# Committee to Evaluate Drugs (CED)

## Recommendations and Reasons

**Document Posted: January 2016**

# Regorafenib for gastrointestinal stromal tumours

**Product:** regorafenib (Stivarga®)

**Class of Drugs:** multikinase inhibitor

**Reason for Use:** gastrointestinal stromal tumours (GIST)

**Manufacturer:** Bayer Inc.

**Date of Review:** May 14, 2014

## CED Recommendation

The CED did not recommend regorafenib (Stivarga®) for funding for the treatment of metastatic and/or unresectable gastrointestinal stromal tumours (GIST) due to concerns with cost. Regorafenib has been shown to improve progression-free survival. The CED acknowledged there are limited treatment options for patients whose disease has progressed despite standard therapies.

## 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 regorafenib (Stivarga®) for the treatment of metastatic and/or unresectable gastrointestinal stromal tumours (GIST) according to specific criteria.

## Funding Status*

Funded through the Ontario Drug Benefit's Exceptional Access Program 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:

- One randomized controlled study demonstrated a meaningful improvement in progression-free survival with regorafenib compared to placebo in previously treated patients with metastatic and/or unresectable gastrointestinal stromal tumours (GIST).
- In the study, substantially more patients reported serious adverse events in the regorafenib group than in the placebo group. Regorafenib is also associated with liver toxicity.
- Regorafenib costs $6,100.08 per 28-day treatment cycle. Regorafenib does not appear to be cost-effective.
- The CED acknowledged there are limited treatment options for patients whose disease has progressed despite available therapies.

## Background:

Gastrointestinal stromal tumours (GIST) are a rare type of stomach and intestinal cancer.

Currently, there are two funded drugs for recurrent or metastatic GIST in Ontario. Imatinib is funded in the first-line setting (i.e., as initial therapy), and sunitinib is funded as a second-line treatment after failure or intolerance to imatinib. There has been no known treatment option in the third-line setting for patients whose disease has progressed despite treatment with imatinib and sunitinib or who are intolerant to these two drugs.

## 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;
    - One patient group submission;
    - Feedback from Cancer Care Ontario's Sarcoma Disease Site Group.
- One double-blind randomized controlled trial, the GRID study, evaluated the efficacy and safety of regorafenib compared to placebo in patients with metastatic or unresectable GIST after failure of imatinib and sunitinib.
- The primary endpoint of the study was progression-free survival (PFS). There was a statistically significant and clinically meaningful improvement in median PFS in favour of regorafenib compared to placebo. Median PFS was 4.8 and 0.9 months for the regorafenib and placebo arms, respectively (HR, 0.27; 95% CI, 0.19-0.39 [$p<0.0001$]).
- The study found no statistically significant improvement in overall survival (OS) with regorafenib. The cross-over design of the study, which allowed patients in placebo group to receive regorafenib treatment upon disease progression, may have impacted the OS results.
- Health-related quality of life outcomes were generally similar between the regorafenib and placebo groups in the study.
- Substantially more patients reported serious adverse events (AEs) in the regorafenib group than in the placebo group (59.8% vs. 9.1%, respectively). The most common grade 3-4 AEs

were hypertension, hand-foot skin reaction and diarrhea. Regorafenib is also associated with liver toxicity. These AEs are considered to be manageable through dose modifications and close monitoring of liver enzymes.

- There are no data to support the appropriateness of regorafenib use post-progression.
- Regorafenib costs $6,100.08 per 28-day treatment cycle. Regorafenib does not appear to be cost-effective.
- One patient group submission highlighted the need for additional treatment options. The CED acknowledged there are no standard therapies for GIST in the third-line setting and the disease often progresses very quickly without treatment.
- Overall, regorafenib has been shown to provide meaningful improvement in progression-free survival in patients with metastatic or unresectable GIST after failure of imatinib and sunitinib. The CED recognized there is a clinical care gap in this setting. Regorafenib is not considered to be cost-effective.

**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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