinlar OR taffiner OR tafinra OR drb436 OR “drb-436” OR “gsk-2118436” OR gsk2118436) AND (trametinib OR mekinist OR Megsel OR Meqsel OR Mekinst OR Spexotras OR “gsk-1120212” OR gsk1120212 OR “jtp-74057” OR jtp74057 OR “snr-1611” OR snr1611 OR “tmt-212” OR tmt212) AND glioma]

#### *WHO ICTRP*

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- (dabrafenib OR tafinlar OR finlee OR rafinlar OR taffiner OR tafinra OR drb436 OR “drb-436” OR “gsk-2118436” OR gsk2118436) AND (trametinib OR mekinist OR Megsel OR Meqsel OR Mekinst OR Spexotras OR “gsk-1120212” OR gsk1120212 OR “jtp-74057” OR jtp74057 OR “snr-1611” OR snr1611 OR “tmt-212” OR tmt212) AND glioma]

#### *Health Canada’s Clinical Trials Database*

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- Dabrafenib, tafinlar, trametinib, mekinist, finlee, glioma]

#### *EU Clinical Trials Register*

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- (dabrafenib OR tafinlar OR finlee OR rafinlar OR taffiner OR tafinra OR drb436 OR “drb-436” OR “gsk-2118436” OR gsk2118436) AND (trametinib OR mekinist OR Megsel OR Meqsel OR Mekinst OR Spexotras OR “gsk-1120212” OR gsk1120212 OR “jtp-74057” OR jtp74057 OR “snr-1611” OR snr1611 OR “tmt-212” OR tmt212) AND glioma]

*EU Clinical Trials Information System (CTIS)*

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- dabrafenib, tafinlar, trametinib, mekinist, finlee, glioma]

### Grey Literature

**Search dates:** October 22 to 23, 2024

**Keywords:** glioma, dabrafenib, Tafinlar, Finlee, trametinib, Mekinist

**Limits:** none

Relevant websites from the following sections of the grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

### Study Selection

Two reviewers independently selected relevant studies for inclusion in 2 stages, first by titles and abstracts and then by full texts. Any record considered relevant by either reviewer at the title and abstract stage was reviewed by full text. The 2 reviewers agreed on the studies included in the report.

### Data Extraction and Critical Appraisal

One reviewer extracted relevant data from the included studies with verification by a second reviewer. One reviewer appraised the internal and external validity of the available evidence in consideration of inputs by the clinical experts, and patient and clinician groups, with input from a methodologist.

### Excluded Studies

Only the studies that were reasonably expected to appear in the systematic review but were excluded are listed in this section. The list does not contain all the studies that were excluded in the review.

### Table 7: Excluded Studies

| Study | Reason for exclusion |
|---|---|
| **Studies excluded from the systematic review** | |
| Bouffet E, Geoerger B, Moertel C, et al. Efficacy and Safety of Trametinib Monotherapy or in Combination With Dabrafenib in Pediatric *BRAF* V600-Mutant Low-Grade Glioma. *J Clin Oncol*. 2023;41(3):664 to 674. doi:10.1200/JCO.22.01000 | Comparator |

## Appendix 3: Statistical Testing and Analysis Populations

### Bouffet et al. Study

The study was powered to detect a 30% relative increase in the overall response rate with 80% power and 2.5% one-sided significance level, with an expectation of enrolling 102 patients. Efficacy analysis included all enrolled patients, the intention-to-treat population (ITT), regardless of whether they received treatment. Safety was determined in in all patients who received at least 1 dose of treatment. Overall response rate, the primary end point was summarized by descriptive statistics and Clopper-Pearson method for two-sided exact binomial 95% CIs. Treatment effect for dabrafenib plus trametinib compared with chemotherapy was estimated using odds ratios and risk ratios with 95% confidence intervals and P values were computed by means of the chi-square test (Mantel–Haenszel method) at a 2.5% one-sided significance level. PFS, OS and duration of response were assessed by the Kaplan-Meier method. Hazard ratios and two-sided 95% CIs for the estimates of PFS and OS were determined using the Cox model one-sided log-rank test at the 2.5% significance level. Hierarchical testing was performed for independently assessed PFS and OS to control for type I error.

### ROAR LGG Study

An adaptive Bayesian hierarchical model design was used to increase the power by borrowing information across all 9 cohorts in the ROAR basket trial while controlling the type I error. Given the historical response rates was 10% for LGG, the threshold for a clinically meaningful ORR was 50%. Efficacy analysis set was performed on the evaluable ITT population. Evaluable patients included those whose disease progressed, initiated new anticancer therapy, withdrew consent to participate, had died, had stable disease for at least 6 weeks after the first dose day or had at least 2 post-baseline disease assessments (other than not evaluable). Point estimates and 95% CI for the primary end point of ORR was analyzed using the frequentist method. PFS, OS and duration of response were estimated using the Kaplan-Meier method with the 95% CI estimates were determined using the Brookmeyer-Crowley method with a complementary log-log transformation of the survivor function. 95% CIs were used for uncertainty estimates and were investigator assessed. Patients with an unknown or missing response were counted as non-responders and were included in the denominator when calculating the percentage. Time-to-event secondary end points were right censored if the event was not observed during the study follow-up. Safety population included all patients who received at least 1 dose of dabrafenib or trametinib.

# Economic Review Appendices

## Appendix 4: Cost Comparison Table

The comparators presented in Table 8 and Table 9 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on product monographs and Cancer Care Ontario regimen monographs and validated by clinical experts. If discrepancies in dosing between the monographs and Canadian clinical practice exist, the dose specified by clinical experts was used. Pricing for comparator products was based on Ontario Drug Benefit Exceptional Access Program[5] prices and wholesale prices reported by the IQVIA DeltaPA database.[6]

For adult patients, the recommended dose of dabrafenib is 150 mg twice daily, while that of trametinib is 2 mg once daily (Table 8). At $75.35 per 75 mg capsule, the treatment acquisition cost of dabrafenib is $301.39 daily. At $342.13 per 2 mg tablet, the treatment acquisition cost of trametinib is $342.13 daily. When used together, the treatment acquisition cost of dabrafenib plus trametinib is $643.52 daily, or $18,018 per patient per 28 days.

For adult patients, the incremental cost of dabrafenib plus trametinib compared with carboplatin plus vincristine is at least $16,608 per patient per 28 days. When compared with vinblastine monotherapy, the incremental cost of dabrafenib plus trametinib is $17,255 per patient per 28 days. Results may differ by jurisdiction depending on individual list prices for the drug under review compared to those presented in Table 8.

### Table 8: CDA-AMC Cost Comparison Table for Adult Patients (≥ 18 years) With Low-Grade Gliomas With Residual Disease and Known *BRAF* V600 Mutations

| Treatment | Strength / concentration | Form | Price ($) | Recommended dosage | Daily cost ($) | Cost per 28 days ($) |
|---|---|---|---|---|---|---|
| Dabrafenib (Tafinlar) | 50 mg<br>75 mg | Capsules | 50.3255[1]<br>75.3473[1] | 150 mg twice daily until disease progression or intolerable toxicity[2,7] | 301.39 | 8,439 |
| Trametinib (Mekinist) | 0.5 mg<br>2 mg | Tablets | 86.4933[1]<br>342.1279[1] | 2 mg once daily until disease progression or intolerable toxicity[3,7] | 342.13 | 9,580 |
| Dabrafenib plus trametinib | | | | | 643.52 | 18,018 |
| **Carboplatin plus vincristine** | | | | | | |
| Carboplatin (generics) | 50 mg<br>150 mg<br>450 mg<br>600 mg | 10 mg/mL solution for injection | 70.0000<br>210.0000<br>600.0000<br>775.0020 | Target AUC 5 or 6 on Day 1 every 28 days until progression or limited by toxicity[7,a] | Up to 41.52 | Up to 1,163 |

| Treatment | Strength / concentration | Form | Price ($) | Recommended dosage | Daily cost ($) | Cost per 28 days ($) |
|---|---|---|---|---|---|---|
| Vincristine (generics) | 1 mg<br>2 mg<br>5 mg | 1 mg/mL injection | 30.6000<br>62.0000<br>153.0000 | 1.5 mg/m$^2$ days 1, 8, and 15 every 28 days until progression or limited by toxicity[7] | 8.85 | 248 |
| Carboplatin plus vincristine | | | | | Up to 50.37 | Up to 1,410 |
| **Monotherapies** | | | | | | |
| Dabrafenib (Tafinlar) | 50 mg<br>75 mg | Capsules | 50.3255<br>75.3473 | 150 mg twice daily until disease progression or intolerable toxicity[2,b] | 301.39 | 8,439 |
| Vinblastine | 10 mg | 1 mg/mL injection | 176.7900 | 6 mg/m$^2$ on Day 1 every 7 days until progression or unacceptable toxicity[7] | 27.28 | 764 |

AUC = area under the curve.

Note: All prices are wholesale prices from the IQVIA Delta PA database unless otherwise indicated (January 2025).[2] Mean adult body surface area assumed to be 1.8 m$^2$.[3] Patients are assumed to generally be treated in cancer centres where vials may be split between patients, thus wastage has not been assumed.

[a]Dosing assumes a maximum glomular filtration rate of 125 mL/min, leading to a maximum dose of 750 mg (AUC = 5) or 900 mg (AUC = 6) according to the Calvert formula of target AUC*(25 + GFR).[7]

[b]Dabrafenib monotherapy was noted to be a comparator of interest according to clinical expert input, but is not indicated as monotherapy for low grade glioma, nor is it currently funded for this indication by public plans.

For pediatric patients, the recommended doses of dabrafenib and trametinib depend on patient body weight (Table 9). While dabrafenib 10 mg tablets for suspension and trametinib 4.7 mg per bottle of oral solution appear to be marketed in Canada,[2,3] no public pricing for these products could be found, therefore no estimates of the cost of treatment could be made for pediatric patients requiring them. Drug plans confirmed that, at least in some jurisdictions, pediatric patients weighing less than 26 kg receive the trametinib powder for oral solution and the dabrafenib tablet for suspension in current clinical practice. For patients weighing at least 26 kg who can take regular capsules and tablets, the treatment acquisition cost of dabrafenib ranges from $151 to $301 daily, while that of trametinib ranges from $173 to $342, depending on body weight. When used together, the treatment acquisition cost of dabrafenib plus trametinib ranges from $324 to $644 daily, or $9,063 to $18,018 per patient per 28 days.

For pediatric patients weighing at least 26 kg and having a body surface area of at least 0.9 m$^2$ (i.e., approximately the median weight and BSA for children aged 8 years),[8,9] the incremental cost of dabrafenib plus trametinib compared with carboplatin plus vincristine ranges from $7,777 to $16,608 per patient per 28 days, depending on patient weight and size. When compared with vinblastine monotherapy, the incremental cost of dabrafenib plus trametinib ranges from $8,681 to $17,255 per patient per 28 days. Results may differ by jurisdiction depending on individual list prices for the drug under review compared to those presented in Table 9.

## Table 9: CDA-AMC Cost Comparison Table for Pediatric Patients (< 18 years) With Low-Grade Gliomas With Residual Disease and Known *BRAF* V600 Mutations

| Treatment | Strength / concentration | Form | Price ($) | Recommended dosage | Daily cost ($) | Cost per 28 days ($) |
|---|---|---|---|---|---|---|
| Dabrafenib (Tafinlar) | 10 mg | Tablets for suspension | No publicly available price identified | Varies by weight[a] | Unknown | Unknown |
| | 50 mg<br>75 mg | Capsules | 50.3255[5]<br>75.3473[5] | 26 to 37 kg: 75 mg twice daily<br>38 to 50 kg: 100 mg twice daily<br>≥ 51 kg: 150 mg twice daily[2] | 150.69 to 301.39 | 4,219 to 8,439 |
| Trametinib (Mekinist) | 4.7 mg | Powder for 0.05 mg/mL oral solution | No publicly available price found | Varies by weight[b] | Unknown | Unknown |
| | 0.5 mg<br>2 mg | Tablets | 86.4933[5]<br>342.1279[5] | 26 to 37 kg: 1 mg daily<br>38 to 50 kg: 1.5 daily<br>≥ 51 kg: 2 mg daily[3] | 172.99 to 342.13 | 4,844 to 9,580 |
| Dabrafenib plus trametinib | | | | Oral solutions/ suspensions, for patients weighing 8kg | Unknown | Unknown |
| | | | | Tablets/Capsules, for patients weighing ≥ 26kg | 323.68 to 643.52 | 9,063 to 18,018 |
| **Carboplatin plus vincristine** | | | | | | |
| Carboplatin (generics) | 50 mg<br>150 mg<br>450 mg<br>600 mg | 10 mg/mL solution for injection | 70.0000<br>210.0000<br>600.0000<br>775.0020 | Target AUC 5 or 6 on Day 1 every 28 days until progression or limited by toxicity[7,c] | Up to 42.68 | Up to 1,163 |
| Vincristine (generics) | 1 mg<br>2 mg<br>5 mg | 1 mg/mL injection | 30.6000<br>62.0000<br>153.0000 | 1.5 mg/m$^2$ days 1, 8, and 15 every 28 days until progression or limited by toxicity[7] | 2.46 to 8.85 | 69 to 248 |
| Carboplatin plus vincristine | | | | | Up to 50.37 | Up to 1,410 |
| **Monotherapies** | | | | | | |
| Dabrafenib (Tafinlar) | 10 mg | Tablets for suspension | No publicly available price found | Varies by weight[a,d] | Unknown | Unknown |
| | 50 mg<br>75 mg | Capsules | 50.3255[5]<br>75.3473[5] | 26 to 37 kg: 75 mg twice daily<br>38 to 50 kg: 100 mg twice daily | 150.69 to 301.39 | 4,219 to 8,439 |

| Treatment | Strength / concentration | Form | Price ($) | Recommended dosage | Daily cost ($) | Cost per 28 days ($) |
|---|---|---|---|---|---|---|
| | | | | ≥ 51 kg: 150 mg twice daily[2,d] | | |
| Vinblastine | 10 mg | 1 mg/mL injection | 176.7900 | 6 mg/m$^2$ on Day 1 every 7 days until progression or unacceptable toxicity[7] | 7.58 to 27.28 | 212 to 764 |

AUC = area under the curve.

Note: All prices are wholesale prices from the IQVIA Delta PA database unless otherwise indicated (January 2025).[6] Pediatric body surface area is assumed to range from 0.5 m$^2$ to 1.8 m$^2$, approximating means for children aged 1 to 17 years.[8] Patients are assumed to be treated in major cancer centres where vials may be split between patients, thus wastage has not been assumed.

[a]According to the product monograph, dabrafenib tablets for suspension are dosed by patient weight in small increments,[2] similar to the 4.5 mg/kg (≥ 12 years of age) to 5.25 mg/kg (< 12 years of age) per day dosing used in the trial by Bouffet et al., 2023.[10] For patients weighing 8 to 9 kg: 20 mg twice daily; 10 to 13 kg: 30 mg twice daily; 14 to 17 kg: 40 mg twice daily; 18 to 21 kg: 50 mg twice daily; 22 to 25 kg: 60 mg twice daily; 26 to 29 kg: 70 mg twice daily; 30 to 33 kg: 80 mg twice daily; 34 to 37 kg: 90 mg twice daily; 38 to 41 kg: 100 mg twice daily; 42 to 45 kg: 110 mg twice daily; 46 to 50 kg: 130 mg twice daily; ≥ 51 kg: 150 mg twice daily.

[b]According to the product monograph, trametinib powder for oral solution is dosed by patient weight in small increments,[3] similar to the 0.025 mg/kg (≥ 6 years of age) to 0.032 mg/kg (< 6 years of age) per day dosing used in the trial by Bouffet et al., 2023.[10] The reconstituted solution should be discarded if not used within 35 days. For 5weighing 8 kg: 0.3 mg daily; 9 to 10 kg: 0.35 mg daily; 11 kg: 0.4 mg daily; 12 to 13 kg: 0.45 mg daily; 14 to 17 kg: 0.55 mg daily; 18 to 21 kg: 0.7 mg daily; 22 to 25 kg: 0.85 mg daily; 26 to 29 kg: 0.9 mg daily; 30 to 33 kg: 1 mg daily; 34 to 37 kg: 1.15 mg daily; 38 to 41 kg: 1.25 mg daily; 42 to 45 kg: 1.4 mg daily; 46 to 50 kg: 1.6 mg daily; ≥ 51 kg: 2 mg daily.

[c]Dosing assumes a maximum glomular filtration rate of 125 mL/min, leading to a maximum dose of 750 mg (AUC = 5) or 900 mg (AUC = 6) according to the Calvert formula of target AUC*(25+GFR).[7]

[d]Dabrafenib monotherapy was noted to be a comparator of interest according to clinical expert input but is not indicated as monotherapy for low grade glioma, nor is it currently funded for this indication by public plans.

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