

# Committee to Evaluate Drugs (CED)

## Recommendations and Reasons

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### Regorafenib for metastatic colorectal cancer

**Product:** regorafenib (Stivarga®)

**Class of Drugs:** multikinase inhibitor

**Reason for Use:** metastatic colorectal cancer previously treated with a number of regimens including: fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-vascular endothelial growth factor therapy, and, if the cancer is KRAS wild-type, an anti-epidermal growth factor receptor.

**Manufacturer:** Bayer Inc.

**Date of Review:** December 11, 2013

#### CED Recommendation

The CED noted the size of the clinical benefit attributed to regorafenib was modest. The drug did not improve or maintain quality of life, its use was associated with several significant adverse effects, and this treatment was not cost-effective. The CED recommended regorafenib (Stivarga®) not be funded for the treatment of metastatic colorectal cancer previously treated with a number of regimens including: fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-vascular endothelial growth factor therapy, and, if the cancer is KRAS wild-type, an anti-epidermal growth factor receptor. This recommendation is aligned with the pan-Canadian Oncology Review recommendation.

#### Executive Officer Decision\*

Based on the CED's recommendation, the Executive Officer decided not to fund regorafenib (Stivarga®) for the treatment of metastatic colorectal cancer.

#### Funding Status\*

Not funded through the Ontario Public Drug Programs.

*\* 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 CORRECT study demonstrated statistically significant improvements in both overall survival and progression-free survival for regorafenib when compared to placebo. These improvements were small and the magnitude of the clinical benefit was considered modest.
- The CORRECT study indicated that patients in the regorafenib group experienced a decline in their quality of life.
- Side-effects noted with regorafenib include hand-foot skin reaction, fatigue, diarrhea, high blood pressure and rash or desquamation (peeling of the skin). Although some of these adverse events may be managed through dose reductions or interruptions, the data suggest that regorafenib has an unfavourable toxicity profile.
- At the list price, regorafenib costs \$74 per 40mg tablet. At the recommended dose of 160mg daily for 3 weeks, followed by 1 week off treatment, the average cost per 28-day course is \$6,237. Based on economic analyses conducted by the manufacturer and pCODR, regorafenib was not considered cost-effective.
- Overall, the CED noted that the size of the clinical benefit attributed to regorafenib was modest, the drug did not improve or maintain quality of life, and its use was associated with several toxicities. Moreover, this treatment was not cost-effective.

## Background:

Colorectal cancer (CRC) is the second most common cause of cancer death in males and third most common cause of cancer death in females.

Metastatic CRC is considered incurable in the majority of cases. Treatments for metastatic CRC include chemotherapy (e.g., fluoropyrimidines, oxaliplatin, irinotecan) and targeted agents (e.g., bevacizumab, cetuximab, panitumumab).

## 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;
  - Submission from one patient group received by pCODR;
  - Feedback from Cancer Care Ontario's Gastrointestinal Disease Site Group.
- The CED evaluated one phase III, double-blind, randomized controlled trial, the CORRECT study. The study assessed the efficacy and safety of regorafenib 160 mg orally once daily compared to a matching dose of placebo given for 3 weeks of each 4 week cycle.
- The study included patients who were previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-vascular endothelial growth factor (VEGF) therapy, and, if the tumour is *KRAS* wild type, an anti-epidermal growth factor receptor (EGFR) therapy. These heavily pre-treated patients had no further effective treatment options.

- Overall survival (OS) was the primary endpoint. At the second interim analysis, the median OS was 6.4 months in the regorafenib arm compared to 5.0 months in the placebo group (HR: 0.77, 95% CI 0.64 to 0.94), indicating an absolute OS benefit of 1.4 months with regorafenib. Progression-free survival (PFS) was a secondary outcome. The median PFS was 1.9 months in the regorafenib arm compared to 1.7 months in the placebo arm (HR: 0.49, 95% CI 0.42 to 0.58). Although the OS and PFS results were statistically significant, the magnitude of the benefit was considered to be modest and it was uncertain whether the observed benefit was clinically meaningful.
- Results at the end of treatment indicated that patients in the regorafenib group experienced a decline in their quality of life. This deterioration was noted to be similar for both the regorafenib and placebo groups.
- Treatment-related adverse events (AEs) of any grade or type occurred in more regorafenib patients than placebo (93% and 61%, respectively), as did Grade 3 treatment-related AEs (51% and 12% respectively). AEs frequently occurring in regorafenib-treated patients included hand-foot skin reaction, fatigue, diarrhea, hypertension and rash or desquamation. Although some of these adverse events may be managed through dose reductions or interruptions, the data suggest that regorafenib has an unfavourable toxicity profile.
- At the list price, regorafenib costs \$74 per 40mg tablet. At the recommended dose of 160mg daily for 3 weeks, followed by 1 week off treatment, the average cost per 28-day course is \$6,237. Based on economic analyses conducted by the manufacturer and pCODR, regorafenib was not considered cost-effective.
- The CED reviewed one patient submission received by pCODR. The patient submission highlighted the impact of the disease and patients' wishes for additional therapeutic options. Patients indicated a preference for oral drug treatments, such as regorafenib.
- Overall, the CORRECT study demonstrated statistically significant improvements in both OS and PFS for regorafenib when compared to placebo. The magnitude of the observed clinical benefits was considered modest. Regorafenib was not found to improve or maintain quality of life and there were several toxicities associated with its use. At the submitted price, regorafenib was not considered cost-effective. There are several ongoing trials of regorafenib; these may provide further information on the drug's efficacy and place in therapy.

### **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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