Committee to Evaluate Drugs (CED)

Recommendations and Reasons

Document Posted: January 2016

Dabrafenib

Product: dabrafenib (Tafinlar®)

Class of Drugs: BRAF inhibitor

Reason for Use: melanoma with BRAF V600 mutation

Manufacturer: GlaxoSmithKline Inc.

Date of Review: December 11, 2013

CED Recommendation

The CED noted that dabrafenib (Tafinlar®) was shown to improve progression-free survival when compared to dacarbazine, a former standard treatment. There was a lack of data to establish the effectiveness, safety and cost-effectiveness of dabrafenib compared to another BRAF inhibitor, one of the current standard therapies. The CED recommended dabrafenib not be funded for the treatment of unresectable or metastatic melanoma with BRAF V600 mutation. This recommendation is aligned with the pan-Canadian Oncology Review recommendation.

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 dabrafenib (Tafinlar®) through the Ontario Drug Benefit's (ODB) Exceptional Access Program for the treatment of unresectable or metastatic melanoma 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)

* *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.*

Ontario

Highlights of Recommendation:

- The BREAK-3 study showed that dabrafenib improved progression-free survival when compared to dacarbazine. An improvement in overall survival was not observed. The overall survival results could not be interpreted because patients were permitted to crossover from dacarbazine treatment to dabrafenib upon disease progression.
- Due to incomplete data, quality of life results from the study was difficult to interpret. The study suggested that patients treated with dabrafenib experienced an improvement in their quality of life.
- The safety profile of dabrafenib appears acceptable.
- There was no head-to-head study directly comparing dabrafenib to vemurafenib (another BRAF inhibitor). The relative efficacy and safety of these two treatments is unknown.
- At the recommended dose, the average cost per 28-day course of dabrafenib is $7,093. Based on economic analyses conducted by the manufacturer and pCODR, dabrafenib was not considered to be cost-effective when compared to dacarbazine. The cost-effectiveness of dabrafenib compared to vemurafenib could not be determined due to the lack of data.

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

About 5% of melanoma patients present with metastatic disease. Some patients with metastatic disease may benefit from surgical removal of the metastases. For those patients who are not candidates for surgery, systemic treatment with chemotherapy (e.g. dacarbazine) was most commonly offered. More recently, BRAF inhibitors have become the standard treatment if the melanoma has the mutated BRAF gene.

Detailed Discussions:

- For this evaluation, the CED considered:
    - Findings from the pan-Canadian Oncology Drug Review (pCODR) and the recommendation of the pCODR Expert Review Committee;
    - Information in the manufacturer's submission;
    - Submissions from two patient groups received by pCODR.
- The CED evaluated one open-label, randomized controlled trial, the BREAK-3 study. The study assessed the efficacy and safety of dabrafenib 150 mg orally twice daily compared with dacarbazine 1000 mg/m^2 IV every 3 weeks.
- The primary endpoint of the study was progression-free survival (PFS). The median investigator-assessed progression-free survival was 5.1 and 2.7 months at the December 2011 data cut-off in the dabrafenib and dacarbazine groups, respectively (HR: 0.30, 95% CI: 0.18-

0.51), and 6.9 months versus 2.7 months (HR 0.37; 95% CI: 0.23-0.58) at the June 2012 data cut-off. These improvements in PFS were considered significant.

- Overall survival (OS) was evaluated as a secondary outcome. The OS analysis at three data cut-off times showed no statistically significant difference between dabrafenib and dacarbazine. The OS results may have been confounded since patients were permitted to crossover from dacarbazine treatment to dabrafenib upon disease progression.
- The study only included patients who had a confirmed BRAF V600E mutation. The effectiveness of dabrafenib in patients with other types of BRAF mutations, such as BRAF V600K, is unconfirmed. There are some data from phase II studies to suggest that the use of dabrafenib in patients with different types of V600 mutations may be reasonable.
- In the dabrafenib group, quality of life (QOL) improvements from baseline were seen at week 12 for emotional functioning and social functioning, and for all symptoms except fatigue and dyspnea. In the dacarbazine group, role functioning was improved but patients reported worsening of symptoms at week 12. The statistical significance of these QOL measurements was not assessed and the data were incomplete, making the interpretation of the QOL results difficult.
- Although the proportion of patients reporting serious non-fatal adverse events (AEs) and who discontinued treatment due to AEs was similar between dabrafenib and dacarbazine, more patients in the dacarbazine group reported grade 3-4 AEs compared to dabrafenib (41% vs. 33%, respectively). Dabrafenib was considered to have an acceptable tolerability profile with manageable toxicities.
- There were no direct head-to-head studies comparing dabrafenib to vemurafenib, another BRAF inhibitor which is a current standard of treatment. Although the manufacturer provided an indirect comparison, the efficacy and safety of dabrafenib compared to vemurafenib remain uncertain.
- At the list price, dabrafenib costs $42.22 and $63.33 per 50 mg and 75 mg capsule, respectively. At the recommended daily dose of 150 mg twice daily, the average cost per 28-day course is $7,093. Based on economic analyses conducted by the manufacturer and pCODR, dabrafenib was not considered to be cost-effective when compared to dacarbazine. The relative cost-effectiveness of dabrafenib compared to vemurafenib is unknown.
- The CED reviewed patient input received by pCODR. The patient submissions highlighted the impact of the disease and patients' wishes for new treatment options that increased survival while improving quality of life.
- Overall, dabrafenib was shown to improve progression-free survival when compared to dacarbazine. The effectiveness, safety and cost-effectiveness of dabrafenib relative to vemurafenib could not be established.

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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