

# Committee to Evaluate Drugs (CED)

## Recommendations and Reasons

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### Trametinib

**Product:** trametinib (Mekinist®)

**Class of Drugs:** kinase inhibitor

**Reason for Use:** melanoma with BRAF V600 mutation

**Manufacturer:** GlaxoSmithKline Inc.

**Date of Review:** November 13, 2013

### CED Recommendation

The CED recommended trametinib (Mekinist®) not be funded for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation. Trametinib was found to improve progression-free survival when compared with chemotherapy. The efficacy of trametinib relative to the current standard treatment is unknown, and trametinib was found to be not cost-effective.

### Executive Officer Decision\*

Based on the CED's recommendation and an agreement with the manufacturer to help address concerns raised by the CED, the Executive Officer decided to fund trametinib (Mekinist®) for the treatment unresectable or metastatic melanoma with BRAF V600 mutation through the Ontario Drug Benefit's (ODB) Exceptional Access Program according to specific criteria.

### Funding Status\*

Funded through the ODB's Exceptional Access Program (EAP) according to specific criteria.

(EAP criteria can be found at: [http://www.health.gov.on.ca/en/pro/programs/drugs/eap\\_criteria.aspx](http://www.health.gov.on.ca/en/pro/programs/drugs/eap_criteria.aspx))

*\* This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: [www.health.gov.on.ca/en/pro/programs/drugs/status\\_single\\_source\\_subm.aspx](http://www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx).*

## Highlights of Recommendation:

- The METRIC study showed an improvement in progression-free survival with trametinib compared to chemotherapy in patients who had metastatic melanoma with a BRAF V600 mutation. There was also an improvement in overall survival with trametinib at an early interim analysis that was not seen later.
- Overall safety of trametinib in the METRIC study was acceptable.
- There are no direct head-to-head studies comparing trametinib to vemurafenib, the current standard treatment for metastatic melanoma used in Ontario.
- At the list price, the average cost per 28-day course of trametinib at the recommended 2mg daily dose is approximately \$8,000. Based on economic analyses conducted by the manufacturer and by the pan-Canadian Oncology Drug Review, trametinib could not be considered cost-effective compared with chemotherapy, and its cost-effectiveness compared to the vemurafenib is unknown.

## Background:

Melanoma is a malignancy of melanocytes which are distributed throughout the body including skin, eyes, and gastrointestinal tract. The skin is the most common occurrence site, comprising 95% of cases.

Although only 5% of patients actually present with metastatic disease, the majority of patients who die from melanoma will have developed recurrent and/or distant disease. Approximately one-third of patients with early stage melanoma will develop metastasis whereas half of patients with nodal disease will recur and likely die from the development of metastatic disease. Brain metastases are relatively common in advanced melanoma and occur in up to 75% of patients with overt metastatic disease.

Highly selected patients with Stage IV disease may benefit from surgical removal of the metastases and the five-year survival in these patients ranges from 15 to 25%. For those patients who are not candidates for surgery, systemic treatment with chemotherapy is most commonly offered. Unfortunately, the prognosis for these patients has remained poor.

Approximately 50% of human melanomas appear to have an activated mutation in the BRAF gene.

## Detailed Discussions:

- For this evaluation, the CED took into consideration:
  - Findings from the pan-Canadian Oncology Drug Review (pCODR) and the recommendation of the pCODR Expert Review Committee;
  - Feedback from Cancer Care Ontario's Melanoma Disease Site Group;
  - Information in the manufacturer's submission;
  - One patient group submission received by pCODR.
- The CED evaluated one open-label, randomized controlled trial, the METRIC study, that assessed the efficacy and safety of trametinib 2mg orally once daily compared with

chemotherapy (i.e., dacarbazine (DTIC) 1000mg/m<sup>2</sup> every 3 weeks or paclitaxel 175 mg/m<sup>2</sup> every 3 weeks).

- The primary endpoint of the METRIC study was progression-free survival (PFS) in the primary efficacy population. Median PFS was found to be 4.8 and 1.5 months in the trametinib and chemotherapy groups, respectively, representing a significant improvement in PFS with trametinib.
- Overall survival (OS) in the intention-to-treat population was evaluated as a secondary outcome in the METRIC study. Median OS was statistically significantly longer in the trametinib arm at the October 2011 analysis but not at the May 2013 analysis. OS may have been confounded by crossover, as patients were permitted to switch from chemotherapy treatment to trametinib upon disease progression.
- Quality of life (QOL) did not appear to deteriorate in patients receiving trametinib, but there was no statistical assessment of the QOL data.
- The proportion of patients with serious side effects was similar between trametinib and dacarbazine, and trametinib was considered to have an acceptable tolerability profile.
- There are no direct head-to-head studies comparing trametinib to vemurafenib. The manufacturer provided an adjusted indirect treatment comparison, but limitations were identified with the findings. Since data from indirect comparisons are not as robust as those from head-to-head clinical trials, the relative efficacy and safety of trametinib compared with vemurafenib remain uncertain.
- Patients who received prior vemurafenib therapy were excluded from the METRIC study. As such, there is no evidence to support the use of trametinib after progression on vemurafenib.
- At the list price, the average cost per 28-day course of trametinib is approximately \$8,000. Based on economic analyses conducted by the manufacturer and by pCODR, trametinib was found to be not cost-effective when compared with chemotherapy. The cost-effectiveness of trametinib compared to vemurafenib could not be determined given the uncertainty in the relative efficacy and safety of the two treatments.
- The CED considered a patient group submission received by pCODR. The patient submission highlighted the impact of the disease and patients' wishes for more treatment options that can prolong their life with fewer side effects. Patients may be willing to tolerate side effects if the treatment extends their life.
- Overall, trametinib, when compared to chemotherapy, was shown to improve progression-free survival, and overall survival at an interim analysis. There are no head-to-head studies comparing trametinib to vemurafenib and therefore the relative efficacy and safety of these two treatments are uncertain. Trametinib was found to be not cost-effective compared with chemotherapy, and its cost-effectiveness compared to vemurafenib is unknown.

### **Committee to Evaluate Drugs (CED)**

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

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