pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Dinutuximab (Unituxin) for Neuroblastoma

March 26, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by United Therapeutics Canada Corp.** compared dinutuximab (Unituxin) immunotherapy as part of a multimodal post-consolidation treatment (in combination with GM-CSF, isotretinoin, and IL-2) to isotretinoin monotherapy for paediatric patients with high-risk neuroblastoma. Of note, isotretinoin is also referred to as 13 cis-retinoic acid (RA) in the Clinical Guidance Report.

Table 1. Submitted economic model.

Funding Request/Patient Population Modelled	The objective of the submitted analysis was to: "determine the economic value of Unituxin, administered as part of a multimodal therapeutic regimen, for the curative treatment of pediatric patients with high-risk neuroblastoma in the post-consolidation setting." The patient population was based on the DIV-NB-301 study. Outcomes for pediatric patients with high-risk neuroblastoma and mean age similar to those in the DIV-NB-301 study were modelled. The patient population modelled aligned with the submitted funding request.
Type of Analysis	*CEA and CUA*
Type of Model	*Partitioned-survival*
Model Cycle Length	*One month*
Time Horizon	*Lifetime, or 100 years*
Perspective	*Canadian public payer perspective*
Cost of dinutuximab regimen (all six cycles): $273,201 *Dinutuximab is administered in combination with GM-CSF, isotretinoin, and IL-2 over six cycles of treatment. In the model, body surface area of 0.65m^2 is assumed, as per average body surface area in DIV-NB-301 study.*	Dinutuximab costs $12,850 per 17.5mg vial, to be administered intravenously. The recommended dose of dinutuximab is 17.5mg/m^2 per day on days 4-7, of chemotherapy cycles 1, 3, and 5. In cycles 2 and 4, the recommended dose of dinutuximab is 17.5mg/m^2 per day on days 8-11. Granulocyte macrophage colony-stimulating factor (GM-CSF) is administered by subcutaneous injection on days 1-14 of cycles 1, 3, and 5 at a dose of 250μg/m^2/day. The cost of GM-CSF is $323.72 per 250μg vial. Isotretinoin is administered twice orally per day at a dose of 80mg/m^2, for a total daily dose of 160mg/m^2/day, on days 11-24 of cycles 1, 3, and 5, and on days 15-28 of cycles 2, 4, and 6. The cost of isotretinoin is $1.92 per 40mg tablet. Interleukin-2 (IL-2) is administered at a dose of 3 million international units (MIU)/m^2/day by continuous intravenous infusion over 96 hours on

	days 1-4 and 4.5 MIU/m^2 on days 8-11 of cycles 2 and 4. The cost of IL-2 is $530.27 per 18MIU vial. IL-2 administration requires admission to the ICU for 11% of cases, and admission to a standard hospital bed for the remainder of cases.
Cost of isotretinoin (all six cycles): $483.84	Isotretinoin costs $1.92 per 40mg tablet. Isotretinoin is administered twice orally per day at a dose of 80mg/m^2, for a total daily dose of 160mg/m^2. Isotretinoin is administered for 14 days during each of 6 cycles.
Model Structure	*The model was comprised of 3 health states: stable, failure, and death. Health states were selected in accordance with the clinical pathway. The model structure is identical for patients treated with dinutuximab or the comparator therapy as the structure is based on disease progression. The "failure" health state was defined by the occurrence of a relapse, progressive disease, or secondary cancer, and the "stable" health state was defined as alive patients without failure.*
Key Data Sources	*Overall survival and event-free survival:* *DIV-NB-301 trial* (1) *Adverse Event Rates:* *DIV-NB-301 trial* (1) *Drug Costs: Published literature or databases, United Therapeutics Canada Corp.* (2) *Utilities:* *published literature(3-5) and expert opinion*

1.2 Clinical Considerations

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

Relevant issues identified by the CGP included:

- *Efficacy:* It is possible the clinical benefit of dinutuximab based immunotherapy may be in delaying early recurrence rather than contributing to long-term cure. Even if this were the only therapeutic benefit, it would still be of significant clinical importance to the patient population, given the additional period of remission and avoidance of or delay to the need for toxic relapse therapies. Because the combination of dinutuximab, IL-2, GM-CSF, and isotretinoin was compared to isotretinoin alone, the benefits of each component cannot be isolated; therefore, dinutuximab can only be recommended when the intention is to administer in combination with IL-2 and GM-CSF cytokines.

  Quality of life data were not collected during the randomised study informing efficacy of dinutuximab. The CGP notes that in a survey of patient input, half of respondents strongly agreed or agreed that dinutuximab improved quality of life while the other half were neutral. However, the CGP recognized the lack of available utility data in pediatric patients. Using the same estimates of utility for both arms are likely to minimize the impact of utility assumptions.

- Safety: The toxicities of dinutuximab (and associated cytokines) are significant and the therapy can only be safely administered in an experienced centre with an appropriately trained medical and nursing team. Management of expected neuropathic pain is a vital consideration and often requires coordination by acute pain/anaesthetic services to manage high doses of opiate analgesia. Familiarity with other acute toxicities such as capillary leak, hypotension, and respiratory distress is required; and availability of paediatric intensive care facilities is an important consideration in the rare circumstances in which this is required for management of immunotherapy-related toxicities. The CGP suggests that the overall clinical benefit outweighs the concerns about toxicity and tolerability, and that as the current standard of care, treating teams are already familiar with the management of side effects. With appropriate supportive care, toxicities can be managed and often controlled. According to CGP, relevant side effects are captured in the model and the EGP notes that adjustment of costs for adverse events has little impact on outcomes. More specifically, CGP noted that the toxicities in that the adverse events considered in the model captured the breath of the serious adverse events. However, CGP and EGP suggests that the expected adverse event costs per events are at times overestimated or underestimated; however, ultimately, EGP notes that adjustment of these adverse events costs has minimal impact on outcomes.

- Burden of Illness & Need: Approximately half of neuroblastoma patients have high-risk disease at presentation, and poor overall survival. Therefore, there is need for additional therapeutic options in order to achieve disease control and reduce risk of relapse. Since 2010, upfront therapy in Canada for high-risk neuroblastoma has included dinutuximab-based immunotherapy as part of standard of care. There are approximately 70 new cases of neuroblastoma annually in Canada, of which 35-40 are likely to be high-risk disease. Of these patients, 25-35 patients might be expected to receive dinutuximab. The CGP suggests that the manufacturer submitted estimate of the eligible population is larger than is likely to be observed in Canada. Therefore, in EGP scenario re-analysis, the size of the population eligible for treatment with dinutuximab is reduced to 35 patients in year one, and 36 patients in years two and three. This information is captured in the budget impact analysis.

Summary of registered clinician input relevant to the economic analysis

Registered clinician input suggests that dinutuximab in combination with GM-CSF and IL-2 is part of the current standard of care (SOC) for the front-line treatment of patients with high-risk neuroblastoma – which was captured in the model. Clinicians also noted the occurrence of serious side effects of treatment, which were also captured in the model.

Summary of patient input relevant to the economic analysis

Patients considered the wide range of side effects related to treatment, which was adequately captured in the model. Patients also reported spending a significant portion of time in hospital, which was also captured in the model for administration of all treatments in hospital.

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 dinutuximab which are relevant to the economic analysis:

- Eligibility for patients with non-high-risk neuroblastoma. *If considered for patients that are non-high-risk neuroblastoma, this would increase the number of patients eligible for this treatment, and would increase the predicted budget impact*
- Wastage due to single use vial. In the base case analysis, wastage was not considered (i.e., no assumption of vial-sharing was made, owing to the rarity of the disease). *In scenario analysis submitted by the manufacturer, the scenario in which the maximum observed BSA from the DIV-NB 301 trial was applied to all patients was considered. In EGP scenario re-analysis, the scenario in*

which the cost per mg is kept constant, and the vial size matches the dose required is considered; which highlights the proportion of drug costs that will be wasted. EGP scenario re-analysis also included the scenario in which 15% of patients require two vials of dinutuximab. Costs of dinutuximab strongly affected the ICER.

- PAG identified that up-to-date COG chemotherapy protocols or active COG clinical trials could be considered standard of care. Treatment options include multi-agent chemotherapy regiments (and autologous stem cell transplant if eligible) or isotretinoin. *In this analysis, the comparator was isotretinoin.*
- PAG noted that additional resources and costs will also be required for GM-CSF, IL-2, and retinoic acid. It was also noted that GM-CSF is not available in Canada; GM-CSF requires Health Canada Special Access Programme approval and some provinces do not fund Health Canada Special Access Programme drugs, these are barriers to implementation. *In scenario analysis performed by the EGP, the cost of dinutuximab was reduced to $0 to explore the impact of other costs on the ICER. Ultimately, the cost of dinutuximab is a driving factor for the ICER. Other costs, such as GM-CSF have little impact on the ICER.*

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates.

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)		
Progression-free	6.55	6.53
Post-progression	-0.14	
ΔE (QALY)		
Progression-free	4.74	4.74
Post-progression	-0.05	
ΔC ($)		
ICER estimate ($/QALY)	$70,824	$73,391

***manufacturer submitted estimates of life years and QALYs stratified by health state were provided in checkpoint meeting, and not extractable from the submitted model. Therefore, EGP reanalysis results could not be stratified by health state.

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

- ICU Admission for IL-2 administration: In the manufacturer submitted base-case, it was assumed that for 11% of patients, admission to ICU was required for IL-2 administration, and the remainder of patients required only hospital admission. The CGP suggests that no admission to ICU is required for IL-2 administration. This overestimates costs for the 11% of patients that required ICU admission.
- Estimated cost per day in hospital: In the manufacturer submitted pharmacoeconomic report, the estimated cost per day spent in hospital was $1,397.02. The EGP suggests that this cost likely underestimates the true cost of hospitalization for the administration of chemotherapy in this patient population.
- Lack of ability to adjust the "cure" time point to values greater than 6.5 years: May result in overestimation of survival benefits attributed to dinutuximab.
- Time horizon: Another limitation was the 100 year (life time horizon) selected by the Submitter. The CGP suggests a time horizon of 75 years is more reasonable, due to uncertainty in long-term outcomes, and a lack of data to inform this time horizon that is much greater than the follow-up times in available data.

1.4 Detailed Highlights of the EGP Reanalysis

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

- Re-calculation of hospitalization cost associated with Dinutuximab. The manufacturer submitted pharmacoeconomic report includes admission to the intensive care unit for 11% of administrations of IL-2, which the CGP suggests is an unnecessary use of resources. In the opinion of the CGP, this patient population would be admitted to hospital for monitoring during treatment, but would not require intensive care unit admission.
- The cost of hospitalization in the manufacturer submitted materials of $1,397.02 is a low estimate of the cost per night in a pediatric specialty hospital. The EGP proposes the cost of $1,822.89 per hospital bed day. This was calculated using the "Patient Cost Estimator" from the Canadian Institute for Health Information for patients with age 1-7 years, across Canada (6). The average cost per hospital stay for case mix group 638: "Chemotherapy/Radiotherapy Admission for Neoplasm" of $6,927 was divided by the average acute length of stay of 3.8 days for this case mix group and age category (6).
- Time horizon: Adjusted from 100 years to 75 years, which the CGP suggests is more appropriate.
- Time Threshold: The time to cure threshold, assumption of a "cure" at the five-year time threshold for event-free survivors, was adjusted from 5 years to 6.5 years as CGP felt this was more appropriate. This reduces the magnitude of the benefits that are extrapolated over the time horizon of the model. It is worth noting the lack of certainty in long-term outcomes.
- Utility after time threshold for "failure" health state: The assumption that utility of patients in the "stable" state after the time threshold is similar to the general population likely applies to any survivors after the time threshold. The same assumption regarding utility that was applied to survivors in the "stable" state was also applied to survivors in the "failure" state after the time threshold. For any survivors after the time threshold, utility is unlikely to differ.
- Costs for liver function tests were miscalculated in the manufacturer submitted pharmacoeconomic report. The cost of $6.40/test was multiplied by five tests, to reach a cost of $25.60 for liver function tests, due to a multiplication error. In EGP re-analysis, the cost of five liver function tests at $6.40/test was $32.00.
- Wastage (In EGP Scenario Analysis): No assumption of vial-sharing was made in the Submitter's base-case, owing to the rarity of the disease. All patients in the model are treated at the cost of a full vial per administration, though a substantial fraction of each vial is wasted. For patients requiring less than one vial per administration, wastage is already incorporated in the Submitter's base-case. A scenario is also provided by the Submitter using the maximum body surface area from the DIV-NB 301 trial. The submitter estimates that fewer than 15% of patients will require a second vial per administration. The EGP has explored wastage through scenario re-analysis, in which the cost per vial is adjusted to 65% of the current cost, which corresponds to an equivalent cost per mg as the manufacturer submitted base case, but assumes that the dose in each vial matches the dose that each patient receives. This represents the most optimistic case. *Costs of dinutuximab strongly affected the ICER*. If Dinutuximab is stable enough that wastage from one day can be used in the following dose, three vials of dinutuximab per cycle would be required. This would reduce the amount of wastage, and significantly impact cost outcomes. The CGP advises that dinutuximab is currently provided in single use vials, and the reconstituted solution has a maximum expiry of 24hours, and given the rarity of the disease vial sharing is unlikely. The EGP has also

conducted scenario analysis in which 15% of patients require a second vial of dinutuximab.

Table 3. Detailed Description of EGP Reanalysis.

EGP's Reanalysis for the Best Case Estimate (Discounted)					
Description of Reanalysis	ΔC	ΔE (QALYs)		ICUR	Δ from baseline submitted ICER
Probabilistic Baseline (Manufacturer Submitted base case analysis)	$333,116	4.6		$72,508/QALY	--
1. Liver function test cost re-calculated	$376,897	4.70		$70,830/QALY	-2.3%
2. No admission to ICU for IL-2 administration, cost of $1397.02 used for all nights in hospital	$330,887	4.70		$70,423/QALY	-2.9%
3. Recalculated monitoring cost, using EGP suggested value for hospital cost per night, assumes 11% of cases require IL-2 administration in ICU at manufacturer submitted cost (deterministic)	$339,397	4.70		$72,235/QALY	-0.38%
4. time horizon = 75 years (deterministic)	$332,767	4.70		$70,853/QALY	-2.3%
5. Time threshold = 6.5 years (deterministic)	$334,686	4.72		$70,879/QALY	-2.2%
6. Utility after time threshold (deterministic)	$332,769	4.71		$70,721/QALY	-2.5%
Probabilistic EGP Re-analysis Results (with changes 1-6 above)	**$348,578**	**4.72**		**$75,987/QALY**	**+4.8%**
EGP Scenario Reanalysis					
Description of Reanalysis	ΔC	ΔE (QALYs)		ICUR	Δ from EGP Re-analysis baseline
Cost of Dinutuximab set to 65% of original value (perfect match between dose and vial size, using EGP re-analysis inputs)	$263,221	4.74		$55,544/QALY	-26.9%
Three Vials of Dinutuximab per cycle	$287,384	4.74		$60,643/QALY	-20.2%
15% of patients require a single vial of dinutuximab per dose	$384,038	4.74		$81,039/QALY	+6.6%

1.5 Evaluation of Submitted Budget Impact Analysis

Key limitations of the BIA include the inability to explore wastage. Sixty five percent of each vial is used in the typical dose, and the remaining 35% is wasted. This parameter was not able to be modified and explored by the EGP. All limitations in the manufacturer submitted model are inherent to the budget impact analysis.

1.6 Conclusions

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

- The EGP re-analysis estimate of the ICER is $73,391/QALY. In the case that 15% of patients require a second vial of dinutuximab, the ICER is likely to be $81,039/QALY.
- When wastage is considered, the ICER is likely between $55,544/QALY and $137,836/QALY. The lower estimate represents the case where each vial is perfectly matched to the receiving patient and the cost per mg is maintained. The upper estimate, provided by the manufacturer, represents the scenario in which the maximum body surface area observed in the trial is applied to all patients in the model.
- The extra cost of dinutuximab is $347,793 in EGP re-analysis. Differences in cost are strongly influenced by the cost of the drug, wastage, and monitoring costs associated with administration.
- The extra clinical effect of dinutuximab is approximately 4.74 QALYs in EGP re-analysis. Survival benefits offered by dinutuximab beyond trial follow-up are a major contributor to this difference in QALYs.
- The CGP suggests that the manufacturer submitted estimate of the eligible population is larger than is likely to be observed in Canada. The CGP suggests that of the 41-42 patients with high-risk neuroblastoma per year used in the BIA, a small group will have primary progressive disease and will not qualify for "upfront" immunotherapy; and that the true estimate is closer to 35 patients per year. In EGP scenario re-analysis, the size of the population eligible for treatment with dinutuximab is reduced to 35 patients in year one, and 36 patients in years two and three. The estimate budget impact is sensitive to the number of patients that receive dinutuximab.

Overall conclusions of the submitted model:

- Given the data available to inform this model, it is likely an accurate representation of our current understanding. However, significant uncertainty remains in the long-term outcomes for this patient population and the outcomes of this model are sensitive to the time horizon selected. In EGP re-analysis, a time horizon of 75 years is explored. But this model is informed by five-years of follow-up data from a single RCT. Outcomes are uncertain beyond this point.
- Although re-analysis was conducted by the EGP, the results of this re-analysis differed little from the manufacturer submitted base-case analysis. CGP recommendations regarding clinical assumptions incorporated into the model suggest that this model accurately represents our current understanding of the impact of dinutuximab in the treatment of neuroblastoma. Although slightly longer term follow-up data is included in the CGR report, the duration of outcomes predicted in the economic model significantly exceeds that for which data is available. The EGP would highlight the lack of data in the very long-term to validate model predictions against – even follow-up data to 2016 is short relative to the time horizon of 75 years.
- Model outcomes using observed Kaplan-Meier survival data over 83 months were compared to model outcomes using parametric survival curves, and the impact of the time to cure threshold were tested. Together, parametric survival curves informing progression through health states and the assumption of a time to cure threshold result in overestimation of

QALYs offered by Dinutuximab relative to isotretinoin, and underestimation of costs of Dinutuximab relative to isotretinoin. Although these differences are not large, they make the ICER for Dinutuximab vs isotretinoin appear more favorable than what was obtained using observed data.

- In EGP re-analysis the impact of having the vial size of Dinutuximab matched to the patient, or zero wastage, was explored - the ICER was $55,544/QALY. The scenario in which 15% of patients require a second vial of dinutuximab is also explored in EGP re-analysis.
- The dinutuximab treatment regimen includes GM-CSF at a cost of $323.72 for each 250mcg vial, which is not controllable in the Canadian setting.
- In EGP scenario re-analysis, the cost per vial of Dinutuximab was set to $0. Although unrealistic, this scenario demonstrates the proportion of the ICER attributable to dinutuximab drug costs. The ICER was much lower in this scenario, indicating that the cost of dinutuximab strongly affects 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 Neurological 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 dinutuximab for neuroblastoma. A full assessment of the clinical evidence of dinutuximab for neuroblastoma 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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