The CADTH 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 reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (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:** Vandetanib (Caprelsa)

**Submitted Funding Request:**
For the treatment of symptomatic and/or progressive medullary thyroid cancer (MTC) in adult patients with unresectable locally advanced or metastatic disease

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**pERC RECOMMENDATION**

pERC recommends reimbursement of vandetanib (Caprelsa) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients who have symptomatic and/or progressive medullary thyroid cancer (MTC) with unresectable locally advanced or metastatic disease and with a good performance status. Treatment should continue until disease progression or unacceptable toxicity.

The Committee made this recommendation because it was satisfied that there is a modest net clinical benefit of vandetanib based on a clinically meaningful improvement in progression-free survival (PFS) compared with placebo, and a need for more effective treatment options. The Committee noted uncertainty in overall survival (OS) and quality of life benefits, and manageable but not insignificant toxicities. pERC also concluded that vandetanib partially aligned with patient values in that it offers an improvement in PFS and it provides patients with a treatment option in addition to best supportive care, but with a risk of toxicities.

However, pERC concluded that vandetanib could not be considered cost-effective at the submitted price.

**POTENTIAL NEXT STEPS FOR STAKEHOLDERS**

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there is a modest net clinical benefit with vandetanib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of vandetanib to an acceptable level.

Guidelines to Define Treatment Population, and to Monitor Side Effects
Although pERC noted that patients with progressive and/or symptomatic MTC may benefit from treatment with vandetanib, the
Committee noted that there are no Canadian clinical practice guidelines that define progressive and/or symptomatic MTC. Therefore, provinces may want to consider developing guidelines to outline appropriate clinical criteria to define both progressive MTC as well as symptomatic MTC. Furthermore, pERC also noted that there is a need for guidelines on monitoring toxicities related to treatment with vandetanib, especially for those noted as black box warnings in the Health Canada product monograph, such as the need for regular electrocardiogram (ECG) monitoring for QTc prolongation.

Additional Resources Required Due to Controlled Distribution
pERC noted that vandetanib can be prescribed and provided only by physicians and pharmacists who are registered with the controlled distribution program, which patients acknowledge may be a potential barrier to accessing treatment, especially in provinces that have a limited number of pharmacies registered with the program. Controlled distribution programs introduce additional diligence and requirements for patient monitoring and dispensing that may add additional resource use to the system. pERC also acknowledged that the controlled distribution program ensures safety for patients, and appropriate distribution from registered centres.

Factors Affecting Dosing and Dose Wastage
pERC noted the non-linear pricing of the different tablet strengths, which has cost implications because of the potential for drug wastage, in particular when there is a dose adjustment prior to the patient completing the strength initially provided. Furthermore, the economic model did not account for wastage and no data were available from the trial regarding time to dose reductions and interruptions. Therefore, the dose intensity of vandetanib provided to patients in the ZETA study was unclear. The Committee noted that the efficacy results of an ongoing, randomized, double-blind trial comparing vandetanib 150 mg and 300 mg (expected completion in December 2019) may provide additional information on dosing (NCT01496313).
SUMMARY OF pERC DELIBERATIONS

MTC accounts for less than 5% of thyroid cancers. There is no current standard of care for the treatment of patients with unresectable locally advanced or metastatic MTC who have symptomatic and/or progressive disease. pERC noted that cabozantinib may be considered a first-line therapy option; however, it is not available in Canada. Current treatment practice in Canada is best supportive care. The Committee agreed with the registered clinician input that there is an unmet need for available treatment options that prolong survival, and that do not have a detrimental impact on patients’ quality of life.

pERC deliberated upon the results of a phase III, randomized, double-blind, placebo-controlled study (ZETA), comparing vandetanib 300 mg once daily (n = 231) with placebo (n = 100) in patients with unresectable locally advanced or metastatic MTC. The Committee noted that the trial enrolment was not limited to patients with symptomatic or progressive disease and that the requested indication for symptomatic and/or progressive MTC is a subset of the trial population. However, according to a post-hoc analysis conducted by the European Medicines Agency, the trial comprised mostly patients who would meet the requested reimbursement criteria of symptomatic and/or progressive MTC (95%; n = 313). The Committee noted a PFS benefit of vandetanib compared with placebo in the overall trial population, and a similar trend was observed in the post-hoc analyses conducted by the FDA. However, because the submitter did not provide data on the “and/or” population as requested by pCODR, pERC was unable to conclude on the magnitude of the PFS benefit of vandetanib in the requested indication. The Committee noted that the OS results were not statistically significant and that there was uncertainty in the OS results due to the potential for confounding by crossover of patients from the placebo arm to receive open-label vandetanib. pERC discussed the appropriateness of PFS as a surrogate for OS, and they noted a lack of evidence to inform a conclusion either for or against its use. pERC noted that the Clinical Guidance Panel (CGP) and registered clinician input identified PFS as a clinically meaningful outcome and agreed with the CGP and registered clinicians that PFS was a likely surrogate outcome for OS in MTC. The Committee also discussed the limited quality-of-life data from the ZETA study and noted that no statistical comparisons of the data were conducted. Therefore, pERC was unable to draw a conclusion on the quality-of-life impact of vandetanib.

pERC discussed the safety of vandetanib and noted that the rate of serious adverse events was higher with vandetanib than with placebo. Specifically, pERC discussed the black box warnings on the Health Canada product monograph (QTc prolongation, heart failure, hypertension, and hypertensive crisis), noting that the Grade 3 or higher black box adverse events occurred more frequently with vandetanib than with placebo. pERC concluded that although toxicities with vandetanib were not insignificant, they were manageable. The Committee agreed with the CGP that there is a need for regular side effect monitoring, especially with respect to QTc prolongation. pERC discussed that patients with symptomatic and/or progressive MTC would likely derive a clinical benefit from treatment with vandetanib; however, pERC acknowledged that there is uncertainty in the precise definitions of symptomatic disease and progressive disease. As there are no Canadian guidelines to guide practice, pERC noted the importance of having jurisdictions to define criteria for symptomatic MTC as well as progressive MTC. pERC therefore concluded that there is a modest net clinical benefit to treatment with vandetanib in patients with symptomatic and/or progressive unresectable locally advanced or metastatic MTC.

pERC deliberated upon input from one patient advocacy group concerning vandetanib and noted the following factors were most important to patients: improvement in quality of life, slowing the rate of disease progression, and improvement in disease-related symptoms. The Committee agreed that vandetanib was associated with a PFS benefit, and offers a treatment option other than best supportive care. However, the Committee also noted uncertainty in improvements of OS and quality of life, toxicities associated with vandetanib, and potential barriers to accessing treatment in the community. Therefore, the Committee concluded that vandetanib partially aligned with patient values. Upon reconsideration and feedback from the patient group regarding pERC’s Initial Recommendation, pERC reaffirmed its...
acceptance of PFS as a clinically meaningful endpoint and its agreement with the CGP that PFS is a likely surrogate of OS in MTC.

pERC deliberated upon the cost-effectiveness of vandetanib and concluded that, at the submitted price, it is not cost-effective compared with best supportive care. pERC considered the estimates provided by the submitter and the reanalysis estimates provided by the pCODR Economic Guidance Panel (EGP). The Committee noted the high uncertainty in the incremental cost-effectiveness ratio (ICER). Specifically, pERC noted that the EGP’s upper bound was likely an underestimation, given that the modelled OS benefit was based on the PFS benefit from the post-hoc analysis of patients with symptomatic and progressive MTC and that this PFS benefit was added to the relative survival of the best supportive care arm, adjusted for natural mortality. This may be a favourable extrapolation of the ZETA trial results, given that the ZETA trial did not demonstrate an OS benefit with vandetanib. Although pERC noted the potential for confounding of the OS results due to crossover, the Committee considered there to be a high amount of uncertainty in the OS estimates used to inform the economic model, and that the submitter’s assumption may represent the most favourable OS estimate. pERC also noted that quality-of-life decrements in the post-progression state were derived from a survey of patients with melanoma, a rapidly progressing cancer, rather than from the pivotal trial in this review. pERC noted that the best estimate of the cost-effectiveness would likely be above the high end of the EGP reanalysis range. The Committee noted that the cost of vandetanib accounted for 98.7% of the difference in costs between vandetanib and best supportive care. Given the non-linear pricing of different tablet strengths and the frequency of dose reductions reported in the ZETA trial, the Committee stated that drug wastage may have a significant impact on the ICER. However, the Committee was unable to comment on the impact of drug wastage (i.e., when dose adjustments are made and a different tablet strength is required prior to the patient completing the strength initially provided) because wastage was not explicitly examined in the model. The submitted model instead assumed that approximately 14% of patients would have their drug dose reduced to 100 mg daily, and assumed an eight-month time period to dose reductions and interruptions. Without specific data on wastage for the requested indication, pERC noted that the EGP could not fully explore the impact of drug wastage on the ICER.

Upon reconsideration of the Initial Recommendation and feedback from the submitter, pERC discussed the Submitter’s proposal to have pERC accept the cost-effectiveness results provided by the Submitter at face value, and to have pERC use a decision framework “for rare disorders like MTC... based on principles of multi-criteria decision analysis, not solely on the application of traditional pharmacoeconomic methods”. Similarly, patient group feedback also identified that conventional health technology assessment methods are not well suited for evaluating MTC. pERC noted that, while MTC has a low prevalence, the deliberative framework applied by pERC considers the unmet need, burden of illness, clinical effectiveness, and safety for each review deliberated upon by the Committee. Given compelling evidence that these factors play a more important role in funding decisions for Canadians than prevalence, pERC felt that the current deliberative framework is appropriate for diseases with a lower prevalence, such as MTC. Furthermore, the use of multi-criteria decision analysis using criteria identified as important to funding decisions in low prevalence diseases would not be expected to change the current recommendation.

pERC also considered factors affecting the feasibility of implementing a positive reimbursement recommendation for vandetanib for the treatment of patients who have symptomatic and/or progressive unresectable locally advanced or metastatic MTC. The Committee agreed with pCODR’s Provincial Advisory Group (PAG) that the cost of vandetanib is high. Given that the 300 mg tablet strength is priced the same as two 100 mg tablets, pERC agreed with PAG that the non-linear pricing structure would be a barrier to implementation. pERC noted that efficacy results of a randomized, double-blind trial comparing vandetanib 150 mg and 300 mg are forthcoming. The Committee agreed that the results would inform provinces in determining the optimal treatment dose, as well as costs associated with dose reduction given the toxicity profile of vandetanib. The Committee also agreed with PAG that there is a need to monitor adverse events related to treatment with vandetanib in patients under the current controlled distribution program. With the absence of Canadian practice guidelines, pERC noted that provinces may want to consider developing guidelines on monitoring toxicities, especially those noted as black box warnings in the Health Canada product monograph, such as the need for regular electrocardiogram (ECG) monitoring for QTc prolongation. Upon reconsideration, the Committee agreed with patients that the controlled distribution program with registered physicians and pharmacists is a potential barrier, especially in provinces that may have a limited number of pharmacies registered with the program; however, the Committee also agreed with PAG that the program ensures patient safety. The Committee
noted that provinces may want to consider ways to explore transferring prescription and delivery systems to community centres. Upon reconsideration, pERC noted PAG’s request for guidance on the definition on progressive disease and a recommendation or consensus for patients already using a systemic therapy for progressive disease. pERC reiterated that there are no Canadian clinical practice guidelines and that provinces may want to consider developing guidelines to outline appropriate clinical criteria to define both progressive MTC as well as symptomatic MTC.
EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the submitter’s economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from one patient advocacy group (Thyroid Cancer Canada [TCC])
- Input from one registered clinician
- Input from pCODR’s Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- PAG
- One patient advocacy group, Thyroid Cancer Canada (TCC)
- The submitter, Sanofi Genzyme

The pERC Initial Recommendation was to recommend reimbursement of vandetanib (Caprelsa) conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients who have symptomatic and/or progressive MTC with unresectable locally advanced or metastatic disease and with a good performance status. Treatment should continue until disease progression or unacceptable toxicity.

Feedback on the pERC Initial Recommendation indicated that PAG agreed with the Initial Recommendation, while the submitter and patient advocacy group agreed in part with the Initial Recommendation but supported conversion to a Final Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of vandetanib compared with placebo for the treatment of symptomatic and/or progressive medullary thyroid cancer (MTC) in adult patients with unresectable locally advanced or metastatic disease.

Studies included: Phase III, randomized, double-blind, placebo-controlled study

The pCODR systematic review included ZETA, a phase III, randomized (2:1, intervention: control), double-blind, placebo-controlled study. The ZETA trial enrolled patients with unresectable locally advanced or metastatic disease MTC; however, the enrolment was not limited to patients with symptomatic or progressive disease. According to a post-hoc analysis conducted by the European Medicines Agency, the symptomatic and/or progressive MTC population represented a majority of the ZETA trial (95%; n = 313). Currently, there are no Canadian clinical practice guidelines that define progressive and/or symptomatic MTC. pERC noted feedback on the Initial Recommendation from the Provincial Advisory Group (PAG) on this absence, and reiterates that provinces may want to consider developing guidelines to outline appropriate clinical criteria to define both progressive MTC as well as symptomatic MTC.

There were 331 patients randomized to vandetanib (300 mg once daily) or matching placebo (n = 100). Key inclusion criteria included adults aged 18 years or older, with unresectable, locally advanced or metastatic hereditary or sporadic MTC, one or more measurable lesion, World Health Organization (WHO) performance score 0 to 2, and life expectancy ≥12 weeks. Key exclusion criteria included patients with brain metastases and certain cardiovascular conditions. The study was conducted in 23 countries, including Canada (12 Canadian patients).

The primary outcome of the trial was progression-free survival (PFS) assessed by independent central review; secondary outcomes included overall survival (OS), objective response rate (ORR), disease control rate, health-related quality of life, time to worsening of pain, calcitonin response, and carcinoembryonic
antigen response. Dose reductions, dose interruptions, and crossover to open-label vandetanib were permitted. Of note, AstraZeneca funded the study, before Sanofi Genzyme acquired vandetanib.

The pCODR review also provided contextual information, in the form of comparison with other literature on whether PFS is an appropriate surrogate for OS in patients with MTC. The pCODR review did not identify any studies that investigated a correlation between PFS and OS in patients with MTC. It is the opinion of the Clinical Guidance Panel (CGP) that PFS, as reported in the ZETA trial, is a very likely surrogate outcome for OS in MTC.

Patient populations: Similar baseline characteristics; majority with ECOG performance status 0-1
Baseline characteristics between the two treatment groups were similar, with a few differences likely due to correlated characteristics: The vandetanib group had more patients with a WHO performance status of 0 (67% versus 58%), more patients with hereditary MTC (12% versus 5%), and patients who were younger (mean: 51 versus 53 years). Sensitivity analyses conducted by regulatory bodies to adjust for these baseline differences demonstrated results similar to the primary analysis.

Key efficacy results: Clinically meaningful progression-free survival, immature survival data
The key efficacy outcomes deliberated on by pERC were PFS and OS.

The median PFS, as assessed by central review, was not reached in the vandetanib group (estimated to be 30.5 months using a Weibull model) and 19.3 months in the placebo group (final analysis, September 2015 data cut-off). Vandetanib was associated with a 54% reduction in the estimated risk of disease progression or death (hazard ratio [HR] = 0.46; 95% confidence interval [CI], 0.31 to 0.69; \(P = 0.0001\); interim analysis). The primary end point (PFS) was supported by using numerous sensitivity analyses, which demonstrated results that were consistent with the primary analysis. Sensitivity analyses included the following: per-protocol analysis (HR = 0.45; 95% CI, 0.30 to 0.68); the exclusion of events that occurred during open-label treatment (HR = 0.27; 95% CI, 0.18 to 0.41); investigator-determined progression (HR = 0.40; 95% CI, 0.27 to 0.58); and an analysis using the Whitehead method to assess the potential impact of a differential frequency of assessments in the two treatment groups (0.51; 95% CI, 0.35 to 0.72). In addition to the above, similar results were obtained using a Cox proportional hazards regression model adjusting for RET mutation status, number of prior therapies, response to prior therapies, hereditary or sporadic MTC status, pre-randomization doubling time in calcitonin and carcinoembryonic antigen (HR = 0.46; 95% CI, 0.32 to 0.68).

Subgroup analyses were conducted by Kreissl et al. on the progressive and symptomatic patient population for the primary end point, PFS. The analysis plan for the progressive and symptomatic subgroup was not pre-specified. The analysis excluded patients who received treatment with open-label vandetanib. The effect size reported for the progressive and symptomatic subgroup was consistent with the effect size reported for overall population for PFS (HR of 0.32 and 0.27, respectively; no CIs provided). The subgroup data were limited to a single conference abstract with some additional data provided in the manufacturer’s submission.

Exploratory subgroup analyses were conducted by the FDA using alternative criteria to define symptomatic and progressive disease for patients in the ZETA trials. The FDA conducted its subgroup analyses using all available progression events confirmed by independent central review (i.e., including both double-blind and open-label treatment). The submitter’s analyses were conducted using only progression events that occurred during double-blind treatment. The post-hoc subgroup analyses by the FDA were similar to the primary analysis of PFS.

Data for OS were immature at the interim analysis (July 2009). The pre-planned interim analysis of OS demonstrated a non-statistically significant HR of 0.89 (99.98% CI, 0.28 to 2.85; \(P = 0.7115\)). The final analysis of OS was performed when \(\geq 50\%\) of patients had died (September 7, 2015). In this final analysis, 50.2% and 52.0% of the patients randomized to the vandetanib and placebo groups had died, respectively. There was no statistically significant difference in OS between the two groups. As the study protocol permitted patients with documented disease progression to receive open-label treatment with vandetanib, the OS end point could be biased against vandetanib, as those in the placebo group received active treatment. pERC received feedback from the patient group that patients felt PFS is a clinically meaningful surrogate of OS in MTC, which is also the opinion of the CGP and was accepted by pERC.
Quality of life: Limited data on FACT-G measurements
Health-related quality of life data were captured using the Functional Assessment of Cancer Therapy-General instrument (FACT-G) as total scores and subscale scores. Statistical analyses were not conducted on quality of life. pERC felt there was an absence of data and could not draw a conclusion on whether improvements in quality of life were demonstrated.

Safety: Vandetanib associated with more toxicities compared with placebo but manageable; frequent monitoring recommended
Compared with placebo, a greater proportion of vandetanib-treated patients experienced at least one adverse event (AE) (99.6% versus 90.9%), AE of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher (55.4% versus 24.2%), serious AE (30.7% versus 13.1%), or an AE that led to discontinuation from the study (12.1% versus 3.0%). The proportion of patients who died as a result of AEs was similar between the vandetanib and placebo groups (2.2% versus 2.0%, respectively).

The CGP identified the following AEs of special interest, all of which were reported more commonly in vandetanib-treated patients than in placebo-treated patients: QTc prolongation (15.6% versus 4.0%), diarrhea (56.7% versus 27.3%), and hypertension (32.9% versus 5.1%). The CGP noted that the AEs are manageable and require frequent monitoring upfront (i.e., for QTc prolongation, heart failure, hypertension and hypertensive crisis, diarrhea).

Limitations: Some potential sources of bias
Overall, the data for PFS from the ZETA trial appear to be internally valid and were considered by the CGP to be generalizable to the treatment of MTC in the Canadian setting. pERC noted that no evidence was identified in the literature for or against PFS as a surrogate for OS in MTC patients. Although the ZETA trial did not limit enrolment to patients with symptomatic or progressive disease, post-hoc subgroup analyses conducted by the submitter and the FDA demonstrated results that were similar to those conducted using the full analysis set (FAS) data set. Due to extensive crossover to open-label treatment with vandetanib, pERC noted uncertainty in the non-statistically significant OS results. Without data on the time to dose reductions and interruptions in the requested indication, the dose intensity of vandetanib provided to patients in the ZETA study was unclear. Health-related quality-of-life data were captured using the FACT-G instrument. pERC noted there were limited quality-of-life data from the ZETA study and that no statistical comparisons were conducted. Therefore, pERC was unable to draw a conclusion on the quality-of-life impact of vandetanib.

Registered clinician input: Fills gaps in therapy, increase in progression-free survival, high objective response rate and disease control rate, and manageable side effects
One registered clinician provided input on vandetanib for MTC. pERC agreed with the input that vandetanib would fill a gap in therapy for the very small number of patients with MTC. Key benefits identified are the increase in PFS, high ORR, and high disease control rate. The harms identified are the side effects associated with vandetanib, which are manageable, and the contraindications for patients with prolonged QT interval or on other medications that prolong QT interval.

Need: Absence of reliably effective therapeutic alternatives
MTC accounts for less than 5% of thyroid cancers. For progressive MTC, there is currently no reliably effective treatment option in Canada. The current approach to MTC in recently updated guidelines of the American and European Thyroid Associations recommends vandetanib or cabozantinib as single-agent first-line therapy for patients with advanced progressive MTC. Vandetanib would provide an effective treatment option for the very small number of patients with symptomatic and/or progressive MTC.

Time and logistical coordination are significant issues given that vandetanib must be prescribed and dispensed by healthcare providers who are registered in the controlled distribution program and patients may therefore be limited to certain centres to access treatment.
PATIENT-BASED VALUES

Values of patients with medullary thyroid cancer: Ongoing symptoms of thyroid cancer affect day-to-day life
In addition to the standardized quality of life trial data collected every 12 weeks in the ZETA study, pERC considered the national online survey and telephone interviews conducted as part of the patient advocacy input. From a patient’s perspective, it was reported that the ongoing symptoms of thyroid cancer that impact day-to-day life include feeling tired and listless, which affects emotional well-being and ability to work. Respondents reported using the following therapies to treat thyroid cancer: Levothyroxine, sorafenib or other tyrosine kinase inhibitors, vandetanib, radioactive iodine treatment, surgery, chemotherapy, and external beam radiation. All respondents felt that their current treatment for thyroid cancer was good to excellent at controlling disease progression, but was less effective at controlling weight gain and fatigue. Respondents commented on AEs that included low energy, weight loss, high blood pressure, loss of appetite, muscle pain, and voice disorder.

pERC acknowledged that patient expectations included managing weight issues, fatigue, and disease. Other issues identified were bowel issues, diarrhea, and skin rashes.

Caregivers identified the following issues: Fear of recurrence or progression, fatigue, frequent physician visits, access to specialists, cost of treatment and effect on income, demands on personal time, and management between work and caregiving.

Patient values regarding treatment: Expect vandetanib to slow disease progression and have fewer side effects
Respondents who do not have experience with the drug under review expect that it will manage their disease progression and have fewer side effects, such as weight loss, fatigue, and pain, among others, than other available treatments.

Respondents who have experience with vandetanib indicated that it helped to slow their disease progression, as confirmed by physicians. Respondents stated that their side effects including vomiting, weight loss, diarrhea, and skin rash were better managed than with previous treatments. However, patients reported transient acne and diarrhea, although these were milder than with other treatments. Respondents also reported that vandetanib was easy to use.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis
The cost-effectiveness analysis and cost-utility analysis submitted to pCODR by Sanofi Genzyme compared vandetanib to best supportive care (BSC) for the subgroup of symptomatic and progressive MTC patients with unresectable locally advanced or metastatic disease. BSC was symptomatic patient management including pain medications, anti-diarrheal medications, and over-the-counter hand creams.

Basis of the economic model: Partitioned survival model
The partitioned survival model comprised three health states: Stable disease, disease progression, death.

Kaplan-Meier curves from the trial were used, after which derived parametric curves were used to extrapolate beyond the trial follow-up period. The base-case analysis used a 50-year time horizon. Efficacy data were sourced from one randomized phase III, double-blind, placebo-controlled trial (ZETA) of symptomatic and progressive MTC patients with unresectable locally advanced or metastatic disease. Utility values were based on a mapping study of data from the FACT-G quality-of-life questionnaire to the EuroQol 5-Dimensions questionnaire (EQ-5D) using a published algorithm, combined with utility values of advanced melanoma patients from a published study. Resource use was based on expert opinion. Cost information was taken from Canadian sources.
Drug costs: High drug costs
Vandetanib costs $97.50 per 100 mg tablet and $195.00 per 300 mg tablet. At the recommended daily dose of 300 mg, vandetanib costs $195.00 per day, and $5,460.00 per 28-day course. At a reduced daily dose of 100 mg, vandetanib costs $97.50 per day, and $2,730.00 per 28-day course.

Cost-effectiveness estimates: Best estimate driven by the overall survival assumptions in the post-trial period
The extra cost of vandetanib is between $128,963 and $131,365. The Committee noted that the cost of vandetanib accounted for 98.7% of the difference in costs between vandetanib and best supportive care. The incremental cost is relatively stable; it is slightly affected by the assumed time to dose reduction and interruption, and percentage of patients reduced to 100 mg per day of vandetanib. The extra clinical effect of vandetanib is between 0.30 and 0.42 quality-adjusted life-years (QALYs). The clinical benefits are influenced by the PFS benefit seen in the ZETA trial and the assumption of its effect on OS and the included health state utility values.

pERC noted some uncertainty regarding the modelled OS benefit for vandetanib, which was based on an assumption that the PFS benefit could be added to the relative survival of the placebo arm, adjusted for natural mortality, in order to obtain an estimate of the OS for the vandetanib arm. The Economic Guidance Panel’s (EGP) best estimate is driven by revised assumptions on the quality-of-life benefit, decrease in the time to dose reduction or interruption, reduction in the frequency of dosage reduction and interruptions, and reduction to the time horizon.

pERC noted the main assumptions and limitations of the submitted model identified by the EGP. The OS benefit prediction for vandetanib compared with BSC was likely to overestimate the effectiveness of vandetanib over placebo. The survival benefit calculated by the submitter was based on the estimated benefit of PFS from the ZETA subgroup. The benefit in PFS was added to the relative survival of the placebo arm, and was adjusted for natural mortality. The submitter’s approach was in contrast to the ZETA trial results, which did not reveal any survival benefit between the vandetanib and placebo arms. The modelling of health state utility values used a combination of mapped FACT-G data from the ZETA trial for the pre-progression health state, and a difference between the pre- and post-progression utility values based on a published study in advanced melanoma patients. The submitted model used the percentages of patients receiving dose reductions and interruptions based on the ZETA trial, but assumed the time to dose reduction and interruption. With feedback from the CGP, the EGP noted the frequency of dose reductions and interruptions is likely lower, and the time to dose reduction and interruption is likely shorter. EGP reanalysis showed a decrease in frequency of dose reductions and interruptions increased the ICER. pERC acknowledged the CGP’s comments that disease progression does not necessarily correlate with a significant change in quality of life, that time to dose reduction and interruption is likely shorter than that modelled, and that the 50-year time horizon modelled was unrealistic.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Oral administration once daily, restricted distribution program, monitoring of black box warnings, non-linear pricing of two tablet strengths
PAG noted that BSC or palliative chemotherapy with doxorubicin in some provinces is available.

PAG indicated that vandetanib fills a gap in therapy for the very small number of patients with symptomatic or progressive MTC. With the absence of Canadian clinical practice guidelines, pERC noted that provinces may want to consider developing guidelines to outline appropriate clinical criteria to define both rapidly progressive MTC and symptomatic MTC.

PAG noted that the drug’s continuous once-daily dosing schedule, the flat dose of 300 mg, and one tablet per dose would be enablers to implementation. There are some concerns with drug wastage if dose reductions require change in tablet strength prior to the previously dispensed strength being completely used. pERC noted that the upcoming efficacy results of a randomized, double-blind trial comparing vandetanib 150 mg and 300 mg may provide additional information on dosing (expected completion in...
Vandetanib has black box warnings for QT interval prolongation, heart failure, grade 4 hypertension, and hypertensive crisis. PAG noted that additional health care resources are required for regular ECG monitoring and consultations with cardiologists to monitor for serious cardiac toxicities.

PAG identified the oral route of administration as an enabler to implementation. However, PAG noted that only prescribers and pharmacies certified with the restricted distribution program are able to prescribe and dispense vandetanib. pERC agreed with PAG’s concerns about the significant time and logistical coordination required to address the fact that vandetanib must be prescribed and dispensed by healthcare providers who are registered in the controlled distribution program and that patients may therefore be limited to certain centres to access treatment. pERC also noted from patient feedback that, in provinces where oral and intravenous cancer drugs have different routes of reimbursement, provincial reimbursement policies also act as a barrier to access.

PAG indicated that the non-linear pricing of the 100 mg and 300 mg tablets is a barrier to implementation.
DRUG AND CONDITION INFORMATION

Drug Information
- Vandetanib is an orally administered vascular endothelial growth factor receptor tyrosine kinase inhibitor
- 300 mg tablet reviewed by pCODR
- Recommended dosage of 300 mg tablet once daily (oral)

Cancer Treated
- Medullary thyroid cancer (MTC)

Burden of Illness
- MTC accounts for less than 5% of thyroid cancers
- For progressive MTC, there is currently no reliably effective treatment option in Canada

Current Standard Treatment
- Best supportive care
- Palliative chemotherapy with doxorubicin in some provinces
- Cabozantinib (approved by FDA, but not Health Canada)

Limitations of Current Therapy
- Absence of reliably effective therapeutic alternatives

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee
Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)                      Dr. Anil Abraham Joy, Oncologist
Dr. Paul Hoskins, Oncologist (Vice-Chair)                  Karen MacCurdy Thompson, Pharmacist
Dr. Scott Berry, Oncologist                                Valerie McDonald, Patient Member Alternate
Dr. Kelvin Chan, Oncologist                                 Carole McMahon, Patient Member
Dr. Matthew Cheung, Oncologist                              Dr. Catherine Moltzan, Oncologist
Dr. Craig Earle, Oncologist                                 Jo Nanson, Patient Member
Dr. Allan Grill, Family Physician                           Dr. Marianne Taylor, Oncologist
Don Husereau, Health Economist                              Danica Wasney, Pharmacist

All members participated in deliberations and voting on the Initial Recommendation, except:
- Kelvin Chan and Scott Berry, who were not present for the meeting.
- Valerie McDonald, who did not vote because of her role as a patient member alternate.

All members participated in deliberations and voting on the Final Recommendation, except:
- Jo Nanson, Dr. Scott Berry, and Dr. Craig Earle, who were not present for the meeting.

Avoidance of conflicts of interest
All members of pERC 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 of vandetanib for medullary thyroid cancer...
cancer, through their declarations, four members had a real, potential, or perceived conflict and, based on application of the pCODR Conflict of Interest Guidelines, none of these members was excluded from voting.

Information sources used
pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group, registered clinician, and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its 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 pERC 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 pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers 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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