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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Carfilzomib (Kyprolis) for Multiple Myeloma

March 30, 2017

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FUNDING

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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.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Amgen Canada** compared carfilzomib plus dexamethasone (Cd) to bortezomib plus dexamethasone (Bd) for patients with relapsed multiple myeloma who have received one to three prior therapies.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*As above*
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned-survival*
Comparator	*Bortezomib plus dexamethasone*
Year of costs	*Not stated*
Time Horizon	*20 years*
Perspective	*Government*
Cost of carfilzomib	Carfilzomib costs $1,533.33[&] per single-use vial of 60 mg Administered via IV on two consecutive days, each week for three weeks (days 1, 2, 8, 9, 15, 16) followed by a 12-day rest period (days 17 – 28). Starting dose of 20 mg/m^2 in Cycle 1 on Days 1 & 2. If tolerated, dose increased to 56/ m^2 for all subsequent doses. Without wastage: • $409.53 per day and $11,466.84 per 28-day course (cycle 1) • $521.22 per day and $14,594.16 per 28-day course (cycles 2 and subsequent) With wastage: • For Cycle 1 carfilzomib costs $547.50 per day and $15,330.00 per 28-day cycle. • For all subsequent cycles, carfilzomib costs, $657.00 per day and $18,396.00 per 28-day cycle.
Cost of bortezomib * *Price Source: IMS Brogan accessed [March 1, 2016]*	Based on a list generic price, bortezomib costs 1,402.4200 per 3.5mg vial. At a recommended dose of 1.3 mg/m2 on days 1, 4, 8, 11 of each 21-day cycle bortezomib cots: • $168.6720 per day • $4,722.8160 per 28-day course
Cost of dexamethasone * *Price Source: IMS Brogan accessed [March 1, 2016]*	Dexamethasone costs 0.3046 per 4mg tablet. When combined with bortezomib and at the recommended dose of 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 of a 28-day cycle dexamethasone costs: • $0.5802 per day • $16.2456 per 28-day course When combined with carfilzomib and at the recommended dose of 20 mg oral or IV infusion on days 1,2,8,9,15,16,22,23 of a 28-day cycle, dexamethasone costs: • $0.4351 per day • $12.18 per 28-day course
Model Structure	A three-state partitioned survival model was developed with a 20-year time horizon. The three health states were progression-free, progressed and death.
Key Data Sources	*ENDEAVOR trial* *SEER registry*
[&]Amgen confirmed previously that a 10mg and 30mg vial size for carfilzomib are expected to become available February 2017. The anticipated cost of the 10 mg and 30 mg carfilzomib vial is $255.55 and $766.66 respectively [#]Costs are calculated using a body surface area of 1.7m^2. In the submitted economic model a BSA of 1.7m^2 was used to calculate costs. **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. The Clinical Guidance Panel considered that a bortezomib based regimen, including both bortezomib plus dexamethasone and cyclophosphamide plus bortezomib plus dexamethasone, to be the clinically relevant comparator in this setting. The Submitter did include this comparison in modifications to the main economic analysis.

- Relevant issues identified by the CGP included:
  - There is a net overall clinical benefit to carfilzomib plus dexamethasone compared to bortezomib plus dexamethasone, acknowledging that progression-free survival is a reasonable surrogate endpoint for overall survival in myeloma
  - While there is no efficacy data for using carfilzomib plus dexamethasone in patients with ECOG performance status (PS) greater than 2, based on the data available and the manageable toxicity profile of this regimen, PS alone should not be a criteria to exclude patients from treatment. In patients with disease-related ECOG performance status of 3 or greater, carfilzomib plus dexamethasone may be appropriate, and this would be consistent with standard practice with other myeloma therapies.
  - The CGP recommends dosing carfilzomib plus dexamethasone as per the ENDEAVOR trial, and not the lower doses examined in the ASPIRE trial that were used in conjunction with lenalidomide.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered improved progression-free survival and increased choice of treatment in this population as important factors to be considered in this review. These were considered in the economic analysis.

Summary of patient input relevant to the economic analysis
Patients considered maintaining quality of life, managing/minimizing side effects and disease control as the three most important factors in treatment multiple myeloma. These factors were 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 plus dexamethasone, which are relevant to the economic analysis:

<u>Enablers</u>

- Additional treatment option for patients who cannot receive bortezomib.

<u>Barriers</u>

- Cost of carfilzomib;
- Drug wastage (though this will be minimized with 10mg and 30mg vials);
- Intense dosing schedule for intravenous infusion;
- Intense hydration protocol and required health care resources;
- Additional resources to monitor adverse effects;
- Unknown treatment duration; and
- Dosing at 56 mg/m^2

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
ΔE (LY)	0.791	0.595	0.595
Progression-free	0.985	0.974	0.974
Post-progression	-0.194	-0.379	-0.379
ΔE (QALY)	0.765	0.602	0.553
Progression-free	0.828	0.819	0.739
Post-progression	-0.063	0.217	-0.186
ΔC ($)	$147,701	$157,554	$163,029
ICER estimate ($/QALY)	$192,997	$261,648	$294,931

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the economic model:

- Shortening of time horizon: The base case analysis used 20 years as the time horizon for patients. The CGP has identified that given the stage of disease patients eligible for carfilzomib plus dexamethasone are in, 10 years is an appropriate time horizon for these patients based on their clinical practice.
    - Following the receipt of feedback on the initial recommendation the manufacturer provided feedback on the appropriateness of using a shortened 10 year time horizon for the EGP's reanalysis estimates as compared to 20 years used in the base case results. In consultation with the CGP, it was acknowledged that with newer agents, a small percentage of patients can live greater than 10 years from the time of diagnosis. The patient population in the ENDEAVOR trial however focused on patients with relapsed/refractory disease. For patients in second relapse (after receiving lenalidomide and bortezomib therapy) the likelihood of living an additional 10 years is exceedingly small, as the most effective agents that are known to prolong survival have already been used, and patients have quite advanced disease at this time. Given that carfilzomib and dexamethasone is likely to be used in second relapse, it is the opinion of the CGP that effective treatment options after this are unlikely to lead to a substantially prolonged survival.
    - The CGP also noted that a number of trials were referred to by the manufacturer to support a 20 year time horizon. The CGP agreed that these data sources were inappropriate as the populations represented by them did not match patients in the ENDEAVOR trial and the setting in which carfilzomib plus Dex is expected to be used (SEER registry included patients with smoldering/asymptomatic myeloma, Kumar et al trial which looked at survival of patients from diagnosis, ASPIRE trial which included patients in first relapse and Orlowski study which included patients naïve to bortezomib treatment).
- Bortezomib dosing 1 x week: The base case analysis used twice per week dosing for bortezomib. The EGP however used once per week dosing. This is a conservative estimate and was based on feedback from the CGP, who indicated that in clinical practice bortezomib is given once per week. However, the EGP recognizes that changing this parameters requires the assumption that the efficacy of the drug (bortezomib) would be equal whether the dosing is once or twice a week. There is no evidence to suggest different efficacies based on dosing.

    - Following the receipt of feedback on the initial recommendation the manufacturer provided feedback disagreeing with the use of once weekly dosing of bortezomib citing the lack of randomised clinical trial evidence to support one weekly dosing in this population. The CGP agreed that an RCT, comparing the efficacy and safety of once weekly to twice weekly dosing of bortezomib, has not been conducted in a population similar to the ENDEAVOR trial. Other trials in patients with multiple myeloma (Bringhen et al 2010 and Reeder et al 2010) have demonstrated similar efficacy between the two dosing regimens however lower toxicity was associated with the once weekly dosing. Given these trials, clinical practice has shifted from twice weekly to once weekly dosing. The CGP agree that it is unlikely treating oncologists will switch to using the bi-weekly dosing in the absence of evidence supporting the superior efficacy of twice weekly dosing compared to once weekly.
- OS modeling using a parametric curve, not the SEER data: In the base case analysis, data from a large United States based registry (the US SEER database) was used to model OS as the ENDEAVOR trial data was immature and medians had not been reached. The CGP indicated that the SEER database includes patients with inactive (smoldering) myeloma, which may overestimate the survival of patients with multiple myeloma. Following inspection of the modeled OS with the Weibull curve over the full time horizon (Figure 4), the EGP chose to include this as a conservative best estimate. Therefore the Weibull curve was used over the full time horizon in the EGP re-analysis.
    - The manufacturer's feedback on the pERC initial recommendation referred to adjustments being made in the SEER registry data to match for baseline characteristics of patients in the ENDEAVOR trial. The submitted information does specify that the SEER registry data was matched to ENDEAVOR in terms of key variables such as age, gender, and time since diagnosis however no information is available on whether or not the data was matched for the presence of smoldering/asymptomatic myeloma which is expected to have an impact on the prognosis of patients.
- Time on subsequent treatments: the base case analysis assumed that patients progressing on the carfilzomib group would go on to receive 16 cycles of subsequent treatment while patients in the bortezomib group would receive 17 cycles of subsequent treatment. As there is no clinical plausibility to have different lengths of time on subsequent treatments, the EGP set this parameter to be equal to 16 cycles for both treatment arms.
- Utilities: In the base case analysis utilities were derived from the literature and adjusted to trial values. The CGP felt the literature values used in the base case were high and may not be reflective of the population under review. As utilities were collected in the trial were mapped and could be imputed into the model, given that there is no strong rationale to not use trial data for the utilities, the EGP chose to us utilities directly from the trial.

Table 3. EGP Reanalysis Estimates

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	$147,701	0.765	$192,997	-----
EGP's Reanalysis for the Best Case Estimate				
LOWER BOUND				
Time horizon – 10 years	$143,559	0.595	$241,195	$48,198
Bortezomib once weekly dosing	$161,442	0.765	$210,952	$17,955
OS – Weibull parametric curve for time horizon	$147,906	0.760	$194,609	$1,612
Best case estimate of above parameters	$157,554	0.602	$261,648	$68,651

UPPER BOUND				
Time on subsequent treatments- 16 cycles for both arms	$153,176	0.765	$200,219	$7,222
Utilities from trial – no adjustment to literatures	$147,701	0.700	$210,987	$17,990
Best case estimate of above parameters	$163,029	0.553	$294,931	$101,934

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

- An assumption that the time horizon of patients with relapsed or refractory multiple myeloma who have received one to 3 prior lines of therapy will be 20 years.
- An assumption that a twice per week administration of bortezomib would be used. The CGP identified that in clinical practice, bortezomib is most likely given once a week.
- That the time on subsequent treatment would differ between the two treatment groups.
- Unknown duration of treatment effect due to immaturity of trial data.
- Both treatment arms in the submitted base case models had large gains in benefit (QALY and LY's) in the post-progression period, though the incremental difference during this period was minimal (-0.063 QALY),
- Use of registry data to extrapolate overall survival as median overall survival was not reached in the ENDEAVOR trial.

1.5 Evaluation of Submitted Budget Impact Analysis

Key limitations of the BIA model include the absence of the trial comparator and the use of pricing from Quebec. Though the model did not include the comparator bortezomib plus dexamethasone (Bd), as included in the economic model, it was possible to infer the impact of this comparator on the budget impact analysis by excluding the cost of cyclophosphamide from the costing, and assuming all other parameters in the analysis remain the same. Though this is only an estimate, the result is a minimal decrease in the budget impact.

The factors that most influence the budget impact analysis include treatment duration, transplant ineligible patient treatment pathway, number of eligible patients, and market uptake. An increase in treatment duration of CyBorD (from 6.7 to 10 cycles) and Pd (from 3.1 to 10 cycles) results in a decrease of 48% of the BIA. If transplant ineligible patients receive either Cd or CyBorD after fewer treatment failures, the BIA increases by 26.1%. Both number of eligible patients and market uptake have a linear relationship with the total BIA: an increase in 25% of the market uptake results in a 25% increase in the BIA.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for carfilzomib plus dexamethasone when compared to bortezomib plus dexamethasone is:

- Between $261,648/QALY and $294,931/QALY
- The extra cost of carfilzomib plus dexamethasone is between $157,554 and $163,029. The most relevant factors that influence cost are: the choice of parametric curve for progression-free survival, the dosing of bortezomib, and the cost of carfilzomib.
- The extra clinical effect of carfilzomib plus dexamethasone is between 0.553 and 0.602 QALYs (ΔE). The most relevant factors that influence effectiveness are: the time horizon and the choice of utilities.

Overall conclusions of the submitted model:

- *The model was comprehensive with a large choice of data inputs. However, many of these data inputs relied on assumption that were not readily available from the clinical trial.*

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) plus dexamethasone for multiple myeloma. A full assessment of the clinical evidence of carfilzomib (Kyprolis) plus 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 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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