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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Vandetanib (Caprelsa) for Medullary Thyroid Cancer

March 30, 2017

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Sanofi Genzyme** compared vandetanib to best supportive care (BSC) for the treatment of symptomatic or progressive medullary thyroid cancer (MTC) in adult patients with unresectable locally advanced or metastatic disease based on efficacy data from the ZETA trial. The Submitter is requesting listing as per the Health Canada indication.

Table 1. Submitted Economic Model

For the treatment of symptomatic or progressive medullary thyroid cancer (MTC) in adult patients with unresectable locally advanced or metastatic disease. For the purposes of this report, "symptomatic or progressive" MTC refers to these three groups of patients: (1) symptomatic MTC only, (2) progressive MTC only, and (3) symptomatic and progressive MTC.	This population was modelled based on a sub-group of the patient population treated with vandetanib in the ZETA study
Type of Analysis	Cost Utility Analysis and Cost Effectiveness Analysis
Type of Model	Partitioned-survival analysis with three health states (stable disease, progressed disease, and death)
Comparator	Best supportive care (BSC): symptomatic patient management including pain medications, anti-diarrheal medications and OTC hand creams
Year of Costs	2016
Time Horizon	50 years (base case)
Perspective	Canadian public payer
Cost of Vandetanib	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 • $5,460.00 per 28-day course At a reduced daily dose of 100 mg, vandetanib costs: • $97.50 per day • $2,730.00 per 28-day course
Model Structure	The partitioned survival model was comprised of 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 response. See Figure 1 in Section 2.1 of the Technical Report

Key Data Sources	• 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 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.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of vandetanib to BSC is appropriate.

- Relevant issues identified included:
  - The CGP concluded that there is a net clinical benefit to vandetanib on progression-free survival in the treatment of progressive or symptomatic MTC in adult patients with unresectable locally advanced or metastatic disease based on ZETA trial compared with placebo.
  - The CGP also noted that although an increase of overall survival could not be demonstrated in the ZETA trial, it is most likely to be observed. This is due to the crossover of the ZETA trial and often slow progression of the disease.

Summary of registered clinician input relevant to the economic analysis
A registered clinician considered vandetanib as the first line treatment in patients with metastatic or locally progressive MTC in which comparable treatments are not available. The clinician noted that metastatic or progressive disease can be confirmed by CT, PET/CT or ultrasound scan but treatment with vandetanib will require additional EKGs to assess QT interval. The clinician input noted that side effects with vandetanib therapy can be managed with dose reductions or other medications, and that vandetanib should be contraindicated in patients with prolonged QT intervals or who are receiving medications that would prolong QT interval.

Summary of patient input relevant to the economic analysis
Patients considered the following factors to be important to consider for the review of vandetanib: improvement in quality of life, slowing the rate of disease progression, and improvement in disease-related symptoms.

- The economic model submitted by the manufacturer takes into account quality of life, progression free survival and overall survival, as well as adverse events.
- As per pCODR guidelines, the perspective of the model was that of the publicly funded healthcare system and did not consider patient or caregiver time costs.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors to be relevant enablers or barriers to the implementation of a funding recommendation:

- According to PAG, the unmet clinical need is in a very small number of patients with symptomatic or progressive MTC. PAG noted that vandetanib could potentially be used in patients with indolent, asymptomatic or slowly progressive disease. However, given the potential serious toxicities associated vandetanib, PAG noted that the use of vandetanib would be limited to patients with symptomatic or progressive disease.
- PAG noted that palliative chemotherapy with doxorubicin is available in some provinces but that

there is currently no standard treatment available for medullary thyroid cancer. The Submitter's economic analysis only considered best supportive care as a comparator to vandetanib.

- PAG identified the oral route of administration as an enabler to implementation as vandetanib can be delivered to patients more easily than intravenous therapy in both rural and urban settings.
- PAG noted that only prescribers and pharmacies certified through the restricted distribution program are able to prescribe and dispense vandetanib. PAG expressed concerns about the significant time and logistical coordination required for the healthcare providers to register in the controlled distribution program. Patient access to vandetanib may be limited to certain facilities.
- PAG also noted the availability of a continuous once daily dosing schedule of 300mg is an enabler to implementation. However, as there are different strengths, PAG is concerned that there may be drug wastage when patients change dose levels prior to completing the pack of the previous strength. The economic model assumed approximately 14% of patients would have their drug dose reduced to 100mg daily; however, drug wastage was not accounted for in the model.
- PAG indicated that the non-linear pricing of the 100mg and 300 mg tablets is a barrier to implementation.

1.3 Submitted and EGP Reanalysis Estimates

The main cost drivers in the submitter's model were the cost of vandetanib over the time horizon, the assumed time to dose reduction and interruption, and the percentage of patients whose dose of vandetanib was reduced to 100 mg per day. The drivers of the clinical impact were the assumed effects of progression-free survival with vandetanib on overall survival and the modeling of utility values for the PFS and OS health states.

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	0.50	0.45
Progression-free	0.69	0.69
Post-progression	-0.19	-0.24
ΔE (QALY)	0.45	0.37
Progression-free	0.57	0.57
Post-progression	-0.12	-0.20
ΔC ($)	$128,566	$131,250
ICER estimate ($/QALY)	$285,627	$352,641

Δ = difference; EGP = Economic Guidance Panel; LY = life-year; QALY = quality-adjusted life-year

The main assumptions and limitations with the submitted economic evaluation were:

- **OS benefit prediction for vandetanib compared to BSC is associated with uncertainty.** The survival benefit of patients treated with vandetanib was calculated by the submitter based on the estimated benefit of PFS from the ZETA trial in the subgroup of patients with symptomatic and progressive MTC in adult patients with unresectable locally advanced or metastatic disease. 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 (HR=0.89 [95% CI: 0.48 to 1.65]). Feedback from the CGP noted that this simplified approach to modelling survival with vandetanib was likely to overestimate the effectiveness of vandetanib over placebo. However, the CGP also noted that the prolongation in the PFS observed in the trial, could potentially result in an increase in OS.
- **The modelling of health state utility values.** The submitter derived health state utility values from a combination of mapped FACT-G data from the ZETA trial for the pre-progression health state (0.84) and a difference between the pre- and post-progression utility values based on a published study in advanced melanoma patients (Beusterien et al, 2009). The difference between the pre- and post-progression values in advanced melanoma was 0.77-0.59 = 0.18 and this was

subtracted from the mapped pre-progression utility value (0.84) to give a post-progression utility value of 0.66. Feedback from the CGP suggested that differences in quality of life are highly variable from patient to patient depending on whether they are symptomatic or not; disease progression does not necessarily correlate with a significant change in quality of life.

- **The time to dose reduction and interruption.** The submitter set the time to dose reduction and interruption in the model at 8 months. Feedback from the CGP suggested that in clinical practice 3 months would be a more realistic time for dose reductions or interruptions to occur.
- **The frequency of dosage adjustment and interruption.** The submitter based the percentages of patients receiving dosage reductions and interruptions on the results from the ZETA trial. CGP noted that the frequency of dose interruptions and dose reductions would likely to be lower in clinical practice as more susceptible patients would most likely be treated with lower starting doses.
- **A 50-year horizon would overestimate the expected patient lifetime.** Feedback from the CGP suggested that a time horizon of 50 years was unrealistic; however given the population included in the ZETA trial and the clinical assumptions, unless the time horizon is limited to less than 10 years, the time horizon had little impact on the ICUR.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- **Health state utility values based on ZETA trial were used.** Based on feedback from the CGP on the variability of quality of life in MTC patients in the progressive disease state, the utility values applied to the pre- and post-progression health states in the model were derived directly from the mapped FACT-G data from the ZETA trial (Pre-progression = 0.84, post-progression = 0.83).
- **Mean time to dose reduction or interruption was set at 3 months.** Based on feedback from the CGP, the EGP conducted a reanalysis using 3 months as the representative time to dose reduction and interruption.
- **Frequency of dosage reductions and interruptions was reduced**. Based on CGP feedback, the frequency of dosage reductions and interruptions was expected to be lower in clinical practice. EGP undertook a reanalysis assuming a 50% reduction in the frequency rates used by the submitter in the base case analysis.
- **Time horizon was reduced to 10 years.** Feedback from the CGP suggested that the 50-year time horizon was not realistic. A 5-year time horizon was considered reflective of patients with symptomatic progressive MTC while a 10-year time horizon was representative of the total MTC patient population (i.e. symptomatic or progressive patients).

Table 3: Detailed Description of EGP Reanalysis

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICUR
Submitter's best case	**$128,566**	**0.45**	**0.36**	**$285,627**	--
ONE-WAY REANALYSES					
Utility values based on ZETA trial for pre- and post-progression health states	$128,566	0.42	0.50	$309,499	+$23,872
Time to dose reduction and interruption set at 3 months	$126,743	0.45	0.50	$281,575	-$4,052
Frequency of dosing interruptions and reductions reduced by 50%	$132,363	0.45	0.50	$294,062	+$8,435
Time horizon reduced to 5 and 10 years	$128,963	0.36	0.36	$360,217	+$74,590
	$128,365	0.42	0.45	$307,881	+$22,254
EGP BEST ESTIMATE					
EGP best estimate - All of the above over a 10-year time horizon	**$131,365**	**0.37**	**0.45**	**$352,641**	**+$67,014**
EGP BEST ESTIMATE (LOWER BOUND)					
EGP best estimate - Using submitter's base case health state utility values over a 10-year time horizon	**$131,250**	**0.42**	**0.45**	**$314,801**	**+$29,174**
EGP BEST ESTIMATE (UPPER BOUND)					
EGP best estimate - Using submitter's base case health state utility values over a 5-year time horizon	**$128,963**	**0.30**	**0.36**	**$434,852**	**+$149,225**

Δ = difference; BSC = best supportive care; EGP = Economic Guidance Panel; ER = Emergency Room; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include: the prevalence of symptomatic or progressive MTC in adult patients with unresectable locally advanced or metastatic disease in Canada, the additional cost of vandetanib, patient eligibility criteria and assumptions around market share.

Key limitations of the BIA model include:

- The prevalence of patients with symptomatic or progressive MTC in adult patients with unresectable locally advanced or metastatic disease in Ontario is uncertain, as the submitter's model is based on the assumption that 23% of all MTC cases would be candidates for vandetanib and that this percentage remains constant over time. Feedback from the CGP indicated that the assumed prevalence was realistic. One-way analyses by the submitter assumed a variance of 10% significantly affected the budget.
- The assumption that only 50% of patients with symptomatic or progressive MTC with unresectable locally advanced or metastatic disease would be eligible for treatment. One-way analyses undertaken by the EGP assuming 75% and 100% patient eligibility would increase the baseline budget impact estimates by 40% and 100% respectively.
- The submitter assumed that 50% of the eligible patient population would be treated with vandetanib in year 1 (uptake) with an estimated rise to 75% and 90% in years 2 and 3, respectively.

Feedback from CGP suggested uptake would likely initiate at 30% for year 1, and increase to 50% and 100% in years 2 and 3, respectively. EGP conducted a test of the alternate uptake estimates by the CGP; the budget impact estimates decreased in years 1 and 2.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for vandetanib when compared to BSC is:

- Between $314,801/QALY and $434,852/QALY. Within this range, the best estimate would likely be $352,641/QALY. As was noted in the CGR, the CGP indicated there was a clinical benefit associated with vandetanib; however, the CGP expressed concern regarding magnitude of the benefit, given the uncertainty around the overall survival benefit and patient quality of life.
- The extra cost of vandetanib is between $128,963 and $131,365. The incremental cost is relatively stable; it is slightly impacted 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 QALYs (ΔE). 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.

Overall conclusions of the submitted model:

- There is some uncertainty regarding the modelled benefit for vandetanib on overall survival based on the progression-free survival results from the ZETA trial.
- The EGP best estimate is driven by revised assumptions on the quality of life benefit, as well as assumptions on frequency and time to dose reductions and interruptions.
- Future research should provide additional data regarding the overall survival benefit associated with vandetanib and the quality of life of patients with symptomatic or progressive advanced MTC on vandetanib.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Endocrine Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of Vandetanib for medullary thyroid cancer. A full assessment of the clinical evidence of Vandetanib for medullary thyroid cancer is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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