CADTH Reimbursement Recommendation

Dinutuximab (Unituxin)

**Indication:** For the treatment of high-risk neuroblastoma patients in their first relapse or determination of refractory disease, in combination with irinotecan, temozolomide, and granulocyte macrophage colony-stimulating factor

**Sponsor:** United Therapeutics Corporation

**Final Recommendation:** Reimburse with conditions
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FUNDING: CADTH receives funding from Canada’s federal, provincial, and territorial governments, with the exception of Quebec.
What Is the CADTH Reimbursement Recommendation for Unituxin?
CADTH recommends that Unituxin (in combination with irinotecan, temozolomide, and granulocyte macrophage colony-stimulating factor [GM-CSF]) should be reimbursed by public drug plans for the treatment of patients with relapsed or refractory high-risk neuroblastoma if certain conditions are met.

What Are the Conditions for Reimbursement?
Unituxin should only be reimbursed if delivered in a specialized pediatric cancer centre by health care professionals with experience and knowledge of managing neuroblastoma and the toxicities of anti-GD2 therapy and if the cost of Unituxin is reduced.

Which Patients Are Eligible for Coverage?
Unituxin should only be covered for patients who have not had previous treatment for relapsed or refractory high-risk neuroblastoma or have not had a severe reaction or progressive disease with upfront anti-GD2 immunotherapy.

Why Did CADTH Make This Recommendation?
• Evidence from a clinical trial demonstrated that treatment with Unituxin showed an improvement in objective response rates in patients with relapsed or refractory high-risk neuroblastoma.
• Based on public list prices, Unituxin is not considered cost-effective at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) for the indicated population compared with standard chemotherapy alone. A price reduction is therefore required.
• Patients expressed a need for an effective treatment that has an impact on disease outcomes and is tolerable and manageable, both of which were met by the dinutuximab regimen in the key study.
• Economic evidence suggests that with price reductions approaching 100%, Unituxin is not cost-effective at a $50,000 per QALY threshold.
• Based on public list prices, the 3-year budget impact of Unituxin is at least $37,891,509.

Additional Information
What Is Neuroblastoma?
Neuroblastoma is a disease in which cancer cells form in the nervous system, most often in children. First-line treatment will not work in many patients, and many of them will relapse. Approximately 76 patients are diagnosed with neuroblastoma each year in Canada, and half of these patients have high-risk disease, meaning that only approximately 50% of them will be alive in 5 years.

Unmet Needs in Neuroblastoma
The chemotherapy regimens currently used to treat patients with relapsed/refractory high-risk neuroblastoma are not very effective, and some patients do not respond to these treatments. Combined treatment with dinutuximab and chemotherapy is the first choice of most oncologists to treat these patients.

How Much Does Unituxin Cost?
Treatment with Unituxin (in combination with GM-CSF, temozolomide, and irinotecan) is expected to cost approximately $74,811 per person per 28-day cycle.
Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that dinutuximab should be reimbursed for the treatment of patients with high-risk neuroblastoma in their first relapse or determination of refractory disease, in combination with irinotecan, temozolomide, and GM-CSF, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In a phase II, open-label study (ABNL1221, N = 71), treatment with dinutuximab was associated with a clinically meaningful improvement in objective response rates (ORRs) in patients with relapsed or refractory (R/R) high-risk neuroblastoma. In the randomized cohort, after 6 cycles of therapy, the ORR among patients who received dinutuximab and GM-CSF in combination with irinotecan and temozolomide was 52.9% (9 of 17; 95% CI, 27.8% to 77.0%). Further, the ORR among all patients who received the dinutuximab regimen was 41.5%. Results of exploratory analyses suggest that treatment with dinutuximab may have beneficial effects on duration of response (DOR), progression-free survival (PFS), and overall survival (OS), and were considered clinically meaningful by clinical experts. Patients expressed a need for an effective treatment that has an impact on disease outcomes and that was tolerable and manageable, both of which were met by the dinutuximab regimen in study ABNL1221. Further, pERC noted that high-risk neuroblastoma is a rare, severe disease, and no effective treatment options are available for patients who are relapsed or refractory to front-line treatment.

Using the sponsor-submitted price for dinutuximab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for dinutuximab-based immunotherapy for relapsed patients was $495,696 per quality-adjusted life-year (QALY) compared with standard chemotherapy alone and $459,747 for refractory patients. Even with price reductions approaching 100%, the ICER does not fall below $50,000 per QALY, which is due to the additional health care costs (non-drug) related to dinutuximab and uncertainty regarding the magnitude of benefit associated with dinutuximab.
**Implementation Guidance**

1. In study ABNL1221, refractory disease was defined as inadequate response to treatment that included at least 4 cycles of 2 or more chemotherapy agents, including an alkylator and a platinum-containing compound. Refractory neuroblastoma is detected by increased size of existing disease or new sites of metastatic disease noted by cross-sectional imaging MRI or CT scan, MIBG scan, or bone marrow examination. First designation of relapse was defined as recurrence after response to treatment or disease progression that may present with patient symptoms or be noted by routine follow-up.

   2. Dinutuximab therapy is intended to be given with GM-CSF (sargramostim), which is not marketed in Canada and must be obtained through Health Canada's Special Access Programme. GM-CSF may not be equally accessible to all patients in Canada as not all jurisdictions fund medications obtained through the Special Access Programme.
3. In study ABNL1221, dinutuximab was evaluated in combination with GM-CSF and irinotecan plus temozolomide. The clinical experts consulted for this review suggested that dinutuximab could be used with other chemotherapy backbones (e.g., cyclophosphamide and topotecan or ifosfamide, carboplatin, and etoposide) if a patient is intolerant to irinotecan or temozolomide.

4. Clinicians expect to see a benefit or response from dinutuximab by the end of 6 cycles. Clinical experts consulted for this review noted that dinutuximab should be continued for patients who demonstrate a clinical or radiological response, but that the additional benefit of continuing dinutuximab beyond 6 treatment cycles in patients who exhibit a complete response is unknown. Although the clinicians recommend additional cycles be given to these patients, the clinical experts consulted for this review recognized that the maximum of 17 treatment cycles would not likely be necessary.

5. Evidence from the ANBL1221 study showed that responses to dinutuximab occurred in R/R patients who had received dinutuximab previously as well as in dinutuximab-naive patients. Therefore, it may be appropriate to treat patients who have received prior dinutuximab as upfront therapy with the dinutuximab regimen in the R/R setting. However, it is not advisable to re-treat patients with a history of severe and/or unacceptable toxicity to previous dinutuximab.

6. Treatment of high-risk R/R neuroblastoma is complex and requires inpatient care at a tertiary pediatric hospital by a multi-disciplinary team with relevant experience. Patients may be required to travel to receive treatment with dinutuximab, and out-of-province care may be needed. pERC suggests the creation of interprovincial agreements to ensure equitable access to eligible patients in all jurisdictions, including consideration of financial and logistic support for required travel and short-term relocation.

Discussion Points

• There is considerable uncertainty associated with results of study ANBL1221 due to the small sample size, early discontinuation, the exploratory nature of the efficacy end points, and the potential for bias in comparisons of a non-randomized expansion cohort to a randomized cohort. However, pERC acknowledged that high-risk neuroblastoma is an aggressive disease with few effective therapeutic options.
• pERC noted that it was difficult to determine the magnitude of clinical benefit of the dinutuximab regimen compared with historical treatment options (e.g., various traditional cytotoxic chemotherapy regimens) due to limited comparative data. The only comparative data available for this review were for the primary efficacy outcome in study ANBL1221, which compared the dinutuximab regimen to temsirolimus in combination with irinotecan and temozolomide. Although this regimen is not clinically relevant because it is not available in Canada, pERC noted a benefit in the response rates for dinutuximab treatment over temsirolimus.
Background

Dinutuximab is a chimeric monoclonal antibody that binds to GD2 on neuroblastoma cells and induces antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. It is available as an IV injection, and the Health Canada–approved dose is 17.5 mg/m² per day over 10 hours to 20 hours for 4 consecutive days per treatment cycle. The indication under review is for the treatment of high-risk neuroblastoma patients in their first relapse or for determination of refractory disease, in combination with irinotecan, temozolomide, and GM-CSF.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

• a review of 1 phase II randomized controlled trial in patients with relapsed or refractory high-risk neuroblastoma
• patients’ perspectives gathered by 3 patient groups, including Neuroblastoma Canada, the Canadian Organization for Rare Disorders (CORD), and Ontario Parents Advocating for Children with Cancer (OPACC)
• 3 clinical specialists with expertise diagnosing and treating patients with relapsed or refractory high-risk neuroblastoma
• input from 2 clinician groups: the Pediatric Oncology Group of Ontario (POGO) and 10 clinicians from the Pediatric Oncology Department of BC Children’s Hospital
• a review of the pharmacoeconomic model and report submitted by the sponsor.

Patient Input

Neuroblastoma Canada, CORD, and OPACC submitted a joint patient input for this review. Patient perspectives were obtained from online surveys and telephone interviews. The following is a summary of key input from the perspective of the patient groups.

• Patients reported that the diagnosis of high-risk neuroblastoma is often delayed and the disease has many adverse effects on quality of life, including pain, persistent fevers, uncharacteristic behaviours, constipation, low energy levels, weight loss or gain, and loss of appetite. The disease also impacts the mental health, parenting ability, ability to work, financial resources, and home lives of parents and families.
• Patients and their families found various aspects of front-line treatment to be difficult and often overwhelming. In both the upfront and relapsed or refractory setting, adverse events and lack of efficacy were significant drawbacks of current therapies and had a significant impact on the mental and physical health of patients and mental health of families.
• Parents stated that their intense desire was to find an effective treatment for their child. There was frustration that more advanced or experimental therapies were not available, even as options. All caregivers stated that they selected a treatment with their child’s quality of life in mind.
For relapsed therapy, respondents reported challenges accessing dinutuximab in combination with irinotecan and temozolomide for treatment. In the relapsed setting, most reported side effects of dinutuximab chemoimmunotherapy were manageable and comparable to those experienced in front-line therapy. Compared with traditional therapies, which often have significant, long-term adverse effects, the side effects of dinutuximab chemoimmunotherapy were temporary and could be managed by supportive medications. Overall, respondents were willing to tolerate the challenges with access to treatment and the side effects associated with dinutuximab, especially if this treatment could address the disease burden, help to deter relapse, and potentially be lifesaving.

Drug Plan Input

Drug programs identified several key issues related to implementation. First, drug programs requested clarification of the specific definitions of relapsed versus refractory neuroblastoma. Clinical experts consulted by CADTH for this review explained that although there is some degree of overlap between these terms, the major distinction is response to induction chemotherapy allowing patients to proceed to high-dose chemotherapy (refractory: no; relapsed: yes). This comes down to a case-by-case clinical decision based on response. Second, drug programs asked whether there were differences in treatment strategies for patients with relapsed versus refractory neuroblastoma. Clinical experts answered that there are substantial differences. For patients with refractory neuroblastoma, the goal is to move to second-line treatment options and obtain a response, then return to and complete the original treatment protocol, including high-dose chemotherapy with autologous stem cell transplant rescue, radiotherapy, and immunotherapy. Patients with relapsed neuroblastoma most likely already received high-dose chemotherapy and would not receive it again. Third, drug programs inquired whether there was evidence to support dinutuximab treatment beyond 17 cycles in patients with R/R high-risk neuroblastoma. Clinical experts stated that the only available evidence is based on a trial that used an arbitrary maximum of 17 cycles. However, there is no clear evidence that treatment with dinutuximab beyond 17 cycles would not be considered, and this is a balance of risks and benefits made by the treating physician. Finally, drug programs inquired whether, for patients who received prior dinutuximab, there was evidence on re-treatment with the same drug in the R/R setting. The clinical experts responded that there is evidence of the efficacy of combination therapy with dinutuximab in combination with irinotecan, temozolomide, and GM-CSF in patients with R/R high-risk neuroblastoma even if dinutuximab was used in upfront therapy. There is also anecdotal evidence that patients can respond again to the same combination after relapse. Drug programs also noted that coverage and funding of inpatient cancer drugs differs by province.

Clinical Evidence

Clinical Trials

The systematic review included 1 phase II, multi-centre, open-label randomized controlled trial (ANBL1221, N = 71) in patients with R/R high-risk neuroblastoma in their first relapse or for designation of refractory disease. In the first stage of the study, patients (N = 35)
were randomized 1:1 to receive either temsirolimus (Regimen A) or dinutuximab and GM-CSF (Regimen B), both with standard chemotherapy (irinotecan and temozolomide). Dinutuximab was dosed at 17.5 mg/m² per day on 4 consecutive days (days 2 to 5) per 3-week treatment cycle while temsirolimus was dosed at 35 mg/m² on days 1 and 8. Randomization was stratified by disease status at baseline (relapsed versus refractory), prior anti-GD2 immunotherapy, and MYCN status. No concomitant systemic anticancer therapies were permitted while on protocol therapy. Patients were evaluated after 2 cycles, then at cycles 4 and 6, and then every 4 cycles thereafter to a maximum of 17 cycles. Response was assessed using International Neuroblastoma Response Criteria (INRC). The primary efficacy end point was the proportion of patients achieving at least a partial response as their best overall response by the completion of 6 cycles; patients with progressive disease at evaluation were taken off protocol therapy and were classified as treatment failures.

Exploratory objectives included comparison of the ORRs of the dinutuximab and temsirolimus regimens as well as DOR, PFS, and OS. Following completion of the randomized stage, the Regimen A (temsirolimus) arm was closed to accrual based on failure to demonstrate a potential treatment effect using pre-specified selection criteria. Enrolment was expanded to permit accrual of 36 non-randomized patients treated with Regimen B (dinutuximab with GM-CSF, irinotecan, and temozolomide) to determine the ORR of this regimen more accurately. Patients were followed for up to 5 years; the mean duration of follow-up was 773.2 (SD = 499.4) days.

The mean age of patients in the ANBL1221 trial at enrolment was 6.4 (SD = 3.6) years. Most patients (88.7%) had International Neuroblastoma Staging System stage 4 tumours. The study included patients with both relapsed (43.7%) and refractory (56.3%) disease, patients whose tumours were measurable (69.0%) and not measurable (31.0%) by CT or MRI, and patients whose tumours were MYCN amplified (26.8%) and unamplified (69.0%). The study excluded patients whose disease progressed during dinutuximab immunotherapy in upfront therapy as well as patients in their second or subsequent relapses.

Outcomes

Outcomes were defined a priori in CADTH’s systematic review protocol. Of these, the Committee discussed the following:

- ORR: using INRC after up to 6 cycles of therapy. Imaging results for designation of response were centrally reviewed by the study chair who was unaware of treatment group assignment.
- DOR: calculated as the duration from the time of initial response until documented tumour or disease progression, or the date of last assessment if tumour or disease progression did not occur. If patients received additional anticancer therapy, the DOR was censored at the start date of the follow-up period during which this therapy was administered.
- PFS: calculated as time from enrolment to an event (first relapse, progressive disease, or death attributable to tumour or treatment) or to time of last patient contact if no event occurred.
- OS: calculated as time from enrolment to death from any cause or time to last contact if the patient was alive.

The primary outcome in the ANBL1221 trial was the proportion of patients who achieved a partial response or better as their best overall response after up to 6 cycles of therapy.
Comparisons of ORR between groups as well as all analyses of DOR, PFS, and OS were exploratory. Data on health-related quality of life were not reported in the ANBL1221 study.

**Efficacy**

All comparisons of efficacy outcomes in the ANBL1221 study were exploratory, including comparisons of the primary outcome, ORR, as well as DOR, PFS, and OS; no inferential statistical analysis was required to meet the primary objectives of the study. The ORR in patients treated with Regimen B was 52.9% (9 of 17 patients with a partial response or better; 95% confidence interval [CI], 27.7% to 77.0%) and 5.9% in patients treated with Regimen A (1 of 18 patients with a partial response or better; 95% CI, 0.1% to 27.3%; P = 0.0027). Based on these results, patients were recruited into an expansion cohort and directly assigned to receive Regimen B. The ORRs of patients in the expansion cohort and of the total Regimen B–treated patients were consistent with those of patients treated with Regimen B in the randomized study. In the expansion cohort, 13 of 36 (36.1%) patients had a partial response or better (95% CI, 20.8% to 53.8%; P = 0.0205 versus Regimen A). In all Regimen B–treated patients, 22 of 53 (41.5%) patients had a partial response or better (95% CI, 28.1% to 55.9%; P = 0.004 versus Regimen A).

Median DOR was 35.1 weeks in the single responding patient treated with Regimen A and 33.0 (range = 2.4 to 76.1) weeks among all patients treated with Regimen B. Median DOR based on Kaplan-Meier analysis was 76.1 weeks (95% CI not calculable) among all patients treated with Regimen B. Median PFS was 7.7 (range = 5.9 to 66.0) weeks in patients treated with Regimen A and 57.0 (range = 3.3 to 196.9) weeks in all patients treated with Regimen B. Median PFS based on Kaplan-Meier estimates was 12.9 (95% CI, 6.9 to 47.3) weeks in patients treated with Regimen A and 97.9 (95% CI, 60.3 to 110.6) weeks in all patients treated with Regimen B (hazard ratio [HR] = 0.41; 95% CI, 0.22 to 0.77; P = 0.0054). Median OS was 54.8 (range = 13.1 to 165.9) weeks in patients treated with Regimen A and was 72.8 (range = 6.0 to 219.4) weeks in all patients treated with Regimen B. Median OS based on Kaplan-Meier estimates was 117.3 (95% CI, 23.6 to 165.9) weeks in patients treated with Regimen A and 219.4 weeks (95% CI not calculable) in patients treated with Regimen B (HR = 0.50; 95% CI, 0.2 to 1.04, P = 0.0636).

The key limitations of the ANBL1221 study were uncertain magnitude of treatment effects because of the small number of participants, challenges inherent in comparisons between Regimen A and Regimen B, and the exploratory nature of all efficacy outcomes. Despite these limitations, the clinical experts consulted by CADTH for this review indicated that the single-arm response data (ORR) from the ANBL1221 study suggest a benefit for the addition of dinutuximab.

**Harms (Safety)**

Adverse events (AEs) occurred with similar frequency in the ANBL1221 trial among patients treated with Regimen A (temsirolimus, irinotecan, and temozolomide; 88.9%) and Regimen B (dinutuximab, irinotecan, and temozolomide; 100.0% randomized cohort, 94.1% overall). Some AEs were common in patients receiving both regimens (e.g., myelosuppression, anemia, hypokalemia, and diarrhea). Pain (33.3%), capillary leak syndrome (4.0%), hypotension (9.8%), dyspnea (5.9%), respiratory failure (5.8%), and peripheral motor neuropathy (2.0%) occurred in patients treated with Regimen B, but in few or no patients treated with Regimen A. Serious AEs occurred more often in patients treated with Regimen B (68.8% randomized cohort, 52.9% overall) than in those treated with Regimen A (38.9%). Few patients treated with either
regimen had AEs requiring withdrawal from protocol therapy (Regimen A: 5.6%; Regimen B: 6.3%; randomized cohort, 2.0% overall). Overall, AEs reported for dinutuximab in the ANBL1221 trial were consistent with prior clinical experience and the product monograph.

Economic Evidence

Cost and Cost-Effectiveness

Dinutuximab is available as a 3 mg/5 mL vial at a submitted price of $12,850. At a recommended dose of 17.5 mg/m² per day 4 times per 3 weeks, the cost of dinutuximab alone per 28-day cycle is $68,533. Dinutuximab is given in combination alongside GM-CSF, temozolomide, and irinotecan leading to a total 28-day cycle cost of $74,811.

The sponsor submitted a cost-utility analysis comparing dinutuximab to temsirolimus added to standard chemotherapy of irinotecan and temozolomide. Two separate analyses were conducted, 1 for relapsed patients and 1 for refractory patients. A 3-state partitioned survival model was submitted made up of 3 mutually exclusive states of "progression-free," "progressed disease," and "death." Time spent in each state was based on direct modelling of OS and PFS curves. For the first 5 years of the model, individual patient data from ANBL 1221 was used to derive the PFS and OS curves for both the relapsed and refractory populations. After a period of 5 years, the cohort who have not progressed are assumed to be "cured." Those who have progressed are labelled as “failed.” Therefore, after this time point, the cured cohort and the failed cohort no longer follow trial-based extrapolations with respect to OS or PFS, such that the failure cohort dies more rapidly, whereas the cured cohort realizes a substantial improvement in survival for the remainder of their lifetime.

The following key limitations were identified:

• The sponsor’s assumption — that all patients who are event-free after 5 years would be cured for the remainder of their lifetime with no possibility of progression and significantly lower mortality — was deemed to be optimistic by clinical experts given the paucity of data in this patient population.
• The model was informed by limited data on clinical effectiveness and survival in this population given the small number of patients in the ANBL1221 trial (N = 35) and limited long-term data (5-year trial data were extrapolated to 25 and 75 years for relapsed and refractory patients, respectively). This makes interpolating and extrapolating OS and PFS highly uncertain. PFS interpolation around standard chemotherapy for refractory patients was deemed inappropriate.
• The clinical experts consulted for this review indicated that temsirolimus is not used alongside standard chemotherapy (irinotecan and temozolomide) because it does not provide additional clinical benefit. Therefore, only irinotecan and temozolomide are used as part of standard care in Canadian practice.
• The cost of hospital stay was not considered during administration of dinutuximab.
• Wastage was not considered in the calculation of drug cost for GM-CSF and irinotecan.

CADTH reanalyses included changing the assumption that all patients who are event-free after 5 years to be 7 years, which is in line with previous reviews (CADTH and NICE); changing PFS for the standard chemotherapy arm for refractory patients; removing temsirolimus from...
the comparator regimen; assuming no vial sharing in this population; and adding a hospital stay cost for treatment administration.

In the CADTH base case reanalysis for relapsed patients, dinutuximab-based immunotherapy had incremental costs of $826,899 and incremental QALYs of 1.67 compared with standard chemotherapy alone, resulting in an ICER of $495,696 per QALY gained. For refractory patients, dinutuximab-based immunotherapy had an incremental cost of $593,337 and an incremental QALY of 1.291, resulting in an ICER of $459,747 per QALY gained. In both populations, dinutuximab-based immunotherapy had a 0% probability of cost-effectiveness at a $50,000 per QALY threshold compared with standard chemotherapy. Even with price reductions approaching 100%, the cost-effectiveness of dinutuximab would not be achieved, largely because of the considerable health care costs (non-drug) contributing to the cost of care and the uncertainty regarding the magnitude of benefit associated with dinutuximab. Due to the sponsor's model design, the difference in PFS at the point of cure is fundamental to the cost-effectiveness results, and there are no reliable data to inform what this difference may be. Various scenario analyses that explored the impact of these assumptions showed that the CADTH base case may overestimate the benefits associated with dinutuximab and that the true ICER could be more than $1.4 million per QALY in the refractory cohort and $800,000 per QALY in the relapsed cohort.

**Budget Impact**

The sponsor estimated the incremental budget impact of reimbursing dinutuximab to be $28,136,655 over 3 years. CADTH identified limitations with the submitted analysis and undertook reanalyses which estimated the incremental budget impact of reimbursing dinutuximab to be $37,891,509 over 3 years.

**Members of the pCODR Expert Review Committee**

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

**Meeting Date:** May 14, 2021

**Regrets:** None

**Conflicts of Interest:** None