pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Carfilzomib (Kyprolis) for Multiple Myeloma

June 21, 2016

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FUNDING

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Amgen Canada Inc** compared carfilzomib in combination with lenalidomide and low-dose dexamethasone to lenalidomide plus low-dose dexamethasone for patients with multiple myeloma who have received at least one prior therapy.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*Model and funding request align*
Type of Analysis	*CEA & CUA*
Type of Model	*Partitioned-survival model*
Comparator	*Lenalidomide plus low-dose dexamethasone*
Year of costs	*Not Reported*
Time Horizon	20 *years*
Perspective	*Government*
Cost of carfilzomib	[&]$1,533.33 per single-use vial of 60 mg • 10-minute infusion on days 1, 2, 8, 9, 15, and 16 (starting dose, 20 mg/m2 on days 1 and 2 of cycle 1; target dose, 27 mg/m2 thereafter) during cycles 1 through 12 and on days 1, 2, 15, and 16 during cycles 13 through 18, after which carfilzomib was discontinued [#]Cycle 1 • $ 229.63 per day and $6429.76 per 28 days (no wastage) • $273.81 per day and $7666.65 per 28 days (with wastage) Cycle 2-12 • $251.36 per day and $7037.98 per 28 days (no wastage) • $273.81 per day and $7666.65 per 28 days (with wastage) Cycle 13-18 • $167.57 per day and $4691.99 per 28 days (no wastage) • $219.05 per day and $6133.32 per 28 days (with wastage)
Cost of lenalidomide[%] (for both treatment arms)	$424.00 per 25 mg orally • Administered as 25 mg per day on days 1 – 21 • $318.00 per day and $8904.00 per 28 days
Cost of dexamethasone* (for both treatment arms)	$3.00 per 40 mg orally • Administered as 40 mg per day on days 1, 8, 15 and 22 of a 28-day cycle • $0.44 per day and $12.18 per 28 days
Model Structure	The model was a partitioned survival approach and comprised of 3 health states: progression-free, progressed or post-progression and death.
Key Data Sources	*ASPIRE trial data*

[&]Amgen confirmed that a 10mg and 30mg vial size for carfilzomib are expected to become available between November 2016 and January 2017. The anticipated cost of the 10 mg and 30 mg carfilzomib vial is $255.5556 and $766.6667 respectively
[#]Costs are calculated using a body surface area of 1.7m^2. In the submitted economic model a BSA of 1.75m^2 was used to calculate costs.
[%]Cost of lenalidomide is based on the Ontario Ministry of Health and Long Term Care Exceptional Assess Program's publically posted data. http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx
**Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc.*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

- Relevant issues identified by the CGP included:
  - The need for this novel combination in the relapsed setting.
  - An improvement in progression-free survival.
  - Similar adverse event profiles to current practice.

Summary of patient input relevant to the economic analysis
Patients considered adverse events, quality of life, and survival as important factors in their illness. All three factors were adequately considered in the economic analysis.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for carfilzomib, which are relevant to the economic analysis.

Enablers to implementation:

- Carfilzomib provides another treatment option for patients who cannot receive bortezomib, with lower risk for peripheral neuropathy.
- Future availability of 10 and 30mg vials, which may reduce wastage and costs associated with wastage if priced appropriately.

Barriers to implementation:

- The intense dosing schedule, multiple changes in dosing, and scheduling chair time may be a barrier for some patients and/or patients that travel to receive therapy.
- The requirement of additional resources to monitor for multiple serious adverse effects.
- The potential of a large prevalent population eligible for treatment with carfilzomib.
- Incremental costs due to drug wastage where vial sharing would be difficult. Though the submitter has noted that a 10mg and 30mg vial will be available between November 2016 and January 2017, which may reduce wastage.
- Cost of carfilzomib as well as the relative cost of carfilzomib compared to the cost of bortezomib, which has been significantly reduced with general products now available and bortezomib re-treatment would be less expensive than carfilzomib for treatment in the second-line and beyond.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Estimates

Estimates (range/point)	Submitted	EGP Reanalysis - Lower bound	EGP Reanalysis - Upper bound
ICER estimate ($/QALY)	$201,216	$270,652	$347,640
ΔE (QALY)	0.756	0.573	0.502
Progression-free	0.557	0.529	0.466
Post-progression	0.198	0.044	0.036
ΔE (LY)	0.892	0.634	0.539
Progression-free	0.681	0.639	0.558
Post-progression	0.212	-0.005	-0.019
ΔC ($)	$152,034	$155,134	$174,431

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

- Overall survival is extrapolated using registry data as mean OS was not reached.
- Progression-free survival was the primary outcome in the ASPIRE trial; using progression-free survival as a surrogate marker for a clinical endpoint in a trial may not be appropriate for some diseases or drugs. The CGP confirmed however that progression free survival is a clinically relevant endpoint for multiple myeloma.
- Base case assumed that 80% of patients will receive the drug with no wastage.
- The submitter provided an adjusted base case analysis (in lieu of the intention-to-treat (ITT) population), as they felt the treatment arms between the two groups in the RCT were not balanced for important prognostic factors. An adjusted analysis is a post-hoc exploratory analysis; randomization ensures that baseline differences are simply due to random chance. The use of an adjusted analysis removes the "benefit" of randomization.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the economic model:

- Drug administration costs: PAG noted that there will be additional drug preparation and administration times, as well as additional chemotherapy chair time and nursing resources required for the hydration and administration protocol required with carfilzomib. The estimate in the base case of $31.69 per injection was felt to be exceptionally low; micro-costing data from BC cancer agency estimated a per injection cost of $132.
- Primary effect: The primary effect for the submitted base case for both OS and PFS was based on a regression analysis and not on the ITT population of ASPIRE. The EGP elected to use the published results from the trial (ITT analysis) and not the adjusted results from the submitter that were adjusted based on imbalances in the two treatment groups detected post-hoc.
- Hazard ratio post-trial: The EGP elected to use a hazard ratio of 1 from 42 months and beyond (when the trial follow-up ended) during the period of extrapolation for both progression-free survival and overall survival, which assumes that at 42 months and later, there is no difference in treatment effect between arms. This does not affect the hazard ratio used for the period of 0 – 42 months.
- Wastage: In the submitted base case estimate, 80% of doses had no wastage. Based on feedback from the CGP and PAG, wastage could potentially be a concern in smaller centers where vial sharing would be difficult. The stability of the reconstituted drug is 24 hours refrigerated and 4 hours at room temperature. Therefore, the EGP has chosen to include wastage for all doses (i.e., 0% of doses had no wastage), which is the most conservative estimate and has been included as the upper bound of the EGP reanalysis.

Table 3. EGP Reanalysis Estimates

Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	**$152,034**	**0.756**	**0.892**	**$201,216**	**----**
EGP's Reanalysis for the Best Case Estimate					
LOWER BOUND					
Drug administration costs - $132 per injection	$158,466	0.756	0.892	$209,729	$8,513
Primary effect from primary analysis of ITT population of ASPIRE(not using adjusted values) - both OS & PFS	$148,696	0.573	0.634	$259,420	$58,204
Best case estimate of above two parameters	*$155,134*	*0.573*	*0.634*	*$270,652*	*$69,436*
UPPER BOUND					
HR = 1 at 42 months on both OS & PFS	$148,463	0.652	0.750	$227,867	$26,651
Wastage - all doses accounted for wastage	$171,622	0.756	0.892	$227,141	$25,925
Best case estimate of above four parameters	*$174,431*	*0.502*	*0.539*	*$347,640*	*$146,424*

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the number of eligible patients, market uptake, wastage and drug costs. All factors increase the budget impact in a linear fashion: e.g. an increase of 25% of patients, increases the budget impact by 25%.

A key limitation of the BIA model includes the lack of inclusion of an appropriate comparator, as per the economic model. The results presented above for the budget impact analysis are thus very conservative.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for carfilzomib in combination with lenalidomide plus low-dose dexamethasone when compared to lenalidomide plus low-dose dexamethasone is:

- Between $270,652/QALY and $347,640/QALY
- It is difficult to estimate where, within this range, the best estimate would likely be as the EGP modified four parameters, all of which are plausible.
- The extra cost of carfilzomib in combination with lenalidomide plus low-dose dexamethasone is between $155,134 and $174,431. *The key factors that most influence extra cost are wastage (all doses accounted for wastage), the cost of carfilzomib, total cost per drug administration.*
- The extra clinical effect of carfilzomib in combination with lenalidomide plus low-dose dexamethasone is between 0.502 and 0.573 QALYs (ΔE). *The key factors that most influence effectiveness are the source of effectiveness for both overall survival and*

progression-free survival (regression analysis vs primarily analysis of ASPIRE ITT population) and utilities.

Overall conclusions of the submitted model:

- *The majority of the inputs for the submitted model are adequate. However, the use of non-peer reviewed data that is not based on the ASPIRE ITT population in the submitted base case was a limitation. The EGP was able to modify this.*

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 Lymphoma/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 carfilzomib (Kyprolis) for previously treated multiple myeloma. A full assessment of the clinical evidence of [drug name and indication] 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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