pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Everolimus (Afinitor) **Funding Request:** For treatment of postmenopausal women with hormone receptor-positive advanced breast cancer (HR+ advanced BC) in combination with exemestane, after progression or recurrence (failure) on NSAI therapy	
Submitted By: Novartis Pharmaceuticals Canada Inc.	**Manufactured By:** Novartis Pharmaceuticals Canada Inc.
NOC Date: January 10, 2013	**Submission Date:** September 5, 2012
Initial Recommendation: March 7, 2013	**Final Recommendation:** March 25, 2013

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding everolimus (Afinitor), in combination with exemestane, conditional on the cost-effectiveness of everolimus being improved to an acceptable level. Everolimus should be funded for the treatment of hormone-receptor positive, HER2 negative advanced breast cancer, in postmenopausal women with ECOG performance status ≤ 2 after recurrence or progression following a non-steroidal aromatase inhibitor (NSAI), if the treating oncologist would consider using exemestane. pERC made this recommendation because it was satisfied that there is an overall clinical benefit of everolimus. However, the Committee noted that everolimus could not be considered cost-effective at the submitted price and the Economic Guidance Panel's estimates of the range of incremental cost-effectiveness ratios.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given pERC was satisfied there is a net clinical benefit of everolimus in combination with exemestane, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of everolimus to an acceptable level. pERC noted that jurisdictions need to consider the impact of dose adjustments on tablet burden since everolimus is priced per tablet, not per milligram and as such actual use in clinical practice may significantly increase costs.

Everolimus Use in Patients with Brain Metastases and HER2+ Patients
There was insufficient evidence for pERC to comment on the use of everolimus in combination with exemestane in patients with brain metastases or in patients with HER2 positive breast cancer because these patients were excluded from the BOLERO-2 study. Therefore, pERC is unable to make an informed recommendation on funding everolimus in combination with exemestane in patients with brain metastases or patients with HER2+ breast cancer. However, pERC considered that as it is unlikely a clinical trial would be conducted that included patients with brain metastases it may be clinically reasonable to use everolimus in combination with exemestane in patients with treated and stable brain metastases.

Time-Limited Need in Patients Currently Receiving Exemestane Alone
At the time of implementing a funding recommendation for everolimus, jurisdictions may consider addressing the short-term, time-limited need for everolimus in patients currently receiving exemestane alone, prior to everolimus being available. pERC noted that patients who had previously received exemestane were excluded from BOLERO-2 but considered that, initially, it would be reasonable for this prevalent population of patients to be able to receive everolimus for advanced breast cancer.

SUMMARY OF pERC DELIBERATIONS

pERC discussed that there are a number of therapies that are used to treat post-menopausal women with hormone receptor-positive, advanced breast cancer including exemestane, chemotherapy, tamoxifen or fulvestrant. pERC noted that while there is some clinical benefit with these treatments, all patients eventually develop progressive disease and there is a need for therapies that delay progression and extend survival. One randomized controlled trial, the BOLERO-2 study (Baselga 2012), was included in the pCODR systematic review. It compared everolimus plus exemestane with placebo plus exemestane, which pERC considered a reasonable comparison.

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

pERC discussed the results of the BOLERO-2 study, which evaluated everolimus in hormone receptor positive, HER2 negative patients with advanced breast cancer. Based on a clinically and statistically significant improvement in progression-free survival, pERC considered that there was an overall net clinical benefit of everolimus in combination with exemestane in this patient population. pERC noted that patients who had brain metastases, who had HER2 positive breast cancer or who had previously received exemestane or mTOR inhibitors were excluded from the BOLERO-2 study. Therefore, there was insufficient evidence for pERC to recommend the use of everolimus in these patient populations. However, pERC considered that it is unlikely a clinical trial would be conducted that included patients with brain metastases and that it may be clinically reasonable to use everolimus in combination with exemestane in patients with treated and stable brain metastases.

pERC also considered the toxicity of everolimus based on data from the BOLERO-2 study. It was noted that the adverse event profile was consistent with expectations for everolimus and included fatigue, stomatitis and dyspnea. pERC considered that these adverse events could likely be managed through dose reductions but that patients receiving everolimus should be closely monitored for adverse events. pERC noted that while dose reductions may occur with everolimus in practice, this would not lead to a corresponding reduction in drug costs because the cost of a 2.5 mg, 5 mg and 10 mg tablet is the same price and tablets are not scored to allow for splitting. pERC also noted that in some cases, e.g. if patients receive a dose of 7.5 mg, drug costs would double because there would be two tablets needed to achieve the desired dose. pERC noted that while an everolimus dose of 7.5 mg has not specifically studied or recommended in breast cancer, it may be prescribed in clinical practice.

pERC reviewed input from two patient advocacy groups but noted that there was only one patient who had direct experience with the use of everolimus in advanced breast cancer. While recognizing the difficulty that patient advocacy groups may have in accessing a large number of patients, pERC considered that it would be helpful to get broader patient experiences with everolimus in breast cancer. pERC suggested that other approaches to identifying patients who may be able to provide useful input, such as global patient group collaborations, may be appropriate. The input indicated that patients valued prolonging life and were willing to accept adverse effects if there were a clinical benefit. pERC noted that there was no statistically significant difference in quality of life between the two treatment groups in the BOLERO-2 study, which could indicate that quality of life did not deteriorate due to adverse events in the everolimus group. Patients also valued having another option to treat breast cancer. Therefore, pERC concluded that the addition of everolimus to exemestane aligns with patient values.

pERC discussed the cost-effectiveness of everolimus and noted that there were structural flaws in the economic model that did not permit the pCODR Economic Guidance Panel to provide an upper estimate of the cost-effectiveness of everolimus plus exemestane compared with exemestane alone. pERC also noted that the cost-effectiveness estimates were based on extensive extrapolation of the available clinical trial data due to the immaturity of the data. It was also noted that dose reductions that resulted in the use of two tablets rather than one would result in much less favourable cost-effectiveness estimates for everolimus. Therefore, considering these factors and the pCODR Economic Guidance Panel's best estimates based on a shorter time horizon of five years, pERC concluded that everolimus was not cost-effective.

When considering the feasibility of implementing a recommendation for everolimus, pERC noted that the budget impact may be greater in jurisdictions where exemestane is not currently funded. In addition, until everolimus becomes standard of care, there may be a prevalent population of patients with stable disease who are currently receiving exemestane and for whom the addition of everolimus to their treatment may be an appropriate therapy, which may also increase budget impact. pERC noted that patients who had previously received exemestane were excluded from the BOLERO-2 study but considered that, initially, it would be reasonable for this prevalent population of patients to be able to add everolimus to exemestane. In general, pERC discussed that there is some uncertainty in the proportion of patients with advanced breast cancer who will be eligible for treatment with everolimus, creating some uncertainty in the budget impact.

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 two patient advocacy groups (Canadian Breast Cancer Network and Rethink Breast Cancer)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- the Submitter (Novartis Pharmaceuticals Canada Inc.)

The pERC initial recommendation was to recommends funding everolimus (Afinitor), in combination with exemestane, conditional on the cost-effectiveness of everolimus being improved to an acceptable level. Everolimus should be funded for the treatment of hormone-receptor positive, HER2 negative advanced breast cancer, in postmenopausal women with ECOG performance status ≤ 2 after recurrence or progression following a non-steroidal aromatase inhibitor (NSAI), if the treating oncologist would consider using exemestane.

Feedback on the pERC Initial Recommendation indicated that the pCODR's Provincial Advisory Group agreed with the initial recommendation while the manufacturer agreed in part. The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of this review is to evaluate the effect of everolimus (Afinitor) plus exemestane on patient outcomes compared to placebo plus exemestane in postmenopausal women with hormone receptor-positive, HER2 negative advanced breast cancer after treatment failure with letrozole or anastrozole.

Studies included

The pCODR systematic review included one double-blind, randomized controlled trial, the BOLERO-2 study (Baselga 2012), that compared the safety and efficacy of once daily everolimus (10 mg) plus exemestane (25 mg) to placebo plus exemestane (25 mg). Patients who progressed on exemestane alone during the study were not permitted to cross-over to the everolimus plus exemestane group.

The pCODR review also provided contextual information on the safety of mTOR inhibitors (Lacovelli et al 2012) and the efficacy of everolimus in combination with tamoxifen prior to the use of aromatase inhibitors (TAMRAD study, Bachelot 2012).

Patient populations: Women with brain metastases, prior exemestane use and HER2+ breast cancer excluded

The BOLERO-2 study included postmenopausal women with hormone receptor-positive, HER2 negative advanced breast cancer and ECOG performance status ≤ 2, with disease progression despite previous treatment with letrozole or anastrozole. pERC noted that the majority of patients included in the study had an ECOG performance status of 0 or 1 (60% and 36%, respectively). While pERC considered that the BOLERO-2 evidence primarily supports the use of everolimus in patients with ECOG performance status 0 or 1, it does not preclude the use of everolimus in patients with a performance status score of 2. pERC further noted that because of the limited evidence involving patients with the less favourable performance status 2, clinical judgement would need to be exercised when determining if these patients are appropriate candidates for everolimus therapy.

Patients with a history of brain metastasis, HER2 positive breast cancer, and previous treatment with exemestane or mTOR inhibitors were excluded from the study. Therefore, pERC was unable to make an informed recommendation on the use of everolimus in these patient populations. However, pERC considered that it is unlikely a clinical trial would be conducted that included patients with brain metastases and that it would be reasonable to use everolimus in combination with exemestane in patients with treated and stable brain metastases. pERC also noted that, until everolimus becomes standard of care, there may be a prevalent population of patients who are currently receiving exemestane but for whom the addition of everolimus to their treatment would be appropriate. Therefore, pERC considered that, initially, it would be reasonable for this prevalent population of patients to be able to received everolimus in combination with exemestane for advanced breast cancer.

Key efficacy results: clinically meaningful improvement in progression-free survival

pERC deliberated on the outcomes of progression-free survival, the primary endpoint of the BOLERO-2 study, and overall survival. In BOLERO-2, median progression-free survival, as measured by central radiological assessment, was improved in the everolimus plus exemestane group compared with the placebo plus exemestane group (11.0 months versus 4.1 months, respectively, HR=0.38, 95% CI 0.31 to 0.48, P<0.0001). pERC noted the large magnitude of difference between the two groups and considered that this was a statistically significant and clinically meaningful improvement in progression-free survival. pERC discussed whether the improvement in progression-free survival corresponded to an improvement in overall survival. However, pERC noted that BOLERO-2 was an event-driven trial and overall survival data were immature at this time. As of December 15, 2011 there were 200 deaths and the final overall survival analysis will be conducted after 398 deaths have occurred.

Quality of Life: similar between treatments

In the BOLERO-2 study, quality of life was measured as the median time to deterioration (TTD) in quality of life as measured by EORTC QLQ-C30 global health status. pERC noted that there was no statistically significant difference in quality of life between the two groups. However, pERC considered that this may be an indication that quality of life did not deteriorate due to adverse events in the everolimus group.

Safety: side effects manageable through dose reductions

In the BOLERO-2 study, serious adverse events occurred more frequently in the everolimus plus exemestane arm compared with the placebo plus exemestane arm (22.8% versus 12.2%, respectively). The most common serious adverse events reported in the everolimus plus exemestane group included pneumonitis, pneumonia, anemia, dyspnea, pulmonary embolism, pyrexia, fatigue and renal failure. pERC considered the toxicity of everolimus based on these data and noted that the adverse event profile was consistent with expectations for everolimus based on its use in other indications. pERC considered that these adverse events could likely be managed through dose reductions but that patients receiving everolimus should be closely monitored for adverse events.

Need: improved survival and delay in disease progression

pERC discussed that there are many women living with breast cancer and that it can have a variable clinical course. A number of therapies are available for women with hormone receptor positive advanced breast cancer including exemestane, chemotherapy, tamoxifen or fulvestrant. However, pERC noted that all women will eventually develop progressive disease and that there is a need for new treatments. While improving overall survival is the primary goal of therapy, treatments that delay disease progression would also be of benefit. pERC discussed that funding the regimen of everolimus in combination with exemestane would provide these patients with another treatment option.

PATIENT-BASED VALUES

Values of patients with advanced breast cancer: delaying disease progression and access to treatments

pERC deliberated upon patient advocacy group input and considered that although patients understand there is no cure for advanced breast cancer, it is important to patients to have access to as many treatment options as possible to slow down the progression of their disease. Patients indicated that if a therapy can stop the progression of the disease, even if only for a short amount of time and even with potential adverse side effects they want to be able to access these treatments.

Patient values on treatment: tolerable side effects while maintaining quality of life

pERC discussed that from a patient perspective, it is important for patients to have access to therapies that will extend their life without increasing side effects that will negatively impact their daily lives. Patient advocacy group input recognized that there is monitoring of adverse events that must occur with everolimus but that many patients are willing to accept these toxicities if it stops the progression of cancer. pERC noted that in the patient advocacy group input there was only one patient who had direct experience with the use of everolimus in advanced breast cancer. While recognizing the difficulty that patient advocacy groups may have in accessing a large number of patients, pERC considered that it would be helpful to get broader patient experiences with everolimus in breast cancer. pERC suggested that other approaches to identifying patients who may be able to provide useful input, such as global patient group collaborations, may be appropriate. pERC noted that there was no statistically significant difference in quality of life between the two treatment groups in the BOLERO-2 study, which could indicate that quality of life did not deteriorate in the everolimus group despite adverse events. Patients also valued having another option to treat breast cancer. Therefore, pERC considered that everolimus aligns with patient values.

ECONOMIC EVALUATION

Economic model submitted: cost effectiveness and cost utility analysis

The pCODR Economic Guidance Panel assessed a cost effectiveness and cost utility analysis comparing everolimus plus exemestane with exemestane alone for patients with advanced breast cancer previously treated with an alternative regimen.

Basis of the economic model: clinical and economic inputs

Costs included drug costs, costs associated with management of serious adverse events and pre-progression and post-progression background costs.

Key clinical effects included progression-free survival and overall survival estimates from the BOLERO-2 study. The biggest influence on both QALYs and life years was the estimate of survival following tumour progression, which required long-term modelling due to the immaturity of the clinical data.

Drug costs: dose reductions do not lead to lower drug costs

Everolimus costs $186.00 per 2.5 mg, 5 mg, or 10 mg tablets, at the list price. At the recommended dose of 10 mg per day, the average cost per day of everolimus is $186.00 and the average cost per 28-day course is $5,208.00. pERC noted that the price of everolimus tablets is the same regardless of dose and tablets are not scored to allow for splitting. Therefore, dose reductions would not result in a corresponding decrease in drug costs. pERC also noted that in some cases, e.g. if patients receive a dose of 7.5 mg, drug costs would double because two tablets are required. pERC noted that while an everolimus dose of 7.5 mg has not specifically studied or recommended in breast cancer, it may be prescribed in clinical practice. In addition, dose reductions due to toxicities may also result in wastage because tablets are not scored to allow for splitting and a new prescription would be required.

Exemestane is available as 25 mg tablet at a cost of $3.90. At the recommended dose of 25 mg per day, the average cost per day in a 28-day course of exemestane is $3.90 and the average cost per 28-day course is $109.20.

Cost-effectiveness estimates: inadequate model structure and extensive extrapolation of clinical data

pERC discussed the cost-effectiveness of everolimus and noted that there were structural flaws in the economic model that did not permit the pCODR Economic Guidance Panel to provide an upper estimate of the cost-effectiveness of everolimus plus exemestane compared with exemestane alone. This is because the manufacturer submitted a model where survival and progression are modelled independently and where it is assumed that a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state.

pERC also noted that the cost-effectiveness estimates were based on extensive extrapolation of the available clinical trial data due to the immaturity of the overall survival data and a time horizon of ten years. Therefore, the pCODR Economic Guidance Panel considered more conservative options and used a shorter time horizon of five years because the pCODR Clinical Guidance Panel estimated that the majority of patients in the model would likely die within five years of initiating treatment. Considering these factors and the pCODR Economic Guidance Panel's best estimates, including the lowest estimate of $162,049 per QALY, pERC concluded that everolimus was not cost-effective at the submitted price. pERC noted that these estimates were higher than the manufacturer's submitted estimates but considered that the pCODR Economic Guidance Panel's estimates were more reliable. pERC also noted that dose reductions that resulted in the use of two tablets rather than one tablet would result in less favourable cost-effectiveness estimates for everolimus.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: dose reductions and use of exemestane

pERC discussed the feasibility of implementing a funding recommendation for everolimus and discussed potential barriers to implementation. pERC noted that the budget impact would be greater in jurisdictions where exemestane is not currently funded. In addition, until everolimus becomes standard of care, there may be a prevalent population of patients with stable disease who are currently receiving exemestane and for whom the addition of everolimus to their treatment may be an appropriate therapy, which may also increase budget impact. pERC noted that patients who had previously received exemestane were excluded from the BOLERO-2 study but considered that, initially, it would be reasonable for this prevalent population of patients to be able to add everolimus to exemestane. In general, pERC discussed that there is some uncertainty in the proportion of patients with advanced breast cancer who will be eligible for treatment with everolimus, creating some uncertainty in the budget impact. pERC also noted that while dose reductions may occur with everolimus in practice, this would not lead to a corresponding reduction in drug costs because the cost of a 2.5 mg, 5 mg and 10 mg tablet is the same; in some cases, it may even increase drug costs.

DRUG AND CONDITION INFORMATION

Drug Information	• Inhibitor of mammalian target of rapamycin (mTOR) • 2.5 mg, 5 mg, or 10 mg tablets • 10 mg per day administered orally
Cancer Treated	• Hormone receptor-positive, HER2 negative, advanced breast cancer refractory to previous treatment with letrozole or anastrozole.
Burden of Illness	• Breast cancer is the most commonly diagnosed malignancy in Canadian women with an estimated incidence of 23,600 new cases and an estimated 5,100 deaths in 2012 • While many women diagnosed with early stage breast cancer will be cured of their disease, some experience a relapse (spread to other organs) of their disease or present with de novo metastatic breast cancer. • Advanced breast cancer is not curable, with an estimated median life expectancy of 18-24 months.
Current Standard Treatment	• The first-line treatment is usually endocrine therapy using non-steroidal aromatase inhibitors (NSAIs), i.e. letrozole or anastrozole, if no prior exposure to a NSAI in the early stage or advanced stage setting. • In patients with recurrence on an NSAI, a second line treatment option is the use of an alternative aromatase inhibitor, i.e. exemestane, or selected estrogen receptor modulators, i.e. tamoxifen or fulvestrant. • Patients, whose tumours progress on all endocrine therapies or with rapidly progressive and/or symptomatic disease, are usually offered treatment with chemotherapy.
Limitations of Current Therapy	• Despite the clinical efficacy of endocrine therapy, resistance to treatment occurs. While most patients will experience some degree of clinical benefit from 2nd and even 3rd line endocrine therapy all patients eventually develop progressive disease.

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
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 Lister, 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:

- Jo Nanson and Dr. Bill Evans who were not present for the meeting
- Dr. Maureen Trudeau, Dr. Tallal Younis and Carole McMahon who was excluded from voting due to a conflict of interest

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

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 everolimus (Afinitor) for advanced breast cancer, through their declarations, ten members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, three 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*. There was no non-disclosable information in this recommendation document.

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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