pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Dinutuximab

Submitted Reimbursement Request: To be used in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and retinoic acid (RA) for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multi-agent, multimodal therapy

Submitted By: United Therapeutics Corp.	**Manufactured By:** United Therapeutics Corp.
NOC Date: November 28, 2018	**Submission Date:** October 1, 2018
Initial Recommendation: March 7, 2019	**Final Recommendation:** March 26, 2019

Approximate per Patient Drug Costs	Dinutuximab costs $12,850 per 17.5 mg vial. The cost of dinutuximab combination (all six cycles, of which five contain dinutuximab, since the sixth cycle is RA only) is $273,201. Dinutuximab is administered in combination with GM-CSF, RA, and IL-2 over six cycles of treatment. In the model, BSA of 0.65 m^2 is assumed, as per the average BSA in Study 301. • Dinutuximab costs $12,850 per 17.5 mg vial, to be administered intravenously. The recommended dose of dinutuximab is 17.5 mg/m^2 per day on days 4 to 7 of chemotherapy cycles 1, 3, and 5. In cycles 2 and 4, the recommended dose of dinutuximab is 17.5 mg/m^2 per day on days 8 to 11. • GM-CSF is administered by subcutaneous injection on days 1 to 14 of cycles 1, 3, and 5 at a dose of 250 mcg/m^2/day. The cost of GM-CSF is $323.72 per 250 mcg vial. • RA is administered twice orally per day at a dose of 80 mg/m^2, for a total daily dose of 160 mg/m^2/day, on days 11 to 24 of cycles 1, 3, and 5 and on days 15 to 28 of cycles 2, 4, and 6. The cost of RA is $1.92 per 40 mg tablet. • 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 to 4 and 4.5 MIU/m^2 on days 8 to 11 of cycles 2 and 4. The cost of IL-2 is $530.27 per 18 MIU vial. IL-2 administration requires admission to the intensive care unit (ICU) for 11% of cases and admission to a standard hospital bed for the remainder of cases.

pERC RECOMMENDATION ☐ **Reimburse**	pERC conditionally recommends the reimbursement of dinutuximab in combination with granulocyte-macrophage colony-stimulating factor (GM CSF), interleukin-2 (IL 2), and retinoic acid (RA) for the treatment of patients with high-risk neuroblastoma who achieve a response to prior

☒ **Reimburse with clinical criteria and/or conditions*** ☐ **Do not reimburse** *If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.	pediatric protocol first-line multi-agent, multimodal therapy if the following condition is met: • cost-effectiveness being improved to an acceptable level. Eligible patients include patients with high-risk neuroblastoma who achieve a response to prior pediatric protocol first-line multi-agent, multimodal therapy. Treatment should be continued until unacceptable toxicity or disease progression to a maximum of six cycles of dinutuximab in combination with GM CSF, IL 2, and RA (i.e., five cycles with dinutuximab, since the sixth cycle is RA only). pERC made this recommendation primarily due to the high unmet need for this patient population and burden of illness that was described by patients and their families. In recognizing this uncommon disease and potential curative treatment option, the Committee concluded that dinutuximab aligns with patient values because of its possible treatment effect as well as the strong willingness of patients and families to tolerate treatment effects on quality of life. pERC felt that there may be a net clinical benefit of dinutuximab in combination with GM CSF, IL 2, and RA based on potentially meaningful two year event-free survival (EFS) and overall survival (OS) in this patient population. pERC made this recommendation while acknowledging that there was an absence of data on quality of life and uncertain statistical significance of EFS and OS at longer follow-up times (as a result of the early termination of Study 301 for efficacy) and noting that this treatment has considerable but manageable toxicities. pERC concluded that, at the submitted price, dinutuximab in combination with GM CSF, IL 2, and RA may not be considered cost-effective compared with RA (also known as isotretinoin) because of the uncertainty in the cost effectiveness due to the unclear statistical significance of EFS and OS at longer follow-up times and because of wastage given the single-use vial and small incident population. In fact, pERC thought that, given the uncertainty, the incremental cost-effectiveness estimates could be considerably higher than the pCODR Economic Guidance Panel's (EGP's) best-case estimate. Therefore, pERC concluded that dinutuximab would require a price reduction to improve the cost-effectiveness to an acceptable level.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given the uncertainty in the statistical significance of EFS and OS at longer follow-up times and the potential wastage given the single use vial, jurisdictions may want to consider pricing arrangements that would improve the cost-effectiveness of dinutuximab in combination with GM-CSF, IL-2, and RA to an acceptable level. pERC noted that the cost of dinutuximab was extremely high and that the drug price was a key driver of the incremental cost-effectiveness estimates. Therefore, to offset the considerable uncertainty in the clinical effect estimates, pERC concluded that a reduction in drug price would be required in order to improve cost-effectiveness.

Wastage and Budget Impact Likely to Affect Adoption Feasibility
pERC expects that there may be considerable wastage with dinutuximab, given the one size of single use vial and vial sharing would be unlikely due to the small number of pediatric patients with high-risk neuroblastoma who would be eligible for dinutuximab, and given the 24-hour stability of prepared dinutuximab. pERC concluded that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation; this may include advocating for the availability of a smaller vial size.

Continued Availability of GM-CSF
pERC noted that GM-CSF is not readily available in Canada; GM-CSF requires Health Canada Special Access Programme approval, and some provinces do not fund Health Canada Special Access Programme drugs. The available evidence for treatment with dinutuximab in this patient population includes a combination treatment (i.e., dinutuximab in combination with GM-CSF, IL-2, and RA), therefore, pERC concluded that access to GM-CSF should be continued and that jurisdictions will need to consider mechanisms to continue the availability of GM-CSF in Canada.

Collecting Evidence to Reduce Uncertainty About the Magnitude of Clinical Benefit and the Cost-Effectiveness of Dinutuximab Combination
Given the uncertainty in the statistical significance of EFS and OS at longer follow-up times and in the quality-of-life data, pERC concluded that additional prospective evidence of long-term EFS, OS, and quality of life should be collected to decrease the uncertainty in the incremental effect and cost-effectiveness of dinutuximab in combination with GM-CSF, IL-2, and RA. pERC noted that, when such prospectively collected data become available, jurisdictions may want to review these new data.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in the summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

There are approximately 70 new cases of neuroblastoma annually in Canada, of which 35 to 40 would be expected to have high-risk disease. Consequently, 25 to 35 patients might be expected to receive dinutuximab-based immunotherapy as part of upfront treatment each year. Those with high-risk disease have a poor OS rate (five-year OS approximately 50%) despite intensive multimodal therapy. pERC thought that, given the poor overall prognosis in this patient population, there is a need for effective treatment options to be incorporated into upfront therapy that have the potential to delay recurrence or cure the disease.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

The Committee deliberated on the results of a phase III, open-label randomized controlled trial, Study 301, which compared dinutuximab in combination with GM-CSF, IL-2, and RA against RA alone in patients with high-risk neuroblastoma who achieved a pre-ASCT (autologous stem cell transplant) tumour response of complete response, very good partial response, or partial response. pERC noted that patients with at least a partial response to prior first-line multi-agent, multimodal therapy were enrolled in Study 301 and that a subset of patients (those with residual disease following ASCT) were non-randomized and assigned to the dinutuximab combination group. pERC recognized that conducting a randomized controlled trial in patients with (1) minor response, (2) stable disease, or (3) residual disease following ASCT, or (4) in adult patients with high-risk neuroblastoma who are treated according to pediatric protocols was likely not feasible given the low incidence of the disease. pERC concluded that because of the unmet need in this patient population, it would be reasonable to include patients with a response to prior pediatric protocol first-line multi-agent, multimodal therapy.

In discussion, pERC noted that there was demonstrated activity with the use of the dinutuximab combination and noted the potentially meaningful two-year EFS and OS in favour of the dinutuximab combination. However, pERC did have concerns with the trial methodology and design: the multiple interim analyses performed (i.e., every six months, starting after 20% of the planned events occurred), the two protocol amendments regarding early stopping, and the early stopping of the trial (which reduced the power to confirm significance of the trial results). As a result, pERC thought that the statistical significance in the two-year EFS and OS, as well as the long-term effects of the dinutuximab combination, were compromised and pERC therefore reduced confidence in the study results, in particular with the long-term benefits of the dinutuximab combination. Nonetheless, pERC felt that the two-year EFS and OS was potentially meaningful to the patient population given the additinal period of remission and the avoidance of or delay to the need for additional therapies. Moreover, pERC noted the imbalance in prognostic factors (which were not accounted for a priori) such as stage III, MYCN status, DNA ploidy, and histology favouring the dinutuximab combination group. Furthermore, quality of life was not measured in Study 301; consequently, pERC concluded that the impact of dinutuximab on patients' quality of life compared with other treatments is uncertain.

As well, the Committee discussed the toxicity profile of the dinutuximab combination and highlighted that the number of grade 3 or more adverse events were of concern (e.g., pain, hyponatremia, capillary leak syndrome, and diarrhea). However, pERC recognized that the dinutuximab combination has already been part of standard of care for upfront treatment of patients with high-risk neuroblastoma for several years, and acknowledged that centres administering this therapy are already well experienced in management of toxicities and methods to ameliorate immunotherapy-associated symptoms. Therefore, the Committee concluded that the dinutuximab combination has considerable but manageable toxicities.

Given the unmet need, potentially meaningful two-year EFS and OS, limitations in the trial design, and considerable but manageable toxicity profile, pERC thought that there may be a net clinical benefit of dinutuximab in combination with GM-CSF, IL-2, and RA in patients with high-risk neuroblastoma who achieve a response to prior pediatric protocol first-line multi-agent, multimodal therapy.

The Committee deliberated on the joint patient advocacy group input submission and concluded that dinutuximab aligns with patient values in that it offers a possible impact on the disease. pERC commended the efforts of this joint input submission that brought significant light to patient and family challenges and values in this uncommon disease setting. pERC emphasized the need for effective treatment options to be incorporated into upfront therapy and thought that the dinutuximab combination offered a potential curative treatment option. pERC acknowledged the impact and burden of disease on both the patients and their families and noted patients and families' strong willingness to tolerate access challenges and side effects. Moreover, pERC noted that, according to the families and caregivers' input, the dinutuximab regimen was thought to be easier and more manageable than the treatment received prior to the dinutuximab regimen.

The Committee deliberated on the cost-effectiveness of dinutuximab in combination with GM-CSF, IL-2, and RA compared with RA alone. pERC noted that the key cost drivers included drug wastage, monitoring costs, and adverse event costs. The key effect drivers were time horizon and survival curve assumptions. pERC also discussed the long-time horizon (100 years) used in the model, the way in which the model accounted for drug wastage, and the modelling assumptions for survival and noted that the EGP's reanalysis focused on time horizon, impact on wastage, duration of benefit, and survival extrapolation method. pERC noted that the model was informed by five years of follow-up data from Study 301 and acknowledged that although the slightly longer term follow-up data were included in the Clinical Guidance Report, the duration of outcomes predicted in the economic model significantly exceeded that for which data were available. pERC felt that the long-term benefits of the dinutuximab combination remained uncertain due to the trial methodology and design noted above. Furthermore, the Committee recognized that given weight-based dosing, a proportion of each vial of dinutuximab may be wasted; as well, patients may require more than one vial of dinutuximab. Therefore, pERC acknowledged the EGP's exploration of drug wastage. pERC felt that there may be considerable wastage with dinutuximab given the one size single-use vial and vial sharing would be unlikely due to the small number of pediatric patients with high-risk neuroblastoma who would be eligible for dinutuximab, and given the 24-hour stability of prepared dinutuximab. As a result, the Committee concluded that, at the submitted price, dinutuximab in combination with GM-CSF, IL-2, and RA may not be considered cost-effective compared with RA alone. In fact, pERC concluded that given the uncertainty, the incremental cost-effectiveness estimates could be considerably higher than the EGP's best-case estimate.

pERC considered the feasibility of implementing a reimbursement recommendation for dinutuximab. The Committee noted that the factors that most influenced the budget impact analysis included the cost of the drug, the definition of high-risk neuroblastoma, the drug's use in non-high-risk subgroups, monitoring costs, and adverse events. Due to the likelihood that there may be considerable wastage with dinutuximab, pERC concluded that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation, which may include advocating for the availability of a smaller vial size.

Lastly, the Committee deliberated on the input from PAG, in particular on factors related to currently funded treatments, the eligible population, implementation factors, and sequencing and priority of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon the following:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from a joint patient advocacy group submission from Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Canadian Organization for Rare Disorders, and Ontario Parents Advocating for Children with Cancer
- input from four registered clinician submissions representing a total of 13 clinicians: 11 practising oncologists or physicians who treat cancer patients, one nurse practitioner, and one oncology pharmacist
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group representing a total of five oncologists or physicians who treat cancer patients, one nurse practitioner, and one oncology pharmacist
- PAG

The pERC Initial Recommendation was to conditionally recommend reimbursement of dinutuximab in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and retinoic acid (RA) for the treatment of patients with high-risk neuroblastoma who achieve a response to prior pediatric protocol first-line multi-agent, multimodal therapy [if the following condition is met: cost-effectiveness being improved to an acceptable level].

Feedback on the pERC Initial Recommendation indicated that PAG agreed and the registered clinician group agreed in part with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of dinutuximab in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and retinoic acid (RA) for the treatment of pediatric patients with high-risk neuroblastoma who have achieved at least a partial response to prior first-line multi-agent, multimodal therapy.

Included study: One open-label phase III randomized controlled trial

Study 301 was a phase III, parallel-group, open-label randomized controlled trial conducted by the Children's Oncology Group (COG). The objective of this study was to determine whether dinutuximab immunotherapy (dinutuximab, GM-CSF, and IL-2) with RA improved event-free survival (EFS) after myeloablative therapy and autologous stem cell transplant (ASCT) compared with RA alone in patients with high-risk neuroblastoma who achieved a pre-ASCT tumour response of complete response, very good partial response, or partial response.

Patients were randomized in a 1:1 ratio to dinutuximab in combination with GM-CSF, IL-2, and RA or RA alone. High-risk neuroblastoma was defined using the COG system, and tumour response to previous induction therapy at pre-ASCT evaluation was defined using the International Neuroblastoma Response Criteria. Patients could not have progressive disease and had to have completed induction therapy, ASCT, and radiotherapy, with study enrolment between day 50 and day 100 after final ASCT. Patients also had to have a Lansky or Karnofsky Performance Scale score of at least 50% and life expectancy of at least two

months. Patients with biopsy-proven residual disease following ASCT could enroll in the study, but were non-randomly assigned to receive dinutuximab immunotherapy with RA and were included in the safety population only.

Both treatment arms consisted of six consecutive 4-week treatment cycles. Each therapy was administered as follows:

- Dinutuximab IV over 5.75 to 20 hours at 25 mg/m^2 BSA (body surface area)/day for 4 consecutive days during cycles 1 to 5
- GM-CSF subcutaneous (preferred) or IV over two hours at 250 mcg/m^2 BSA /day for 14 days starting 3 days before dinutuximab was started in cycles 1, 3, and 5
- IL-2 IV continuously at 3.0 million international units (MIU)/m^2 BSA/day for 4 days (96 hours) during week 1 and 4.5 million MIU/m^2/day for 4 days during week 2 in cycles 2 and 4
- RA orally 160 mg/m^2 BSA/day (or 5.33 mg/kg/day divided twice daily for patients weighing 12 kg or less) during the last 2 weeks of cycles 1 to 6.

Randomization was halted on January 13, 2009, as it was judged that the early stopping criteria for EFS had been met. All randomized patients enrolled up to this date were included in the intention-to-treat (ITT) analysis set. The results from the January 13, 2009, data set were published and used for the main analysis of the primary end point. Due to corruption of that data set, the closest data set available (June 30, 2009) was used for confirmatory analyses. Follow-up analyses were conducted with data cut-offs of June 30, 2012, and July 1, 2016.

Patient populations: Most pediatric patients were at least two years of age with stage IV neuroblastoma and had received one previous autologous stem cell transplant

In the ITT population, most patients were male (range of 56.6% to 62.8%), white (79.6% to 84.1%), at least two years of age (83.2% to 85.8%), had International Neuroblastoma Staging System (INSS) stage IV neuroblastoma (78.8% to 81.4%), had unfavourable tumour histological features (60.2% to 71.7%), and had received one previous ASCT (90% to 95%). Tumour MYCN status was amplified in 31.9% to 39.8%, tumour ploidy was hyperdiploid in 42.5% to 43.4%, and stem cell infusions were purged in at least one ASCT in 24.8% to 25.7% of patients. Response to induction therapy before ASCT was categorized as complete response in 33.6% to 35.4%, very good partial response in 41.6% to 43.4%, and partial response in 23.0%.

Key efficacy results: Potentially meaningful two-year event-free survival and overall survival

Superiority of dinutuximab immunotherapy with RA over RA alone was demonstrated in the primary end point analysis in the January 13, 2009, data set and in the confirmatory analysis in the June 30, 2009, data set. Analyses performed following the January 13, 2009, analysis are descriptive, as the efficacy stopping criteria were considered to have been met at the 2009 cut-off. Follow-up analyses demonstrated a continued trend of improved EFS with the addition of dinutuximab therapy, though the between-group differences in EFS tended to decrease over time. According to the Methods Lead, this suggests that the effect of dinutuximab on EFS may not have been maintained at longer follow-up times. Post hoc analyses adjusting for prognostic factors yielded results consistent with the primary EFS analysis.

Overall survival (OS) was greater in the dinutuximab group compared with the RA-alone group in the January 13, 2009, data set, though there was no adjustment for multiple outcomes. According to the Methods Lead, the results from the follow-up analyses strongly suggested that the OS benefit with dinutuximab was maintained over time. Post hoc analyses in the June 30, 2009, data set adjusting for prognostic factors yielded results consistent with the unadjusted analysis. While OS was not a pre-specified outcome for the non-randomized group with residual disease, an OS estimate was provided for this group at the July 1, 2016, cut-off (five-year OS of 51.4% with a standard error of 10.4%).

Patient-reported outcomes: Health-related quality of life data not measured

Health-related quality of life data were not collected in Study 301; therefore, the impact of dinutuximab combination on patients' quality of life compared with other treatments is uncertain.

Limitations: Uncertainty in long-term benefits due to interim analyses and early stopping

Interim analyses were performed every six months by the Data Safety Monitoring Committee, starting after 20% of the planned events occurred. Boundaries for efficacy and non-significance for the first three interim analyses were calculated using the Fleming–Harrington–O'Brien method with a cumulative alpha level of 0.05. The next three interim analyses used the same method with a cumulative one-sided alpha

level of 0.025 (the FDA stated they would consider the antibody for licensure if a significance level of 0.025 was reached). For the seventh and last interim analysis, the more conservative Lan–DeMets method with a cumulative alpha level of 0.025 was used. The upper boundary for efficacy (EFS) was determined for the Lan–DeMets method using a spending function of alpha × t2 for a cumulative alpha level of 0.025, and the lower boundary for non-significance was determined based on repeated testing of the alternative hypothesis that relative risk (RA alone versus dinutuximab with RA) was 1.6 (*P* value = 0.005).

The study was temporarily closed on January 13, 2009, over concern about the increased incidence of allergic reactions in the dinutuximab group. However, the stopping rule on unacceptable toxicities was not met. Using the amended rule for stopping based on interim efficacy analyses (Lan–DeMets method with a cumulative alpha level of 0.025) on the January 13, 2009, data set, the observed upper boundary z-value (2.528) was very close to the upper Lan–DeMets boundary z-value (2.55). While the stopping rule for efficacy was not met, the statistician considered the evidence to be sufficient for stopping the study, as it was very likely that the significance level of 0.025 proposed by the FDA would be met should the study reach full accrual.

All other outcomes besides EFS were secondary outcomes with no adjustment for multiplicity. The same statistical analyses performed for EFS were to be performed for OS, provided the 0.05 significance level for the two-sided log rank test of EFS was met. Subgroup analyses for EFS and OS were pre-specified for patients diagnosed with INSS stage IV neuroblastoma.

According to the Methods Lead, the following limitations of the randomized controlled trial should also be taken into account when interpreting the results:

- The study was open-label due to the complexity of the interventions. There was no risk of assessment bias for OS since it is an objective measure. Definitions of events and time points for follow-up assessments of disease status were pre-specified, such that there was low risk of bias in EFS assessment.
- Imbalances in MYCN status, DNA ploidy, and tumour histology are likely to have favoured dinutuximab, and the planned analysis did not adjust for any prognostic factors. However, post hoc EFS analyses performed for regulatory reviews adjusting for prognostic factors confirmed the primary analysis.
- The study ended before the efficacy stopping criteria were met. The confirmatory EFS analysis in the June 30, 2009, data set was less favourable than the January 13, 2009, analysis, though still statistically significant. There were also two separate amendments to the early stopping criteria for efficacy. Given the less than ideal circumstances surrounding the primary end point analysis, the follow-up analyses and the OS analyses are important for confirming the results of the primary analysis.
- Statistical testing and sample size calculations were based solely on EFS. There was no control for multiplicity of outcomes.
- Since dinutuximab was administered with IL-2 and GM-CSF and these two therapies were not included in the control arm, the results can only inform the efficacy and safety of the combination of dinutuximab, IL-2, and GM-CSF.
- Patients with residual disease following ASCT were not randomized and were all assigned to immunotherapy. Efficacy of dinutuximab in this group was not formally compared against a control arm.

Safety: Considerable toxicity profile

Adverse events (AEs) reported in at least 10% of patients in both treatment groups were as follows: lymphocyte count decreased, platelet count decreased, anemia, neutrophil count decreased, and device-related infection (ranging from 17.0% to 56.0% in the dinutuximab group and ranging from 11.0% to 23.9% in the RA-alone group). All other AEs occurred in no more than 8.3% of patients in the RA-alone group. In addition, the following AEs occurred in at least 20% of patients in the dinutuximab group: pyrexia, hypokalemia, pain, abdominal pain, white blood cell count decreased, anaphylactic reaction, hyponatremia, alanine aminotransferase increased, and capillary leak syndrome (ranging from 22.0% to 40.4% of patients).

The only serious adverse event (SAE) occurring in more than one patient in the RA-alone group was catheter-related infection (1.8%). The most common SAEs in the dinutuximab group were catheter-related

infection, hypotension, anaphylaxis, hypokalemia, fever, and capillary leak syndrome, which occurred in 6.4% to 8.5% of patients.

Need and burden of illness: Need for effective treatment options in this disease setting

Approximately half of patients have high-risk disease at presentation and have a poor OS rate despite very intensive multimodal therapy including chemotherapy, surgery, high-dose chemotherapy with autologous stem cell rescue (also called ASCT), radiotherapy, and differentiation therapy with isotretinoin (also called cis-retinoic acid). Given the poor prognosis, there is therefore a clear need for additional therapeutic options in order to achieve better disease control and reduce the risk of relapse. Since 2010 and the release of the promising results of the randomized COG study, 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 to 40 would be expected to have high-risk disease. Consequently, 25 to 35 patients might be expected to receive dinutuximab-based immunotherapy as part of upfront treatment each year. Given the poor overall prognosis, there is a clear need for effective treatment options to be incorporated into upfront therapy.

Registered clinician input: Dinutuximab combination is part of current standard of care for front-line treatment

All four clinician input submissions stated that dinutuximab in combination with GM-CSF and IL-2 is part of the current standard of care for the front-line treatment of patients with high-risk neuroblastoma. The addition of dinutuximab therapy to the previous standard of care has led to improvements in EFS and OS of patients with high-risk neuroblastoma. However, there are serious side effects that require intense medical and nursing management, including pain, hypotension, fluid retention, capillary leak syndrome, and risk of infection.

The four clinician input submissions agreed that the patient population of the reimbursement request reflects the patients who would be treated with dinutuximab therapy in clinical practice. However, the definitions of high-risk neuroblastoma differed slightly between the submissions. Three of the clinician input submissions noted that patients with relapsed neuroblastoma (one clinician input submission specified relapsed or refractory neuroblastoma) are not part of the reimbursement request and that these patients would potentially benefit from dinutuximab and GM-CSF therapy in combination with irinotecan and temozolomide.

Dinutuximab would be an add-on therapy to the previous standard of care for front-line treatment of high-risk neuroblastoma. Dinutuximab therapy with GM-CSF, IL-2, and RA would follow induction chemotherapy, ASCT, and possibly surgery and radiation therapy. Dinutuximab would be administered only to patients with high-risk neuroblastoma, and the diagnosis of high-risk neuroblastoma uses a combination of imaging modalities and tumour features from biopsy samples. Three clinician input submissions (two groups and one individual) agreed that the effectiveness of dinutuximab therapy would be compromised if GM-CSF was unavailable, while one individual submission considered the administration of dinutuximab without GM-CSF to be a reasonable option with proven effectiveness.

PATIENT-BASED VALUES

Experience of patients with neuroblastoma: Significant burden on patients and families

There is a wide range of symptoms of neuroblastoma and, in many cases, these are nonspecific or general symptoms. The symptoms include pain, stomach ache, lethargy, weight loss or gain, fever, bruising (particularly bruising around the eyes), limping, palpable mass, skin changes, and other infection-like symptoms. Neuroblastoma may initially be misdiagnosed due to the nonspecific nature of the symptoms, and patients may not receive a correct diagnosis until their symptoms are very severe. Front-line treatment of high-risk neuroblastoma involves intensive multimodal therapy and can include all or some of the following: induction chemotherapy, surgical resection, radiation therapy, and high-dose chemotherapy with ASCT. Almost all of the treatment is administered on an in-patient basis, and families spend most of their time in the hospital for almost 18 months. Current therapy for high-risk neuroblastoma has immense negative physical, psychological, and emotional impacts on patients and caregivers. There is a long list of side effects from treatment that can have a large or extremely large impact on patients, including neutropenia, fevers, nausea, vomiting, pain, hair loss, and hearing loss. Serious complications from current treatments including intestinal perforation can occur. The response to

treatment varies widely between patients. Barriers to accessing treatment include limitations of local care centres, the lack of assistance from social workers, the inadequacy of employment insurance compared with the duration of treatment, and the financial burden of transportation to and from hospitals.

Patient values on treatment: More tolerable and manageable side effects; willingness to tolerate access challenges and side effects

The current standard of care for patients with high-risk neuroblastoma includes dinutuximab therapy with GM-CSF, IL-2, and RA. This treatment is also associated with a long list of potentially serious side effects, including fluid retention, pain, high or low blood pressure, fever, respiratory issues, fatigue, sleepiness, nausea, vomiting, allergic reactions, and vision changes. In particular, pain management is a commonly cited concern. Some parents find the side effects of dinutuximab therapy more tolerable and manageable than those of the preceding therapies. Due to the frequency of drug administration and time spent in the hospital, dinutuximab therapy imposes a substantial financial burden. A total of 23 respondents surveyed and all five families interviewed had direct experience with dinutuximab. A total of 16 people in the survey were identified as having experience with dinutuximab in front-line therapy. The overall experience of parents whose children received dinutuximab therapy for high-risk neuroblastoma is that the side effects, though challenging to manage, are worth suffering through for a chance to eliminate their child's cancer and give them the best chance at survival.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analyses

The economic analysis submitted to pCODR by United Therapeutics Canada Corp. compared dinutuximab immunotherapy as part of a multimodal post-consolidation treatment (in combination with GM-CSF, RA, and IL-2) to RA monotherapy for pediatric patients with high-risk neuroblastoma.

Basis of the economic model: Data from Study 301, published literature, and other sources

The submitted model was a partitioned-survival model comprised of three health states: stable, failure, and death. Health states were selected in accordance with the clinical pathway. The model structure was 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. OS, EFS, and adverse event rates were taken from Study 301. Drug costs were taken from published literature or databases, and the submitter (United Therapeutics Canada Corp). Utility data were taken from published literature and expert opinion.

Drug costs: Very high drug costs

The cost of dinutuximab combination (all six cycles) is $273,201. Dinutuximab is administered in combination with GM-CSF, RA, and IL-2 over six cycles of treatment. In the model, BSA of 0.65 m^2 is assumed, as per the average BSA in Study 301.

- Dinutuximab costs $12,850 per 17.5 mg vial, to be administered intravenously. The recommended dose of dinutuximab is 17.5 mg/m^2 per day on days 4 to 7 of chemotherapy cycles 1, 3, and 5. In cycles 2 and 4, the recommended dose of dinutuximab is 17.5 mg/m^2 per day on days 8 to 11.
- GM-CSF is administered by subcutaneous injection on days 1 to 14 of cycles 1, 3, and 5 at a dose of 250 mcg/m^2/day. The cost of GM-CSF is $323.72 per 250 mcg vial.
- RA is administered twice orally per day at a dose of 80 mg/m^2, for a total daily dose of 160 mg/m^2/day, on days 11 to 24 of cycles 1, 3, and 5 and on days 15 to 28 of cycles 2, 4, and 6. The cost of RA is $1.92 per 40 mg tablet.
- 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 to 4 and 4.5 MIU/m^2 on days 8 to 11 of cycles 2 and 4. The cost of IL-2 is $530.27 per 18 MIU vial. IL-2 administration requires admission to the intensive care unit (ICU) for 11% of cases and admission to a standard hospital bed for the remainder of cases.

Cost-effectiveness estimates: May not be cost-effective given the uncertainty in the long-term clinical benefit

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

- 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 pCODR Clinical Guidance Panel (CGP) suggests that no admission to ICU is required for IL-2 administration. This overestimates costs for the 11% of patients who 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. pCODR's Economic Guidance Panel (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: This lack 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.

The EGP's best estimate of incremental cost and effect for dinutuximab combination when compared with isotretinoin:

- The EGP reanalysis estimate of the incremental cost-effectiveness ratio (ICER) is $73,391/QALY (quality-adjusted life year). 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 submitter, represents the scenario in which the maximum BSA observed in the trial is applied to all patients in the model.
- The extra cost of dinutuximab is $347,793 in EGP reanalysis. 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 about 4.74 QALYs in EGP reanalysis. 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 to 42 patients with high-risk neuroblastoma per year used in the budget impact analysis, a small group will have primary progressive disease and will not qualify for upfront immunotherapy; the true estimate is closer to 35 patients per year. In the EGP scenario reanalysis, 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 estimated budget impact is sensitive to the number of patients who 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 reanalysis, a time horizon of 75 years is explored. But this model is informed by five years of follow-up data from a single randomized controlled trial. Outcomes are uncertain beyond this point.
- Although reanalysis was conducted by the EGP, the results of this reanalysis 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 are included in the Clinical Guidance Report, the duration of outcomes predicted in the economic model significantly exceeds that for which data are 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 with 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 RA and underestimation of costs of dinutuximab relative to RA. Although these differences are not large, they make the ICER for dinutuximab versus RA appear more favourable than what was obtained using observed data.

- In the EGP reanalysis, 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 the EGP reanalysis.
- The dinutuximab treatment regimen includes GM-CSF at a cost of $323.72 for each 250 mcg vial, which is not controllable in the Canadian setting.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Inability to explore wastage
Key limitations of the budget impact analysis include the inability to explore wastage. A proportion of each vial of dinutuximab is used in a typical dose and the remaining is wasted. This parameter could not be modified and explored by the EGP. All limitations in the manufacturer-submitted model are inherent to the budget impact analysis.

For other considerations for implementation, refer to Appendix 1: CADTH Pan-Canadian Oncology Drug Review Expert Review Committee Responses to Provincial Advisory Group Implementation Questions.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Daryl Bell, who did not vote due to his role as a patient member alternate.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of dinutuximab for neuroblastoma, through their declarations, no members had a real, potential, or perceived conflict and, based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

Disclaimer

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information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
Currently Funded Treatments • Up-to-date COG chemotherapy protocols or active COG clinical trials could be considered standard of care. Treatment options include multi-agent chemotherapy regimens (and ASCT if eligible) or isotretinoin (RA). Patients are enrolled into clinical trials and in some jurisdictions, treated out of province at pediatric hematology or oncology transplant centres.	• pERC recognized that dinutuximab in combination with GM-CSF, IL-2, and RA has already been considered part of standard of care for treatment of patients in this disease setting for several years.
Eligible Patient Population • Clarity is sought on whether dinutuximab would be limited to patients with high-risk neuroblastoma. PAG is also seeking guidance on the definition of high risk, as this would be an enabler to implementation. • If the dinutuximab combination is recommended for reimbursement, PAG noted that patients currently receiving other treatment (e.g., isotretinoin alone) for high-risk neuroblastoma would need to be considered on a time-limited basis. • PAG noted that patients with relapsed or refractory disease are currently covered under the Special Access Programme. PAG is seeking guidance on whether trial results are generalizable to these patients.	• pERC noted the CGP's response to the generalizability of evidence (in Table 2: Assessment of generalizability of evidence for dinutuximab for neuroblastoma, in the Clinical Guidance Report) regarding the definition of high-risk neuroblastoma and agreed with the CGP that, regardless of the precise definition of high-risk neuroblastoma (which may change slightly over time), those patients for whom dinutuximab should be considered are those treated as high-risk—i.e., with induction chemotherapy, consideration of surgical resection, and high-dose chemotherapy with ASCT (± radiotherapy) prior to immunotherapy. pERC also agreed with CGP that patients initially diagnosed as non-high-risk who later progressed or relapsed to high-risk neuroblastoma should be considered suitable for dinutuximab (as acknowledged within Study 301 inclusion criteria). As well, the Committee agreed with CGP that (with the above exception) there is currently no role for dinutuximab in the non-high-risk neuroblastoma population. • Since the dinutuximab combination has been considered part of the standard of care for treatment of patients with high-risk neuroblastoma for several years now and because of this, pERC felt that it was not likely that patients receiving RA alone in the upfront setting would need to be considered on a time-limited basis. • pERC noted that patients with relapsed or refractory disease are out-of-scope in the submitted funding request. However, pERC acknowledged that funding for this particular patient population is of particular interest to patients (and their families) and clinicians. The clinical trial evidence (Study 301) addressed only the use of dinutuximab in the upfront setting for high-risk neuroblastoma and is not therefore generalizable to the relapsed or refractory setting. The CGP noted encouraging data for dinutuximab in combination with temozolomide/irinotecan in the relapsed or refractory setting and stated that this strategy has become one of the standard approaches to managing relapsed or refractory disease in Canada.

Implementation Factors • PAG noted that the long infusion time would be a barrier to implementation, as patients would need to be in hospital for delivery of treatment. PAG also noted that, as treatment would be administered primarily in hospital, coverage and funding of in-patient oncology treatment differs by province; this would require collaboration with hospitals for implementation of reimbursement of dinutuximab. • Additional nursing and pharmacy resources will be required for pre-medication, drug preparation, administration time, and monitoring for multiple severe adverse effects including infusion reactions and severe neurotoxicity (i.e., severe neuropathic pain and peripheral neuropathy). PAG noted that the significantly increased chair time compared with current treatment is a barrier to implementation, given the additional resources needed as well as slower infusion time to reduce the risk of infusion reactions with dinutuximab. • PAG noted that additional resources and costs will also be required for GM-CSF, IL-2, and RA. 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, so these are barriers to implementation. PAG also noted that limited bed spaces in hospitals would be a barrier to implementation. • PAG noted there would be significant wastage, as there is only one strength available in a single-use vial, which limits dose adjustments, and as vial sharing would be unlikely due to the small number of pediatric patients with high-risk neuroblastoma who would be eligible for dinutuximab. Dinutuximab vials require refrigeration; diluted drugs also must be refrigerated and utilized within 24 hours of preparation, and this is also a barrier to implementation.	• pERC recognized that the dinutuximab combination has been considered part of the standard of care for treatment of patients with high-risk neuroblastoma for several years now and acknowledged that centres administering this therapy are already well-experienced in management of toxicities and methods to ameliorate immunotherapy-associated symptoms. • pERC 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. The available evidence for treatment with dinutuximab in this patient population includes a combination treatment (i.e., dinutuximab in combination with GM CSF, IL 2, and RA), therefore, pERC concluded that access to GM-CSF should be continued and that jurisdictions will need to consider mechanisms to continue the availability of GM CSF in Canada. • The Committee recognized that, given the BSA-based dose, only a proportion of each vial of dinutuximab is used in a typical dose and the remaining is wasted. In addition, patients may require more than one vial of dinutuximab. Therefore, pERC thought that there may be considerable wastage with dinutuximab, given the single-use vial (which limits dose adjustments), given that vial sharing would be unlikely due to the small number of pediatric patients with high-risk neuroblastoma who would be eligible for dinutuximab, and given the 24-hour stability of prepared dinutuximab. pERC concluded that jurisdictions will need to consider mechanisms to minimize wastage upon implementation of a reimbursement recommendation, which may include advocating for the availability of a smaller vial size.
Sequencing and Priority of Treatments • PAG is seeking guidance on the appropriate treatment options following treatment with dinutuximab in this setting.	• pERC noted that, at present, there are no data to support the use of additional treatment options following completion of treatment with dinutuximab-based immunotherapy in this setting. Therefore, pERC concluded that the optimal sequencing of dinutuximab in combination with GM-CSF, IL-2, and RA in this setting is unknown.
Companion Diagnostic Test/Other • None.	

ASCT = autologous stem cell transplant; BSA = body surface area; COG = Children's Oncology Group; CGP = pCODR Clinical Guidance Panel; EFS = event-free survival; EGP = pCODR's Economic Guidance Panel; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL-2 = interleukin-2; OS = overall survival; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; RA = retinoic acid.