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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Ixazomib (Ninlaro) for Multiple Myeloma

June 29, 2017

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Takeda Canada** compared ixazomib plus lenalidomide plus dexamethasone (ILd) to lenalidomide plus dexamethasone (Ld) for the treatment of patients with multiple myeloma who have had at least one prior line of treatment and have high risk cytogenic abnormality, or patients who have received at least two prior therapies.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*Note that the funding request is exclusively for the two sub-populations only and not for the intention to treat population examined in the TOURAMLINE MM1 trial.*
Type of Analysis	*CUA & CEA*
Type of Model	*partitioned-survival*
Comparator	*Lenalidomide plus dexamethasone*
Year of costs	*2016*
Time Horizon	*Lifetime (20 years)*
Perspective	*Government*
Treatment regimen ixazomib	4 mg orally on days 1, 8 and 15 of a 28-day cycle plus lenalidomide 25 mg daily on days 1 – 21 and dexamethasone 40 mg on days 1, 8, 15 and 22 of a 28-day cycle
Cost of ixazomib	$2,964.65 per 4mg, 3mg or 2.5mg capsule. At the recommended dose of 4mg (one capsule) orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle ixazomib costs: • $317.64 per day • $8893.95 per 28-day course
Cost of lenalidomide*	$424.00 per 25 mg orally. At the recommended dose of 25 mg per day on days 1 – 21, lenalidomide costs: • $318.00 per day and $8904.00 per 28 days
Cost of dexamethasone* (for both treatment arms)	$3.00 per 40 mg orally. At the recommended dose of 40 mg per day on days 1, 8, 15 and 22 of a 28-day cycle dexamethasone costs: • $0.44 per day and $12.18 per 28 days
Cost of carfilzomib[4]	$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)
Model Structure	*Partitioned survival model with three mutually exclusive health states: pre-progression, post-progression, and death.*

Funding Request/Patient Population Modelled	*Note that the funding request is exclusively for the two sub-populations only and not for the intention to treat population examined in the TOURAMLINE MM1 trial.*
Key Data Sources	*TOURMALINE-MM1 phase 3 trial (interim analysis 1)*

[#]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.

**Drug costs for all comparators in this table are based on costing information under license from QuintilesIMS. 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 carfilzomib plus lenalidomide plus dexamethasone is also an appropriate comparator however there is no direct evidence comparing these two treatment regimens. The Submitter did address this comparison in the submitted economic analysis through the use of an indirect comparison. However, the inputs for the indirect comparison were not functional in the model.

- Relevant issues identified included:
  - *The uncertainty around the benefit in the sub-groups, as the randomized controlled trial, TOURMALINE-MM1, was not powered to detect differences in the sub-groups of interest. The CGP re-iterated that uncertainty remained on the magnitude of benefit observed in the two subgroup analyses.*
  - *Based on the CGP, while the various analyses submitted trend in the same direction, showing better PFS for the ixazomib treated patients, there is uncertainty regarding the magnitude of the effect in the two subgroup analyses for the economic model given both the multiple analyses performed and the post hoc nature of the analysis for the expanded high risk subgroup (a subgroup not specified a priori).*
  - *A network meta-analysis was presented to help determine the comparative efficacy of ixazomib combination therapy compared to carfilzomib combination therapy. A critical appraisal of this data suggested that a number of limitations were identified.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered that ixazomib, as an oral treatment option for patients with relapsed multiple myeloma, is a convenient option for patients. They noted that the addition of ixazomib to lenalidomide/ dexamethasone improves progression free survival, although overall survival is not yet known.

Summary of patient input relevant to the economic analysis
Patients considered maintaining quality of life or a normal life, followed by managing side effects and disease control as the most important factors when treating their multiple myeloma. These factors were considered for the economic analysis, however, quality of life and adverse events were included as those reported for the entire population, and were not reported separately for the sub-group analyses.

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 ixazomib which are relevant to the economic analysis:

- Clarity on patients who would eligible for treatment
- Sequencing of currently available treatment and upcoming treatments
- Potentially large prevalent patient population eligible for treatment

Barriers to implementation:

- Dosing schedule could be difficult for some patients to manage.
- Potential for large budget impact, as it is an add-on therapy.

Enablers to implementation:

- Multiple strengths of the drug available for ease of dose adjustment.
- Ixazomib is an oral drug, which is cheaper to administer.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates, high-risk cytogenetics

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	1.810	1.451	0.376
Progression-free	0.327	0.327	0.327
Post-progression	1.483	1.124	0.049
ΔE (QALY)	1.183	0.949	0.243
Progression-free	0.25	0.25	0.25
Post-progression	0.934	0.70	-0.006
ΔC ($)	$228,920	$226,509	$222,955
ICER estimate ($/QALY)	**$193,478**	**$238,718**	**$918,518**

Table 3. Submitted and EGP Estimates, 2 prior lines of therapy

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	1.377	1.451	0.376
Progression-free	0.796	0.794	0.794
Post-progression	0.582	0.312	-0.529
ΔE (QALY)	0.927	0.749	0.197
Progression-free	0.588	0.586	0.586
Post-progression	0.339	0.163	-0.389
ΔC ($)	$350,680	$348,272	$345,495
ICER estimate ($/QALY)	**$378,299**	**$464,746**	**$1,751,236**

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

- The EGP identified various issues with the economic model that bring into question the face validity of the model. Certain parameters that are supposed to work, for example dose intensity, do not modify the results when chosen. Several requests were made to Takeda to verify the face validity of the model. While revised models and/or clarifications were received from the submitter, doubt remains in the estimates produced when inputs are changed in the economic model given these functionality issues.
- Based on input from the CGP, CLd is a relevant comparator. Carfilzomib has high resource utilization, rendering the combination CLd more expensive. The CGP's conclusions highlighted uncertainties in results obtained from this indirect comparison therefore the EGP did not provide re-analysis estimates addressing CLd vs. ILd. The EGP considered conclusions made by the CGP on a submitted indirect comparison (given the absence of direct comparative data) between CLd and ILd. Notably, despite the limitations in the data, the ability to change the comparator was not functional in the submitted model further adding to the EGP's concerns on the face validity of the model.

- The current economic model is not based on the ITT population of the TOURAMLINE-MM1 study, but on two sub-populations. Neither of these sub-populations were powered to detect a difference in the clinical trial. Secondly, given that nearly 20% of patients overlapped within the two subgroups (i.e, 20% of patients had both high risk and 2L or more treatment), adjustments were needed when examining efficacy data by sub-group. Further, while the inputs for efficacy were based on the subgroups of interest outlined above, other inputs used were based on the ITT population; it is not known if these estimates would differ for sub-groups (e.g., utility values for ITT population vs sub-groups).

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:
<u>High-risk cytogenetics group</u>

- Time horizon: The submitted base case analysis used 20 years as the time horizon for patients. Given that the patient population has the high risk cytogenetic abnormalities and are at end stage of disease, the CGP confirmed that a 10-year time horizon is more appropriate. This was also in alignment with modifications made to time horizons in other pCODR reviews for similar indications.
- OS survival: At this time, the overall trial results are immature and did not demonstrate an OS benefit in the ITT population of the TOURMALINE-MM1 trial. However the submitter performed post-hoc analyses and found an OS benefit in the subgroup of patients with high risk cytogenetics, though the trial was not powered to detect differences in this subgroup of patients. The CGP agreed that there is likely a benefit with the use of ILd, as the addition of proteasome inhibitors to treatment regimens has demonstrated benefit in a number of other trials. However, the CGP expressed uncertainty in the magnitude of OS benefit reported. Given the absence of comparative efficacy inputs through a phase III trial to estimate what the true OS benefit is with ILd with this group of patients, the EGP presented a range in their re-analysis estimates capturing both the submitted point estimates for OS (lower bound) and the possibility of there being no OS benefit (upper bound through the assumption that there is no overall survival benefit post-trial).

Table 4. Detailed Description of EGP Reanalysis, high-risk cytogenetics

	ΔC	ΔE QALYs	ICUR (QALY)	
Baseline	$228,920	1.83	**$193,478**	-----
EGP's Reanalysis for the Best Case Estimate - Lower Bound				
Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Time horizon- 10 years	$226,509	0.949	**$238,718**	$45,240
Best case estimate - lower bound	$226,509	0.949	**$238,718**	$45,240
EGP's Reanalysis for the Best Case Estimate - Upper Bound				
Time horizon- 10 years	$226,509	0.949	**$238,718**	$45,240
No overall survival benefit post-trial	$223,021	0.246	**$907,538**	$714,060
Best case estimate - upper bound	$222,955	0.243	**$918,518**	$725,040

Ixazomib compared to Carfilzomib combination therapy in patients with high risk cytogenetics:

The submitter provided estimates of cost-effectiveness for ILd compared to CLd in patients with high risk cytogenetics. A number of revisions were requested related to the face validity of the submitted model. Upon inspection of the updated model, the input to change the comparator to CLd was no longer functional. Although the submitter reported that CLd was dominated by ILd, the EGP was not able to verify the base case results in the updated economic model.

However, given the lack of direct comparative data and considerable uncertainty identified in the results presented through a network meta-analysis for ILd and CLd, the EGP did not consider it appropriate to undertake reanalysis of this comparison. Please see a critical appraisal of the network meta-analysis in the Clinical Report (Section 7).

The EGP made the following changes to the submitted economic model:
Subgroup of patients with 2 or more prior lines of therapy

- Time horizon: The submitted base case analysis used 20 years as the time horizon for patients. Given that the patient population has had two or more prior lines of therapy and are at end stage of disease, the CGP confirmed that a 10-year time horizon is more appropriate. This was also in alignment with modifications made to time horizons in other pCODR reviews for similar indications.
- OS survival: At this time the overall trial results are immature and did not demonstrate an OS benefit in the ITT population of the TOURMALINE-MM1 trial. However the submitter performed post-hoc analyses and found an OS benefit in the subgroup of patients with two or more lines of prior therapy, though the trial was not powered to detect differences in this subgroup of patients. The CGP agreed that there is likely a benefit with the use of ILd, as the addition of proteasome inhibitors to treatment regimens has demonstrated benefit in a number of other trials. However, the CGP expressed uncertainty in the magnitude of OS benefit reported. Given the absence of comparative efficacy inputs through a phase III trial to estimate what the true OS benefit is with ILd with this group of patients, the EGP presented a range in their re-analysis estimates capturing both the submitted point estimates for OS (lower bound) and the possibility of there being no OS benefit (upper bound through the assumption that there is no overall survival benefit post-trial).

Table 5. Detailed Description of EGP Reanalysis, 2 prior lines of therapy

	ΔC	ΔE QALYs	ICUR (QALY)	
Baseline	$350,680	0.927	**$378,299**	-----
EGP's Reanalysis for the Best Case Estimate - Lower Bound				
Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Time horizon- 10 years	$348,272	0.749	**$464,746**	$86,447
Best case estimate - lower bound	$348,272	0.749	**$464,746**	$86,447
EGP's Reanalysis for the Best Case Estimate - Upper Bound				
Time horizon- 10 years	$348,272	0.749	**$464,746**	$86,447
No overall survival benefit post-trial	$346,081	0.200	**$1,731,283**	$1,352,984
Best case estimate - upper bound	$345,495	0.197	**$1,751,236**	$1,372,937

A comparison was not provided for ixazomib compared to carfilzomib combination therapy in patients who have had at least two prior lines of therapy.

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis (beyond the cost of the drug) include the annual prevalence increase, the proportion of the population eligible for formulary reimbursement and treatment duration of ixazomib.

Key limitations of the BIA model include the inability to estimate the impact of the multiple lines of therapy that are add-ons for patients with multiple myeloma. Many patients, especially young patients, will receive 4-5 lines of treatment and will eventually be exposed to all of the drugs available. It is therefore difficult to capture the economic impact of new drugs that aren't capturing more market share, but are increasing the market as new lines of therapy are added.

1.6 Conclusions

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

Subgroup of patients with high-risk cytogenic abnormality

- Between $238,718/QALY and $918,518/QALY.
- It is difficult to estimate where within this range, the best estimate would likely be
- The extra cost of ixazomib is between $222,955 and $226,509. Cost is sensitive to the modeling of PFS & OS, given the uncertainty of the estimates, all parameters that could impact progression, or length of time on drug, have an impact on cost.
- The extra clinical effect of ixazomib is between 0.243 and 0.949 (ΔE). The largest factors that impact effectiveness are the time horizon and overall survival.

Subgroup of patients with two or more prior lines of therapy

- Between $464,746/QALY and $1,751,236/QALY.
- It is difficult to estimate where within this range, the best estimate would likely be

- The extra cost of ixazomib is between $345,495 and $348,272. Cost is sensitive to the modeling of PFS & OS, given the uncertainty of the estimates, all parameters that could impact progression, or length of time on drug, have an impact on cost.
- The extra clinical effect of ixazomib is between 0.197 and 0.749 (ΔE). The largest factors that impact effectiveness are the time horizon and overall survival.

Overall conclusions of the submitted model:

- The submitted economic model was to evaluate the cost-effectiveness of ixazomib in two sub-group populations. The biggest limitations with the data inputs are that the clinical trial was not powered for either of these sub-groups, and that many of the inputs in the model are based on the full population in the trial (the ITT population). It is difficult to draw conclusions regarding the cost-effectiveness in the sub-groups, given these large underlying limitations.
- If one accepts that the overall survival estimates within the subgroup analysis in the submitted base case is to be true, then the ICER is likely towards the lower range. If one does not accept the estimates for overall survival reported in the sub-groups, the ICER is closer to the upper range.
- Pessimistic versus optimistic scenarios if applicable.
- The EGP also identified several errors in the submitted model which brought into question the face validity of the model.

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 ixazomib (Ninlaro) for 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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