CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Lenalidomide (Revlimid) plus Bortezomib and Dexamethasone for Multiple Myeloma

June 19, 2019

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FUNDING

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Celgene** compared lenalidomide (Revlimid) in combination with bortezomib (Velcade) and dexamethasone (VLd) to lenalidomide and dexamethasone (Ld) for patients with newly diagnosed multiple myeloma who are ineligible for transplant. *Although Bortezomib in combination with melphalan and prednisone (VMP) is included as a comparator in the manufacturer submitted materials, the CGP noted that Ld is the most relevant comparator, and a lack of evidence complicates the inclusion of VMP as a comparator. Upon guidance from the CGP, VMP is not considered a relevant comparator in this report.*

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	The objective of this model is to assess the cost-effectiveness of lenalidomide (Revlimid) in combination with bortezomib (Velcade) and dexamethasone (VLd) in adult patients with newly diagnosed multiple myeloma (NDMM) in whom transplant is not intended. The modelled population matches the funding request.
Type of Analysis	*CUA*
Type of Model	*Markov cohort, partitioned-survival*
Comparator	lenalidomide (Revlimid) + *dexamethasone (Ld). Although bortezomib (Velcade) + Melphalan + Prednisone (VMP) is included as a comparator in the manufacturer submitted materials, the CGP recommends that Ld is the most relevant comparator; and a lack of evidence complicates the inclusion of VMP as a comparator. Upon the recommendation of the CGP, VMP is not considered a relevant comparator in this report.*
Year of costs	*2017 Canadian Dollars*
Time Horizon	*25 Years*
Perspective	*Publicly funded healthcare system*
Lenalidomide	Lenalidomide costs $424.00 (25mg), $403.00 (20mg), $382.00 (15mg), $361.00 (10mg), $340.00 (5mg) (3) as cited in (1). Induction: 25 mg orally once a day on days 1 – 14 during cycles of a 21-day cycles (8 cycles max) • $282.67 per day • $7914.67 per 28 day cycle Maintenance (cycles 9 onwards): 25 mg orally once a day on days 1-21 for a 28 day cycles (until progression) • $424.00 per day • $11,872.00 per 28 day cycle
Bortezomib	Bortezomib costs $1,402.42 per 3.5mg vial (4) as cited in (1). At the recommended dose, bortezomib is given at 1.3 mg/m^2 iv during cycles on days 1, 4, 8 and 11 for 21 day cycles (8 cycles max) • $200.35 per day • $5609.68 per 28 day cycle
Dexamethasone	Dexamethasone costs $0.30 per 4 mg and $0.08 per 1mg tablet (5) as cited in (1).

	Induction: 20 mg taken orally on days 1, 2, 4, 5, 8, 9, 11 and 12 for 21 day cycles (8 cycles max) • $0.57 per day • $16.00 per 28 day cycle Maintenance (cycles 9 onwards): 40mg taken orally on days 1, 8, 15 and 22 for 28 day cycles (until progression) • $0.43 per day • $12.00 per 28 day cycle
Model Structure	*This partitioned survival model included three health states: progression free disease, post-progression disease, and death. The progression free disease was informed by progression free survival, and post-progression disease was equal to the difference between overall survival and progression-free survival.*
Key Data Sources	*Clinical Outcomes:* *SWOG S0777 trial (6) as cited in (7). **Uses Celgene analysis of SWOG S0777 data, with data cut-off of December 1, 2016* *Drug Costs:* *Ontario Exceptional Access Program, Ontario Formulary, pCODR Report(3-5)* *Utility:* *MM-020 Trial (8)*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The Clinical Guidance Panel considered that CyBorD is also a clinically relevant comparator. The Submitter did not include this comparison in modifications to the main economic analysis however an assumption was made for similar efficacy between VMP and CyBorD. Based on this assumption, VMP was then included in the submitted economic analysis as a proxy for CyBorD. The EGP did not consider this comparison further based on the conclusions provided by the CGP (described below).

- Relevant issues identified included:
  - *There is a net overall clinical benefit of VLd compared to Ld as first line therapy for patients with newly diagnosed myeloma not eligible for transplant based on a statistically significant benefit in progression-free survival (PFS) and overall survival (OS) for VLd compared to Ld.*
  - The adverse event profiles were similar between the two groups and toxicities were predictable and manageable.
  - *Ld and CyBorD have previously been shown to have similar efficacy. Since VLd has demonstrated superiority over Ld, this can serve as an appropriate surrogate for Canadian patients. It is reasonable to believe that the magnitude of benefit would be similar if the comparator was CyBorD.*
  - *The dosing of bortezomib would remain consistent with the Canadian standard using once a week administration subcutaneously.*
  - *The sequencing of agents are dependent on the treatment and responses that patients had to first line therapy, as well as individual characteristics and comorbidities of patients. As a result, the sequence of other therapies remains unclear.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians suggest that VLd is well tolerated, with no significant increases in toxicity compared to Ld or CyBorD. All clinicians agreed that the evidence submitted supports the use of VLd in the first-line for patients ineligible for transplant. Improvements in both PFS and OS are noted by the CGP, and are captured in the pharmacoeconomic model. Clinicians noted that VLd is the first PI-immunomodulatory-steroid combination being evaluated for treatment in the fist-line setting. Clinicians identify that VLd will be important to have while waiting for data on the efficacy and safety of monoclonal antibodies, such as daratumumab, to become available in this setting.

Summary of patient input relevant to the economic analysis
Patients considered disease control and prolonged life as the most important treatment expectations, followed by side effects and a normal life. Disease control and survival are captured in the economic model through overall survival and progression free survival. Patients note that the side effect profile of VLd was tolerable or very tolerable; and side effects are captured in the economic model. Of the 6 patients that responded to a survey, 50% indicated good quality of life, 33% rated fair quality of life, and 17% reported excellent quality of life. The primary outcome of pharmacoeconomic analysis, the incremental cost-effectiveness ratio, incorporates quality adjusted life years - which incorporates quality of life.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified clinical and economic factors that could impact the implementation:

- Clarity on patient groups eligible for treatment
- Incremental costs due to drug wastage, treatment duration, and budget impact

The CGP has determined that the patients modelled in the submission match the funding request. For parenteral drugs, vial wastage was assumed without vial sharing. For oral therapies, it was assumed that patients would receive any left-over tablets/capsules for their next treatment cycle instead of discarding these. The CGP has validated these assumptions regarding wastage. The impact of time horizon on modelled outcomes was explored. Finally, the budget impact over three years was predicted.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Estimates (Probabilistic).

		EGP Reanalysis	
Estimates (range/point)	Submitted	Upper Estimate	Lower Estimate
ΔE (LY)	1.24	1.13	1.11
Progression-free	1.09	0.98	0.98
Post-progression	0.15	0.15	0.13
ΔE (QALY)	0.85	0.78	0.78
Progression-free	0.75	0.68	0.69
Post-progression	0.10	0.10	0.09
ΔC ($)	$42,623	$42,528	$40,099
ICER estimate ($/QALY)	$49,484/QALY	$53,300/QALY	$51,150/QALY

The main assumptions and limitations with the submitted economic evaluation were:
Overall, this model reflects the currently understood effects of VLd relative to Ld accurately. Limitations to the submitted model are related to the time horizon, and application of dose

intensity to pricing. In the submitted model, dose intensity is multiplied by the required dose to arrive at the cost for drug acquisition. This assumes that the cost per mg of the drug is independent of the number of capsules, which is not the case.

The CGP suggests that a time horizon of 25 years is excessively long, and is not reflective of the clinical course of the disease. The CGP suggested that a time horizon of 15 years is most reasonable, and captures the likely survival of patients. Additionally, at 16.85 years, less than 5% of the modelled cohort is alive. In EGP re-analysis, the time horizon is shortened to reduce the effect of modelled outcomes when uncertainty is greatest – although this does not significantly impact the ICER. Other assumptions/limitations, such as the utility of health states, resource use, wastage, adverse events, and terminal care costs do not significantly impact model outcomes.

1.4 Detailed Highlights of the EGP Reanalysis

- Dose intensity: The EGP disagreed with how the effect of dose intensity on the cost of lenalidomide had been applied in the submitted model. In the model, the dose intensity observed in the SWOG S0777 trial was multiplied by the cost, to arrive at the expected cost for each agent. The expected cost per milligram ($19.74/mg) is calculated through the doses received – 68% of patients received 25mg capsules, 28% of patients received 15mg capsules, and 3% of patients received 10mg capsules. The expected cost per milligram is multiplied by the recommended dose and observed dose intensity. This method assumes that the cost is independent of the number of capsulesadministered. In EGP re-analysis, it was shown that the both the strength of each dose, and the number of capsules contribute to the cost of lenalidomide. This was changed in EGP re-analysis. This re-analysis assumes that no doses of lenalidomide were missed. Therefore, EGP re-analysis estimates with and without the corrected dose intensity are provided.
- Time Horizon: The time horizon was shortened from 25 years to 15 years. Resource use assumptions were adjusted with input from the CGP to reflect Canadian practice.
- Terminal Care Costs: Calculation of the costs of terminal care in the last 30 days of life was adjusted from $12,067.22 to $14,309.24 to reflect conversion from US dollars to Canadian dollars with purchasing power parity.

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

- The application of dose intensity was changed to include the number of doses administered in the calculation of cost.
- Time horizon was shortened from 25 years to 15 years to reduce uncertainty introduced by extrapolation of short-term outcomes over the long-term.
- Resource use assumptions were adjusted to reflect the Canadian context.
- Terminal care costs were recalculated using purchasing parity. The value in the manufacturer submitted model was $12,067.22, and the EGP re-calculated value was $14,309.24.

Table 3. Detailed Description of EGP Reanalysis.

One-way and multi-way sensitivity analyses (deterministic)					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case - deterministic)	$36,699	0.86	1.42	$42,659/QALY	--
Dose Intensity Application to Drug Acquisition Costs Corrected	$37,150	0.86	1.42	$47,342/QALY	11.0%
Time Horizon- 15 Years	$34,649	0.79	1.26	$44,063/QALY	3.3%
Modified Resource Use Assumptions	$36,561	0.86	1.42	$42,499/QALY	-0.4%
Terminal Care Costs of $14,309.24	$36,657	0.86	1.42	$42,611/QALY	-0.1%
EGP's Reanalysis for the Best-Case Estimate (probabilistic)					
Description of Reanalysis	ΔC	ΔE	ΔE LYs	ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case - probabilistic)	$42,623	0.86 QALY	1.24 LY	$49,484/QALY	--
EGP Re-Analysis Estimate: dose intensity application to drug acquisition costs corrected, 15-year time horizon, modified resource use assumptions, and terminal care costs of $14,309.24 (probabilistic).	$42,528	0.78 QALY	1.13 LY	$53,300/QALY	7.7%
EGP Re-Analysis Estimate: 15-year time horizon, modified resource use assumptions, and terminal care costs of $14,309.24 (probabilistic)	$40,099	0.78 QALY	1.11 LY	$51,150/QALY	3.4%

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the size of the eligible population and drug acquisition costs.

One limitation of the BIA model was the application of dose intensity to drug costs. The use of 80% for dose intensity of all comparators likely results in an underestimate of the budget impact. This parameter was modifiable by the EGP. In sensitivity analysis conducted by the submitter, dose intensity for all comparators was 100%. The most likely budget impact is likely between the submitted base-case analysis with dose intensity of 80% for all comparators, and the scenario in which dose intensity is 100% for all comparators.

In the manufacturer submitted pharmacoeconomic report, it was assumed that VMP safety and efficacy data could be considered as a proxy for CyBorD, and CyBorD was not formally considered as a comparator in the model. In the first year considered in the budget impact analysis, CyborD and VMP combined have the majority of the market share (more than 50%) and Ld has the remaining market share. Given that CyBorD and VMP are not considered as equivalent in the budget impact analysis, the validity of this assumption is unclear. The assumptions made on comparators differ between the pharmacoeconomic report and the

budget impact analysis, which limits the interpretability of the ICER in relation to the predicted budget impact.

CyBorD accounts for a large proportion of the total market share, and is the least costly comparator. This mismatch between comparators considered in the pharmacoeconomic report/model, and the budget impact analysis likely results in significant underestimates of costs in both the reference scenario and the treatment-funded scenario.

1.6 Conclusions

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

- Between $53,300/QALY and $51,150/QALY.
- Within this range, the best estimate depends on the proportion of doses not given due to toxicity, and the dose intensity of the remaining doses.
- The incremental cost of VLd is likely between $42,528 and $40,099.
- The incremental clinical effect of VLd is likely 0.78 QALY.

Overall conclusions of the submitted model:

- *Overall, the submitted model accurately reflects current understanding of newly diagnosed multiple myeloma treated with VLd compared to Ld. Adjustments made to the model in EGP re-analysis did not significantly impact modelled outcomes.*
- *Although the time horizon was shortened from 25 years to 15 years by the EGP to reduce uncertainty present in longer time horizons and better reflect the clinical course of the disease, this resulted in small changes to the ICER.*

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 Myeloma 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 lenalidomide (Revlimid) plus bortezomib and dexamethasone for multiple myeloma. A full assessment of the clinical evidence lenalidomide (Revlimid) plus bortezomib and dexamethasone for multiple myeloma 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 information redacted from this publicly available Guidance Report.

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.

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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