pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Regorafenib (Stivarga) **Submitted Funding Request:** Treatment of patients with metastatic and/or unresectable gastrointestinal stromal tumours (GIST) who have had disease progression on or intolerance to imatinib mesylate, and sunitinib malate treatment	
Submitted By: Bayer Inc.	**Manufactured By:** Bayer Inc.
NOC Date: October 4, 2013	**Submission Date:** October 11, 2013
Initial Recommendation: March 6, 2014	**Final Recommendation:** May 2, 2014

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) recommends funding regorafenib (Stivarga) in patients with metastatic and/or unresectable gastrointestinal stromal tumours (GIST) who have had disease progression on, or intolerance to, imatinib and sunitinib, conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for patients who have an ECOG performance status of 0 or 1. The Committee made this recommendation because it was satisfied that there is a net clinical benefit of regorafenib based on a clinically meaningful progression-free survival benefit. However, the Committee noted that, at the submitted confidential price and best estimates of the incremental cost-effectiveness ratio, regorafenib plus best supportive care could not be considered cost-effective compared with placebo plus best supportive care.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-effectiveness** Given that pERC was satisfied that there is a net clinical benefit of regorafenib in patients with metastatic and/or unresectable GIST who have had disease progression on or intolerance to imatinib and sunitinib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of regorafenib to an acceptable level.

SUMMARY OF pERC DELIBERATIONS

pERC noted that gastrointestinal stromal tumours (GIST) are an uncommon cancer with an incidence of approximately 500 cases per year in Canada. pERC determined this was a relatively low burden of illness. pERC also discussed treatments for GIST and noted that although imatinib and sunitinib are used as first and second line therapies, there are currently no standard treatments for patients in the third-line setting. Re-challenging patients with imatinib is one possible option in third-line, and has shown some benefit, but this practice is not considered a standard of care. Therefore, pERC considered that there is a need for effective treatments in this setting that provide a clinically meaningful benefit.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The pCODR systematic review included one randomized controlled trial, the GRID study (Demetri 2013), which compared regorafenib plus best supportive care to placebo plus best supportive care. pERC noted that there was a benefit in progression-free survival for regorafenib compared with placebo based on both a relative effect (HR=0.27, P<0.0001) and an absolute effect (4.8 months versus 0.9 months, respectively). pERC considered that this was a clinically meaningful benefit for a treatment in the third-line setting. However, pERC also noted that no statistically significant overall survival benefit was observed for regorafenib compared with placebo. pERC acknowledged that this may be because crossover was permitted from the placebo control group to the treatment group in the GRID study and noted that progression-free survival is a clinically accepted endpoint. pERC also discussed that quality of life outcomes were generally similar between regorafenib and placebo groups. It was noted that a similar decline from baseline in quality of life was observed in both treatment groups but that the magnitude of deterioration was not substantial. Also, pERC noted there was a delay in deterioration of quality of life for regorafenib compared with placebo (median of 6.5 vs. 4.0 weeks, respectively, for global health scores). pERC also considered that this impact was observed despite the higher proportion of grade 3 and 4 adverse events that was observed for regorafenib compared with placebo (59.8% versus 9.1%, respectively). pERC discussed the toxicity profile of regorafenib. It was noted that there were substantially more grade 3 adverse events of hand-foot skin reaction, hypertension and diarrhea for regorafenib compared with placebo in the GRID study. Also, pERC noted that regorafenib has a serious warning in its product monograph related to hepatic toxicity and other significant toxicities. However, pERC discussed that treatment discontinuation due to adverse events was similar between groups in the GRID study and that these adverse events appeared to be manageable through dose modifications and monitoring. pERC considered all of these factors when deliberating on the net clinical benefit of regorafenib in the treatment of GIST. The majority of pERC members concluded that there is a net clinical benefit for regorafenib in the treatment of GIST given the magnitude of the progression-free survival benefit. In addition, pERC considered that the delay in deterioration of quality of life was a very important outcome for later lines of therapy that may be part of end-of-life care. However, pERC acknowledged that an overall survival benefit was not observed in this trial although this may have been because the results of the analysis were confounded by cross-over.

pERC deliberated on patient advocacy group input, which indicated that patients with GIST valued not only the efficacy of treatments but also the side effect profile of drugs and quality of life while on treatment. pERC agreed that regorafenib aligned with patient values based on the improvement in progression-free survival that was observed in the GRID study. It was also noted that patients would value access to treatments in the third-line setting where up until now, there have been no standard therapies and those treatments that have been offered to patients, including cytotoxic chemotherapies and radiation therapy, have been ineffective or accompanied by unmanageable side effects,.

pERC deliberated upon the cost-effectiveness of regorafenib. pERC discussed that the EGP's best estimates of the incremental cost-effectiveness ratio were substantially higher than the manufacturer's estimates. It was also noted that this was primarily because the manufacturer's model overestimated the survival benefit of regorafenib. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the submitter disagreeing with the EGP's reanalysis and estimation of survival benefit. The EGP clarified their approach to the analysis and did not change their best estimates

after re-confirming the underlying clinical assumptions with the pCODR Clinical Guidance Panel (CGP). Therefore, pERC continued to accepted the EGP's best estimate and considered that at the submitted price regorafenib is not cost-effective.

pERC discussed factors impacting the feasibility of implementing a funding recommendation for regorafenib. pERC noted that it is an oral treatment that would be easier to access than intravenous therapies for patients in remote regions. pERC also discussed that the budget impact would likely be small given the low incidence of GIST. However, it was also noted that additional resources would likely be required upon implementation as regorafenib would be a new additional line of therapy rather than a replacement for an existing third-line treatment. Also, additional monitoring to evaluate adverse events due to the serious warning for hepatic and other toxicities associated with regorafenib would be required.

Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback received from the Provincial Advisory Group asking for clarification on whether continuing regorafenib treatment beyond progression is appropriate. pERC noted that in the GRID study, patients received regorafenib for an average of five cycles before progression occurred. Upon progression and at the discretion of the investigator, patients had the option of continuing open-label regorafenib, but administration post-progression was not required as part of the study protocol. A small but significant proportion of patients (18%) received open-label regorafenib post-progression. pERC noted that the CGP had also indicated this was likely to occur in clinical practice. However, considering that the use of regorafenib beyond progression was not a study protocol requirement, pERC was unable to assess the appropriateness of this practice. pERC further noted that both the cost of regorafenib and its assumed clinical benefit in the post-progression period were included in the economic analysis and, therefore would have contributed to the estimates of cost-effectiveness.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy group (Sarcoma Cancer Foundation of Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group
- one patient advocacy group (Sarcoma Cancer Foundation of Canada)
- the Submitter (Bayer Inc.)

The pERC Initial Recommendation was to fund regorafenib (Stivarga) in patients with metastatic and/or unresectable GIST who have had disease progression on, or intolerance to, imatinib and sunitinib, conditional on the cost-effectiveness being improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that pCODR's Provincial Advisory Group and the patient advocacy group agreed with the pERC Initial Recommendation while the manufacturer agreed in part with the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of regorafenib for patient outcomes compared to standard treatment in patients with metastatic and/or unresectable GIST.

Studies included: one randomized controlled trial

The pCODR systematic review included one double-blind randomized controlled trial, GRID (Demetri 2013), which evaluated the efficacy and safety of regorafenib compared to placebo. Patients were randomised 2:1 to receive either oral regorafenib (n=133, 160 mg once daily) or matching placebo (n=66) for the first 3 weeks of each 4 week cycle, along with best supportive care. pERC discussed the study design and noted that blinding may be compromised by the toxicity profiles of regorafenib compared to placebo. However, the tumour responses were independently assessed, which may have reduced this potential bias. Upon progression, patients in the placebo group were permitted to crossover to receive open-label regorafenib. At the time of analysis, 82% (56 of 66) patients from the placebo group had crossed-over to the regorafenib group.

Patient populations: ECOG performance status 0 and 1

Approximately 55% of patients in the GRID study had an ECOG performance status of 0, while 45% had an ECOG status of 1.

Key efficacy results: statistically significant and clinically meaningful improvements in PFS

Key efficacy outcomes deliberated on by pERC included overall survival and progression free survival, which was the primary endpoint of the GRID study.

pERC noted that there was a statistically significant and clinically meaningful improvement in median progression free survival in favour of regorafenib when compared to placebo in patients previously treated with both imatinib and sunitinib. The median PFS was 4.8 and 0.9 months for the regorafenib and placebo arms, respectively (HR=0.27, 95% CI 0.18 to 0.39, P<0.0001). pERC considered that this was a clinically meaningful benefit for a treatment in the third-line setting based on both the relative and absolute effects that were observed.

pERC also noted that an interim analysis of overall survival, conducted at the time of the final progression-free survival analysis (January 26, 2012), demonstrated no statistically significant differences between groups. pERC acknowledged this may be because crossover was permitted upon progression from the placebo to the regorafenib group in the GRID study and noted that progression-free survival is a clinically accepted endpoint.

The majority of pERC members concluded that there is a net clinical benefit for regorafenib in the treatment of GIST, given the magnitude of the progression-free survival benefit, In addition, pERC considered that the delay in deterioration of quality of life was a very important outcome for later lines of therapy that may be part of end-of-life care. However, pERC acknowledged that an overall survival benefit was not observed in this trial but this may have been because the results of the analysis were confounded by cross-over (HR=0.77, 95% CI: 0.43 to 1.41).

Quality of life: decline in quality of life similar to placebo but delay in deterioration favoured regorafenib

Health related quality of life was measured using the EORTC QLQ-C30 questionnaire. pERC discussed that quality of life outcomes were generally similar between regorafenib and placebo groups. It was noted that a similar decline from baseline in quality of life was observed in both arms of the study but that the magnitude of deterioration was not substantial. There were delays in the median time to deterioration for global health (6.5 weeks versus 4.0 weeks, respectively) and for physical functioning (8.0 weeks versus 4.0 weeks, respectively), favouring the regorafenib group compared with the placebo group. pERC agreed with the pCODR Clinical Guidance Panel that these are important outcomes to consider. Also, pERC considered that that this impact was observed despite the higher proportion of grade 3 and 4 adverse events that was observed for regorafenib compared with placebo (59.8% versus 9.1%, respectively). pERC also discussed that quality of life is a very important outcome for later lines of therapy that may be part of end-of-life care. pERC also acknowledged that based on patient advocacy group input, quality of life was an outcome important to patients.

Safety: substantial toxicities but manageable through dose modifications and monitoring

pERC deliberated on the safety data available from the GRID study. Substantially more patients reported grade 3-4 adverse events in the regorafenib versus placebo groups (59.8% vs 9.1%, respectively). The most common regorafenib-related AE's of any grade were hand-foot skin reaction (56% vs 14%), hypertension (49% vs 17%) and diarrhea (40% vs 5%). The most common regorafenib-rated Grade 3-4 AE's were hypertension (24% vs 3%), hand-foot skin reaction (20% vs 0%), diarrhea (5% vs 0%). Also, pERC noted that

regorafenib has a serious warning in its product monograph related to hepatic toxicity and other significant toxicities. From both the double-blind and open label periods in which 188 patients received regorafenib, 16 patients experienced grade 5 adverse events of which 6 were deemed to be related to study drug; one each of cardiac arrest, colonic perforation, hepatic failure, acute renal injury, adult respiratory distress syndrome and thromboembolic event. Despite these concerns, the rate of treatment discontinuation due to adverse events was similar in both groups (6% vs 8% in the regorafenib vs placebo arms, respectively) and these adverse events appeared to be manageable through dose modifications and monitoring through liver function tests.

Need: uncommon cancer with no standard therapies in the third-line setting

The incidence of GIST is approximately 500 per year in Canada. Therefore, pERC considered that GIST is an uncommon cancer with a relatively low burden of illness. Treatment of recurrent or metastatic GIST with imatinib in the first-line setting has significantly improved the overall survival of this patient population. However, pERC noted that there is no standard of care in the third-line setting for patients whose disease has progressed despite treatment with imatinib and sunitinib. Re-challenging patients with imatinib is one possible option in third-line, and has shown some benefit, but is not considered a standard of care. Therefore, pERC considered that there is a need for effective treatments that provide a clinically meaningful benefit in this setting.

PATIENT-BASED VALUES

Values of patients with GIST: quality of life, efficacy and limited toxicity of therapies

Input from one patient advocacy group indicated that the concern for patients is not only the efficacy of the drug, but also its side effect profile and the quality of life that a patient can expect while on treatment. pERC agreed that regorafenib aligned with patient values based on the improvement in progression-free survival that was observed in the GRID study.

Patient values on treatment: access to effective treatment options in third-line setting

It was noted that GIST patients in Canada have been waiting a long time for a new treatment. pERC noted that patients who have had access to regorafenib had positive experiences and appreciated its oral form as it is an accessible and time-saving treatment. Patients value the availability of different treatment options in the event that existing treatments are not effective or prove to have unacceptable side effects. Therefore, pERC considered that patients would value access to regorafenib in the third-line setting, since up until now, they would not have had other effective treatments available to them in this setting.

ECONOMIC EVALUATION

Economic model submitted: cost-utility and cost-effectiveness

The pCODR Economic Guidance Panel assessed a cost utility analysis comparing regorafenib to placebo (hereafter referred to as best supportive care (BSC)) for patients with metastatic or unresectable GIST, who have had disease progression on or intolerance to both imatinib and sunitinib.

Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included drug acquisition and management costs, costs for adverse events, supportive care, and end of life costs.

The clinical effect considered in the analysis was based on extrapolated GRID trial data, adjusted for crossover in the placebo plus best supportive care group, utilities for progression-free and progressed states obtained from the GRID trial, and a time horizon of 10 years.

Drug costs: confidential price submitted, potential cost of treatment beyond progression

At the confidential price submitted by the manufacturer, regorafenib costs $[redacted] per 40 mg tablet. At the recommended dose of 160mg for 21 days of a 28 day cycle regorafenib costs $[redacted] per day and $[redacted] per 28 day cycle. *(Non-disclosable information was provided to pERC in the pCODR guidance reports for deliberation on a recommendation and the manufacturer requested this information not be*

disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed.)

At the list price, regorafenib costs $74.25 per 40 mg tablet. At the recommended dose of 160mg daily for 21 days of a 28 day cycle, the cost of regorafenib is $222.75 per day and $6,237 per 28 day cycle.

Patients require an average of 5 cycles, and may continue treatments beyond progression for a variable number of cycles. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback received from the Provincial Advisory Group asking for clarification on whether continuing regorafenib treatment beyond progression is appropriate. pERC noted that in the GRID study, patients received regorafenib for an average of five cycles before progression occurred. Upon progression and at the discretion of the investigator, patients had the option of continuing open-label regorafenib, but administration post-progression was not required as part of the study protocol. A small but significant proportion of patients (18%) received open-label regorafenib post-progression. pERC noted that the CGP had indicated this was also likely to occur in clinical practice. However, considering that the use of regorafenib beyond progression was not required as part of the study protocol, pERC was unable to assess the appropriateness of this practice. pERC further noted that both the cost of an additional 5 cycles of regorafenib post-progression and its assumed clinical benefit in the post-progression period were included in the economic analysis and would have contributed to the estimates of cost-effectiveness.

Cost-effectiveness estimates: survival benefit overestimated

pERC deliberated upon the cost-effectiveness of regorafenib. pERC discussed that the Economic Guidance Panel's (EGP's) best estimates of the incremental cost-effectiveness ratio were substantially higher than the manufacturer's estimates. It was also noted that this was primarily because the manufacturer's model overestimated the survival benefit of regorafenib. In addition, pERC noted that the EGP was unable to modify the submitted model to address assumptions in the post-progression period that overestimated the benefits of regorafenib. pERC also noted that treatment beyond progression is likely to occur in clinical practice, as agreed upon by the pCODR Clinical Guidance Panel (CGP). Both the costs for these treatments beyond progression and potential clinical benefits were included in Bayer's submitted base case and the EGP's best estimate, and would have influenced the incremental cost-effectiveness ratio. The EGP conducted reanalyses adjusting for these limitations in the submitted model in order to provide pERC with a range of possible incremental cost-effectiveness ratios.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from the Submitter disagreeing with the EGP's reanalysis and estimation of survival benefit. pERC noted that the EGP had further clarified their approach to the analysis and did not change their best estimates after re-confirming the underlying clinical assumptions with the CGP. pERC noted that the Submitter's choice of survival curves was overly optimistic as it was unlikely that the clinical benefits would continue indefinitely beyond the trial. Therefore, pERC agreed that the EGP's assumption of similar benefit, i.e., hazard ratio (HR) = 1, after the end of the trial was more clinically plausible and represents regorafenib outcomes declining over time, not improvement of best supportive care outcomes. pERC also noted that the study used by the Submitter to justify the survival curves (Seddon 2008) included GIST patients starting second-line therapy with sunitinib, who would have a better prognosis than the patients treated with regorafenib in the GRID study. pERC also discussed feedback from the Submitter regarding the EGP's use of the planned dose as compared to the average trial dose in their re-analysis estimates. It was noted that the EGP had used the planned dose to provide an upper boundary for their estimate which is consistent with the approach used in previous pCODR reviews and which pERC considered to be appropriate. Therefore, pERC continued to accept~~ed~~ the EGP's best estimate within that range and, therefore, concluded that at the submitted confidential price regorafenib is not cost-effective.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: new additional therapy, low incidence of GIST

pERC discussed factors impacting the feasibility of implementing a funding recommendation for regorafenib. pERC noted that it is an oral treatment that would be more easily accessible than intravenous therapies for patients in remote regions. pERC also discussed that the budget impact would likely be small given the low incidence of GIST. However, it was also noted that additional resources would likely be required upon implementation as regorafenib would be a new additional line of therapy

rather than replacing an existing third-line treatment so overall costs would increase. Also, additional resources will be required for adverse event monitoring due to the serious warning for hepatic and other toxicities associated with regorafenib. pERC also noted that a generic version of imatinib was recently approved for sale in Canada but considered that the implications on the implementing a funding recommendation for regorafenib are currently unclear.

DRUG AND CONDITION INFORMATION

Drug Information	• Multi-kinase inhibitor • 40 mg film coated tablet • 160 mg (4 tablets, orally) daily for 3 weeks, followed by 1 week off treatment
Cancer Treated	• metastatic or unresectable GIST • third-line setting after progression on or intolerance to imatinib and sunitinib
Burden of Illness	• the incidence is approximately 500 per year in Canada
Current Standard Treatment	• no standard of care in third-line setting • re-challenge with imatinib a possible option, if available but not standard of care
Limitations of Current Therapy	• no standard effective treatments with manageable toxicities in the third-line setting

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Dr. Bill Evans, Dr. Chaim Bell and Carole McMahon who were not present for the meeting.

All members participated in deliberations and voting on the final recommendation except:

- Dr. Maureen Trudeau and Dr. Chaim Bell who were not present for the meeting.
- Carole McMahon who was excluded from voting due to her role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review regorafenib (Stivarga) for gastrointestinal stromal tumours, through their declarations, five members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Bayer Inc., as the primary data owner, did not agree to the disclosure of economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this recommendation

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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