Canadian Journal of Health Technologies
October 2023 Volume 3 Issue 10

CADTH Reimbursement Recommendation

Nelarabine (Atriance)

Indication: Nelarabine (Atriance) for addition to front-line multiagent therapy of pediatric, adolescent, and young adult patients (aged 1 year to 30 years at diagnosis) with intermediate- or high-risk T-cell acute lymphoblastic leukemia

Sponsor: Pediatric Oncology Group of Ontario

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Atriance?

CADTH recommends that Atriance should be reimbursed by public drug plans for the treatment of pediatric, adolescent, and young adult patients with intermediate- or high-risk T-cell acute lymphoblastic leukemia (T-ALL) in addition to front-line multiagent chemotherapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Atriance (nelarabine) should only be covered to treat patients with intermediate- and high-risk T-ALL who are aged 1 year to 30 years.

What Are the Conditions for Reimbursement?

Atriance should only be reimbursed as an addition to front-line multiagent chemotherapy. Atriance should be prescribed by clinicians with expertise and experience in treating T-ALL.

Why Did CADTH Make This Recommendation?

- Evidence from a phase III clinical trial showed that treatment with Atriance, compared with chemotherapy alone, delays disease recurrence and allows patients to live longer.
- Atriance meets patients' needs because it improves the length of time patients are disease-free, has manageable side effects, and may reduce the need for cranial radiation and transplantation.
- Based on CADTH's assessment of the health economic evidence, Atriance may represent a good value to the health care system for pediatric, adolescent, and young adult (aged 1 year to 30 years) patients with intermediate- and high-risk T-ALL, at the public listed prices for Atriance and comparators.
- Based on public list prices, Atriance is estimated to cost the public drug plans approximately $6.6 million over the next 3 years.

Additional Information

What Is T-ALL?

Acute lymphoblastic leukemia (ALL) is a type of cancer in which the bone marrow makes too many lymphocytes (a type of white blood cell). T-ALL is a type of ALL that affects T lymphocytes. T-ALL is an aggressive cancer that progresses quickly. Symptoms of T-ALL are nonspecific and may include fatigue, pain, bleeding, enlarged lymph nodes, and other symptoms. T-ALL is more common in children than in adults. T-ALL can be classified

Summary

as high risk, intermediate, or low risk, which refers to the chance of a good response using standard treatment.

Unmet Needs in T-ALL

Patients with T-ALL have a poor prognosis, and cancer may come back or worsen for some patients who are at high risk for disease recurrence. Patients with relapsed T-ALL require total body irradiation (to kill any cancer cells that are left in the body and help make room in the bone marrow for new blood stem cells to grow) and stem cell transplant (healthy stem cells are transplanted into patient's bone marrow or blood), which exposes patients to a significant risk of morbidity (e.g., infection, secondary cancerous tumours caused by treatment with radiation or chemotherapy, reduced quality of life). Therefore, successful front-line treatment in patients with newly diagnosed T-ALL is important to minimize the recurrence rate, prolong life, and improve health-related quality of life.

How Much Does Atriance Cost?

Treatment with Atriance is expected to cost approximately $34,772 per patient per course in addition to front-line multiagent chemotherapy.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that nelarabine be reimbursed for the treatment of pediatric, adolescent, and young adult patients with intermediate- or high-risk T-cell acute lymphoblastic leukemia (T-ALL) in addition to front-line multiagent chemotherapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase III, randomized, open-label study (COG AALL0434; N = 659) demonstrated that treatment with nelarabine added to augmented Berlin-Frankfurt-Munster (aBFM) multiagent chemotherapy resulted in added clinical benefit in patients aged 1 year to 30 years with newly diagnosed intermediate- and high-risk T-ALL. The COG AALL0434 study showed that, compared with aBFM chemotherapy alone, the addition of nelarabine to aBFM chemotherapy led to a statistically significant and clinically meaningful improvement in disease-free survival (DFS). The 5-year DFS rate was 88.2% (standard error [SE] ± 2.4%) in patients who received nelarabine in addition to aBFM chemotherapy compared with 82.1% (SE ± 2.7%) in patients who received aBFM chemotherapy alone (P = 0.029). The COG AALL0434 study showed that the 5-year cumulative incidence rate of central nervous system (CNS) relapse was lower in patients who received nelarabine in addition to aBFM chemotherapy compared with those who received aBFM chemotherapy alone (1.3% [SE ± 0.6%] versus 6.9% [SE ± 1.4%], respectively), which was considered clinically meaningful by clinical experts. Although notable adverse events, such as central neurotoxicity, peripheral motor and sensory neuropathies, were not insignificant, the safety profile of nelarabine was considered to be expected and manageable in patients with newly diagnosed T-ALL.

Patients identified a need for new treatments targeting the T-ALL population that improve quality of life and have long-term efficacy with fewer and less severe adverse effects. pERC concluded that nelarabine meets some of the needs identified by patients because it improves disease progression and has manageable side effects. Although health-related quality of life (HRQoL) was not evaluated or reported in the COG AALL0434 study, the reduction in CNS relapse rates with treatment with nelarabine may reduce the need for cranial radiation and transplantation; therefore, it has a potential to improve patients' long-term quality of life.

Using publicly listed prices for both nelarabine and all other drug costs, the incremental cost-effectiveness ratio (ICER) for nelarabine plus standard of care (SOC) (defined as aBFM chemotherapy) was $26,362 per quality-adjusted life-year (QALY) gained compared with SOC alone. At this ICER, nelarabine is cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for pediatric, adolescent, and young adult (aged 1 year to 30 years) patients with intermediate- and high-risk T-ALL.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with nelarabine should be initiated as an addition to front-line multiagent chemotherapy in patients aged 1 year to 30 years with intermediate- and high-risk T-ALL.	Evidence from the COG AALL0434 study demonstrated that treatment with nelarabine in addition to aBFM chemotherapy resulted in added clinical benefit for patients aged 1 year to 30 years with newly diagnosed intermediate- and high-risk T-ALL.	—
2. Patients are not eligible for treatment with nelarabine if they meet any of the following criteria: 2.1. prior to induction phase, have any prior cytotoxic chemotherapy, except for steroids and/or IT cytarabine 2.2. have pre-existing peripheral neurotoxicity of CTCAE grade 2 or greater 2.3. pregnant or lactating females.	Patients who had any prior cytotoxic chemotherapy before induction phase, except for steroids and/or IT cytarabine; patients who had pre-existing peripheral neurotoxicity of CTCAE grade 2 or greater; and pregnant or lactating females were excluded from the COG AALL0434 study.	—
Discontinuation		
3. Treatment with nelarabine must be discontinued upon the occurrence of any of the following: 3.1. disease progression 3.2. neurologic toxicity of CTCAE grade 4 related to nelarabine 3.3. signs or symptoms suggestive of an ascending polyneuropathy, including a Guillain-Barré–like syndrome, even if these symptoms resolve.	These discontinuation criteria align with the study protocol and/or clinical experts and clinician group input.	—
Prescribing		
4. Nelarabine should be prescribed by clinicians with expertise and experience in treating T-ALL.	This helps ensure that nelarabine is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—

aBFM = augmented Berlin-Frankfurt-Munster; COG = Children's Oncology Group; CTCAE = Common Terminology Criteria for Adverse Events; ICER = incremental cost-effectiveness ratio; IT = intrathecal; QALY = quality-adjusted life-year; SOC = standard of care; T-ALL = T-cell acute lymphoblastic leukemia.

Discussion Points

- pERC acknowledged the input from clinical experts that the addition of nelarabine to front-line multiagent chemotherapy is currently considered the SOC for pediatric, adolescent, and young

adult patients with newly diagnosed T-ALL. Nelarabine is also reimbursed in some formularies (e.g., through a hospital budget in Ontario, Nova Scotia, and New Brunswick, or by the Children and Women's Health budget for pediatric patients in Newfoundland and Labrador).

- pERC discussed that T-ALL in pediatric, adolescent, and young adult patients is a rare disease with poor prognosis for which there is significant unmet need. pERC acknowledged the input from clinical experts on the importance of ensuring successful front-line treatment of patients with newly diagnosed T-ALL to minimize CNS relapse rates. pERC discussed that, in the COG AALL0434 study, upfront treatment with nelarabine in addition to aBFM chemotherapy resulted in a reduction in CNS relapse rates, which may translate to helping reduce the need for cranial radiation in the real-world setting (which was emphasized by clinical experts and clinician group as a significant burden for patients and their families). pERC also discussed the input from clinical experts that reduction in the CNS relapse rates has a potential to reduce the need for transplantation that exposes patients to a significant risk of morbidity (e.g., infection, second malignant neoplasm, neurocognitive impairment).
- pERC noted that only patients with intermediate- and high-risk T-ALL were included in the COG AALL0434 study. Although there was no clinical evidence reviewed for patients with low-risk T-ALL, pERC acknowledged the input from clinical experts that some centres across Canada are prescribing nelarabine to all patients with newly diagnosed T-ALL, including patients at low risk.
- pERC noted that in the COG AALL0434 study, patients with a prior seizure disorder requiring anticonvulsant therapy were not eligible to receive nelarabine. Although these patients were excluded from the COG AALL00434 study and the results may not be generalizable to these patients, pERC acknowledged the input from the clinical experts that this exclusion criterion is not typical of clinical practice.
- pERC also noted that median DFS rate was not reported and HRQoL was not evaluated. pERC also acknowledged the uncertainty in long-term overall survival (OS).
- pERC discussed the cost-effectiveness of nelarabine plus SOC (defined as aBFM chemotherapy) compared with SOC alone. pERC noted that due to the uncertainty regarding long-term extrapolations of OS, there is uncertainty in the magnitude of the clinical benefit associated with nelarabine plus SOC and thus the ICER. A price reduction may be required to ensure the cost-effectiveness of nelarabine at a willingness-to-pay threshold of $50,000 per QALY gained.

Background

Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children, representing one-quarter of cancer diagnoses in children younger than 15 years. Between 2015 and 2018, the incidence of ALL in Canada was between 1.3 and 1.4 cases per 100,000 persons of all ages. Worldwide, the estimated annual incidence is 1 to 5 cases per 100,000 population based on results of a systematic review searched up to 2019. The latest reported mortality rate from 2017 showed that 144 Canadians died from ALL. The mortality rate from ALL is lowest in individuals diagnosed at an age younger than 15 years, and 90% of children younger than 15 years are cured when treated appropriately. Mortality increases with age, especially

in patients older than 40 years. Patients with ALL had signs or symptoms of bone marrow failure (e.g., fatigue, dyspnea, bleeding, bruising or infection), organ infiltration (e.g., enlarged lymph nodes, mediastinum, liver, and spleen), and systemic complaints (e.g., fevers, fatigue, joint or bone pain, and night sweats). In extramedullary ALL, symptoms of CNS and testicular disease can also be present.

ALL is classified according to the immunophenotype (i.e., if malignant cells originate from B cells or T cells). In children, approximately 80% to 85% of ALL cases are B-cell phenotypes (i.e., B-cell ALL or B-lineage ALL), and 15% to 20% of ALL cases are T-cell phenotypes (i.e., T-cell ALL or T-lineage ALL); whereas in adults, nearly 75% of ALL cases are B-cell ALL, and approximately 25% of ALL cases are T-ALL. T-ALL is more difficult to treat (with lower OS and event-free survival rates) than B-cell ALL in pediatric and young adult patients. Although T-ALL is a high-risk subtype of ALL, studies have demonstrated improved outcomes when treated with appropriate intensive therapy. For example, the event-free survival for patients with T-ALL has increased from 15% to 20% almost 40 years ago to 75% or higher today. Diagnosis of ALL and identification of phenotypes are confirmed by bone marrow histology, immunophenotyping, cytogenetics, and occasionally molecular biology specialized techniques. The adverse prognostic factors for T-ALL may include presence of minimal residual disease (MRD) after induction and/or consolidation therapies, early T-precursor T-ALL, and specific chromosomal abnormalities detected by bone marrow cytogenetics or polymerase chain reaction (PCR) evaluation.

Nelarabine is a water-soluble prodrug of the cytotoxic deoxyguanosine analogue antimetabolite, 9-beta-D-arabinofuranosylguanine (ara-G). With administration of nelarabine, the converted ara-GTP accumulates in leukemic cells. This leads to inhibition of DNA synthesis, resulting in cell death. The approved Health Canada indication for nelarabine is for the treatment of patients with T-ALL and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens. The recommended dosage of nelarabine is 1,500 mg/m^2/day IV over 2 hours on days 1, 3, and 5, repeated every 21 days in adults, and 650 mg/m^2/day IV over 1 hour on days 1 to 5, repeated every 21 days, in children aged 15 years and younger. Nelarabine is available as 5 mg/mL solution for IV infusion. In the sponsor's submission to CADTH, nelarabine (for injection) is indicated for an addition to front-line multiagent therapy of pediatric, adolescent, and young adult patients (aged 1 year to 30 years at diagnosis) with intermediate- or high-risk T-ALL.

Nelarabine received approvals from the US FDA in October 2005 for treatment of patients with T-ALL and T-LBL whose disease has not responded to or has relapsed after treatment with at least 2 chemotherapy regimens. In March 2023, it also included the upfront treatment of patients with T-ALL.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, 2 × 2 pseudofactorial, randomized, open-label trial in patients with intermediate- and high-risk T-ALL

- patients' perspectives gathered by 1 patient group, the Leukemia & Lymphoma Society of Canada (LLSC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with T-ALL
- input from 3 clinician groups, including the Department of Hematology, Oncology, and Bone Marrow Transplant, British Columbia Children's Hospital; the Pediatric Hematology/Oncology program at the Janeway Children's Health and Rehabilitation Centre in St. John's, Newfoundland and Labrador; and Ontario Health-Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full original patient inputs received by CADTH have been included in the stakeholder section at the end of this report.

The patient input for this review was collected by the LLSC. The LLSC is a national charitable organization dedicated to blood cancer with a focus of improving the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. The information for this review was obtained from 2 online surveys conducted in June 2019 (20 respondents; 80% were aged 1 year to 14 years, 20% were aged 15 years and older) and March 2023 (46 respondents; 38% were aged from 1 year to 14 years, 12% were aged from 15 to 19 years, 50% were aged 20 years and older) among patients with ALL aged 30 years or younger at diagnosis or their caregivers. A total of 23 respondents from both surveys were diagnosed with T-ALL. The LLCS input included 9 patient respondents with experience using nelarabine for the treatment of ALL. Of 3 respondents in Survey 2019, 1 patient accessed the drug through compassionate use and 2 patients through a clinical trial.

Patient and caregiver respondents' experiences with the disease are jointly summarized in 4 themes, based on the results of both Survey 2019 and Survey 2023. First, the survey respondents indicated that pediatric ALL is a difficult experience that impacts all aspects of life, including physical and mental health, financial well-being, social life and relationships, and so on. Caregivers of children with ALL indicated that the pathway to diagnosis was not a straight line and, in many cases, took multiple visits to a physician before the diagnosis could be made. Second, survey respondents indicated that the ALL symptoms impeded patients' ability to participate in regular life activities. According to the results of both surveys, the most critical physical effects that individuals with ALL experienced before diagnosis were fatigue, pain, and nausea or vomiting. Caregivers highlighted that children with ALL were particularly distressed by the

instability, disruptions, and changes to their home and family life that they experienced due to ALL. Third, the survey respondents indicated that ALL had a significant effect on patients' and their families' quality of life in several areas, which included more than just physical effects. According to the survey results, the most significant detrimental impacts on patients and their caregivers included daily routines (88%), physical functioning (85%), mental functioning (85%), work life (82%), social life (79%), lifestyle (74%), and family life (71%). The survey respondents noted the associated feelings the respondents had experienced throughout diagnosis and treatment of ALL included sadness (76%); fear (74%); nervousness, anxiety, depression (74%); frustration (72%); stress or worry (72%); overwhelm or feeling out of control (70%); loneliness or isolation (70%); posttraumatic stress (68%); and helplessness or hopelessness (66%).The final theme survey respondents highlighted is that there are considerable consequences for patients with ALL and their families regarding financial stability and the ability to maintain employment and financial status due to ALL diagnosis and treatment schedules. According to the survey results, 38% of patient respondents and 29% of caregiver respondents noted they had missed career development or advancement opportunities due to their experience with ALL. Approximately 79% of survey respondents reported they experienced a decrease in income as a direct result of diagnosis and treatment of ALL.

The survey results showed the types of ALL treatment patients received since their diagnosis included chemotherapy (94%), high-dose chemotherapy (67%), maintenance therapy (51%), radiation (43%), stem cell or bone marrow transplant (22%), immunotherapy (12%), surgery (6%), and other (received steroids as part of their treatment, 4%). The survey respondents reflected that ALL treatment created difficulties and challenges in all areas of life for patients, caregivers, and their families. For example, a caregiver respondent shared their treatment experience in Survey 2019: "Chemo was horrible and continues to get worse. My daughter was high risk and is now one-third way through maintenance. Continues to be sick, not go to school, starting to endure multiple fractures because her bones are so weak. It is horrible and there has to be a better way." For some ALL treatments, the need to travel to and from treatment if required was a significant barrier for patients and caregivers. The Survey 2023 data showed that, among the patients who received ALL treatment other than nelarabine, 37% had to travel long distances by car in their province or state. Approximately 78% of those who did not have nelarabine treatment had to pay out of pocket for drugs not covered by provincial providers, and only 20% of nelarabine users incurred the same expense. The survey respondents who received treatment other than nelarabine expressed that the quality of life for patients, caregivers, and their families was severely impacted by the ALL treatment and noted the adverse effects, including nausea and vomiting, weakness or loss of strength, low white blood cell count, low platelet count, and pain.

The surveys found the patients with ALL and their caregivers hope to return to the comfort of normalcy and quality of life before onset of disease. The survey results showed that the most important factors considered when making decisions about currently available treatments were physician recommendation (82% of the respondents), side effects (79%), quality of life (79%), and possible impact on disease (76%). The survey participants commented that, for any new treatments, they are concerned about the long-term effects and safety that the treatments may have on a child and their future health. It is hoped the new treatment may have fewer and less severe adverse effects, and improved treatment logistics (e.g., fewer trips to

the hospital, steroids removed from treatment, and shortened maintenance period), and provision of the associated mental health supports.

Nine survey respondents with T-ALL reported experience with treatment with nelarabine. Approximately 56% of the respondents reported nelarabine eliminated the disease for some time before relapsing, 11% reported nelarabine kept the disease stable, and 33% of respondents indicated the results were unknown at that time. The 5 respondents rated the following adverse effects as having no impact on the patient during the treatment with nelarabine: seizures, fever, headaches, shortness of breath or persistent cough, infections, increased transaminase, increased bilirubin, and decreased albumin. Approximately 40% of patient respondents rated the following adverse effects as having either a large or extremely large impact on the patient during nelarabine treatment: low platelet count, low red blood count, anemia, low white blood count, and extreme sleepiness. Although the distance from the treatment facility to home and the need to travel for treatment with nelarabine affected quality of life of patients and their caregivers, survey respondents were willing to endure this because the treatment works. Two patient respondents felt that treatment with nelarabine was "neutral" compared with other treatments, 2 patients felt that nelarabine treatment was "less challenging" than their other treatments, and 1 patient felt that nelarabine was "more challenging" than other treatments. According to the patient input received, the responses of patients who received nelarabine reflect that nelarabine gave back life, hope, and normalcy to patients and their families after treatment. The LLSC advocated for nelarabine to be approved for the indication under review and suggested that it will help alleviate the gaps in current T-ALL therapy among patients including pediatrics, and therefore relatively improve quality of life and psychosocial aspects for patients and their families.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of T-ALL.

The clinical experts consulted by CADTH for this review indicated that the main goals of T-ALL treatment are to reduce relapse rates, prolong life, improve HRQoL, and reduce treatment-related morbidity, including treatment with cranial radiation. The clinical experts highlighted the importance of ensuring successful first-line treatment in patients with newly diagnosed T-ALL to minimize the relapse rate because patients with relapsed T-ALL require a total body irradiation–based stem cell transplant. The clinical experts noted that less than half of patients with relapsed or refractory T-ALL are cured by transplantation, and transplantation exposes patients to a significant risk of early morbidity (graft-versus-host disease, infection, and other treatment-related mortality) and late morbidity (second primary malignancy, end organ toxicity, neurocognitive impairment, and reduced quality of life).

The clinical experts consulted for this review emphasized that nelarabine is currently being considered by many centres in Canada and the US as the SOC for patients with newly diagnosed T-ALL, and it is not recommended to prescribe nelarabine only to patients with relapsed T-ALL. The clinical experts mentioned that nelarabine may be used as a single agent (largely in adults in the salvage setting) or in combination with multiagent chemotherapy in patients with newly diagnosed T-ALL. The clinical experts consulted indicated that nelarabine should be used as part of front-line therapy for all patients with newly diagnosed T-ALL, regardless of CNS status at diagnosis. They also noted that while currently available evidence shows nelarabine improves outcomes in patients with intermediate- and high-risk T-ALL, it is biologically reasonable that nelarabine would also be effective in treating patients with low-risk T-ALL. The clinical experts mentioned that patients with T-ALL are identified by the characteristic immunophenotypic proliferation of T lymphoblasts in a bone marrow sample, and misdiagnosis of patients with T-ALL is uncommon. According to clinical experts, it is not possible to identify patients who are likely to demonstrate a response to treatment.

The outcomes used for assessing a patient's response to treatment of newly diagnosed T-ALL include overall and event-free survival, relapse rate, HRQoL, and treatment with cranial radiation. The clinical experts consulted indicated that children with newly diagnosed T-ALL are assessed at defined time points throughout the treatment plan. Responses are assessed through bone marrow biopsy, lumbar puncture, and frequent blood counts. The bone marrow aspirate or biopsy is repeated if the patient's condition does not improve as expected or if the patient's condition deteriorates unexpectedly. The clinical experts pointed out that the most meaningful early outcome in children with T-ALL is the achievement of MRD-negative remission during treatment; failure to achieve such remission or disease relapse during treatment are considered indications for escalation of therapy. The clinical experts indicated that the use of nelarabine in patients with newly diagnosed T-ALL is expected to increase the proportion of patients who achieve MRD-negative complete response and to decrease the proportion of patients who relapse (both extramedullary and marrow) during treatment. According to the clinical experts, the potential reasons for discontinuing treatment with nelarabine include refractory disease, disease progression, significant toxicity (i.e., neurotoxicity grade 4). The clinical experts indicated that nelarabine should be prescribed under the direction of an oncologist in a hospital or outpatient setting.

The clinical experts noted that, in Ontario, nelarabine added to front-line multiagent therapy is offered to patients with intermediate- or high-risk T-ALL patients; however, some centres across Canada are successfully prescribing nelarabine to all patients with T-ALL, including those at low risk. The clinical experts cautioned the impact of a reimbursement recommendation consistent with the reimbursement request and expressed the need for consideration to expand the reimbursement population to include low-risk T-ALL.

Clinician Group Input

The clinician group input was obtained from 3 clinician groups, including the Department of Hematology, Oncology, and Bone Marrow Transplant, British Columbia Children's Hospital (represented by 16 clinicians); the Pediatric Hematology/Oncology program at the Janeway Children's Health and Rehabilitation Centre in St. John's, Newfoundland and Labrador; and OH-CCO Hematology Cancer Drug Advisory Committee. OH-CCO's Cancer Drug Advisory Committees provide guidance on drug-related issues in support of CCO's

mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program. The information in this review was gathered through a review of literature and discussion with T-ALL experts or counselling with the clinicians via video conferencing and email.

The clinician groups indicated that not all patients with T-ALL respond to the currently available treatments. Clinicians from the British Columbia Children's Hospital noted that T-ALL represents 10% to 15% of newly diagnosed pediatric acute leukemia, and with SOC therapy, cure can be achieved in the majority of children. However, nearly 20% of the pediatric patients with T-ALL experience relapsed or refractory disease, and salvage of relapsed or refractory disease is dismal, with a less than 25% overall survival. Currently, the standard treatment for pediatric patients with newly diagnosed T-ALL includes multiagent chemotherapy (pediatric-inspired intensive chemotherapy regimens) delivered over approximately 3 years, with additional craniospinal radiation therapy for patients with CNS disease. Clinicians from the British Columbia Children's Hospital highlighted that the unmet need would be to improve event-free survival and reduce the risk of relapse, including CNS relapse. Patients with CNS disease must include cranial radiation therapy as part of their treatment either at diagnosis or during relapse, and the additional cranial radiation is associated with a significant risk of chronic neurocognitive sequelae, especially in young children.

According to the clinician groups, nelarabine can be used as per the Children's Oncology Group (COG) trial COG AALL0434 that investigated the efficacy and safety of adding nelarabine to SOC. According to the clinician groups, patients between the ages of 1 year and 30 years with newly diagnosed T-ALL are most likely to respond to nelarabine and are the most in need of an intervention. The clinician groups noted that the diagnosis of this disease includes the confirmation of an abnormal clonal population of immature T lymphoblasts in bone marrow, circulating blood, cerebral spinal fluid, or tissue, which is not dependent on any specific cytogenetic or molecular testing. All clinician groups agreed that the use of nelarabine for newly diagnosed T-ALL among patients aged between 1 year and 30 years would be incorporated into a multiagent chemotherapy backbone similar to that used in the COG AALL0434 study. The clinicians from the British Columbia Children's Hospital noted that nelarabine is not a symptomatic management therapy, and that it should be used in the context of newly diagnosed pediatric T-ALL and not as a second-line therapy for those who have responded poorly to first-line therapy. The clinician groups mentioned that patients with non–T-ALL forms of hematological malignancies are least suitable for nelarabine treatment.

The clinicians from the British Columbia Children's Hospital indicated that pediatric patients undergoing standard treatment for T-ALL undergo regular follow-up disease assessments after induction and consolidation cycles of chemotherapy, which may include bone marrow aspirate and biopsy, MRD testing, spinal fluid assessment, peripheral blood assessment, and, as required, imaging and physical examination of extramedullary sites of disease. The clinician groups identified that the following factors should be used to evaluate response to treatment in patients with T-ALL: the achievement of remission (i.e., no detectable leukemic disease) and the persistence of disease remission over time without relapse. The clinician groups pointed out several reasons that may lead to the discontinuation of nelarabine, including disease progression or significant intolerance to the treatment (e.g., severe or progressive neurotoxicity including but not limited to myelopathy, sensory changes, central neurocognitive decompensation, Guillan-Barré–like syndrome, and paralysis). The clinician from the Janeway Children's Health and Rehabilitation Centre indicated that

nelarabine has been considered SOC at their site for several years, without specifying the indication of the drug. Two clinician groups highlighted that nelarabine should be administered by leukemia specialists at outpatient settings or under the direction and supervision of a pediatric hematologist-oncologist who is familiar with the treatment of pediatric T-ALL and is equipped to anticipate and support the potential adverse effects of nelarabine.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
Standard COG protocol (multidrug regimen) for T-ALL.	Comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
Can re-treatment with nelarabine be considered in a later line of therapy in cases of relapsed disease?	The clinical experts indicated that nelarabine could be considered as part of reinduction or reconsolidation treatment before alloHSCT in patients with relapsed T-ALL. pERC noted that this is out of scope for this review.
Considerations for prescribing of therapy	
The recommended dose is a total of 6 courses of 650 mg/m^2/day, administered intravenously over 1 hour on 5 consecutive days with a total of 6 cycles administered as part of a multidrug regimen.	Comment from the drug programs to inform pERC deliberations.
Generalizability	
Should patients with low-risk T-ALL (excluded from trial) be eligible for front-line treatment with nelarabine in combination with multiagent chemotherapy?	There is no clinical evidence available regarding the use of nelarabine in patients with low-risk T-ALL. The clinical experts highlighted that patients with low-risk T-ALL were excluded from nelarabine randomization in COG AALL0434 and therefore did not receive the drug due to concerns about neurotoxicity; however, neurotoxicity rates reported in the study were minimal. The clinical experts indicated that nelarabine is currently considered the standard of care for patients with newly diagnosed T-ALL, and some centres across Canada are prescribing nelarabine to all patients with T-ALL, including those at low risk. Thus, the clinical experts emphasized that nelarabine can be used in patients with low-risk T-ALL. The clinical experts cautioned the impact of a reimbursement recommendation consistent with the reimbursement request and expressed the need for consideration to expand the reimbursement population to include low-risk T-ALL. pERC acknowledged the input from the clinical experts and also noted that there is no clinical evidence available for patients with low-risk T-ALL.

Drug program implementation questions	Response
Should adult patients (> 30 years) be considered for treatment with nelarabine?	The clinical experts indicated that nelarabine can be prescribed to patients with T-ALL older than 30 years, given that the older the patient, the higher the risk of the disease. The clinical experts noted that most patients with newly diagnosed T-ALL are young, and the number of newly diagnosed T-ALL in patients older than 30 years is low. pERC acknowledged the input from the clinical experts and also noted that there is no clinical evidence available regarding the use of nelarabine in patients older than 30 years.
Most pediatric centres are currently using nelarabine (hospital budget) in front-line T-ALL protocols.	Comment from the drug programs to inform pERC deliberations.
Care provision issues	
Nelarabine is prepared as an undiluted solution in either an IV bag or syringe for delivery via infusion pump. Each dose usually requires multiple vials per patient. Vial sharing would not be likely due to the small patient population. However, with published extended stability data, more than 1 daily dose of nelarabine may be compounded at once, which could reduce vial wastage.	Comment from the drug programs to inform pERC deliberations.
Requires monitoring for potential neurologic side effects.	Comment from the drug programs to inform pERC deliberations.

alloHSCT = allogeneic hematopoietic stem cell transplant; COG = Children's Oncology Group; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; T-ALL = T-cell acute lymphoblastic leukemia.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of Studies

The COG AALL0434 trial was a phase III, 2 × 2 pseudofactorial, randomized, open-label trial. The primary objective of the trial was to assess the relative efficacy and safety of nelarabine for addition to front-line aBFM multiagent therapy of pediatric, adolescent, and young adult patients (aged 1 year to 30 years at diagnosis) with intermediate- or high-risk T-ALL. This study was conducted by the COG under an investigational new drug application held by the National Cancer Institute. A total of 1,596 patients with T-ALL were enrolled from January 2007 to July 2014 across 215 sites in the US, Australia, Canada, New Zealand, and Switzerland.

The COG AALL0434 trial used a sequential design to evaluate nelarabine during the initial safety and efficacy phases. First, an initial safety phase was conducted to assess the tolerability of adding nelarabine to the aBFM backbone containing either Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase (C-MTX) or high-dose methotrexate (HD-MTX) with leucovorin rescue. During the initial safety

phase, only patients with high-risk T-ALL (N = 94) were randomized to receive the aBFM backbone with randomization to 1 of 4 treatment arms after completion of induction therapy as follows:

- Arm A: aBFM with C-MTX without nelarabine (n = 24)
- Arm B: aBFM with C-MTX with nelarabine (n = 24)
- Arm C: aBFM with HD-MTX with leucovorin rescue and without nelarabine (n = 23)
- Arm D: aBFM with HD-MTX with leucovorin rescue and nelarabine (n = 23).

The initial safety phase end points included sensory neuropathy, motor neuropathy, central neurotoxicity (encephalopathy, seizure, stroke, extrapyramidal tract symptoms, acute mental status changes, and somnolence), and mortality. After the completion of the initial safety analysis for nelarabine in patients with high-risk T-ALL, the study was approved to move into the efficacy phase of the COG AALL0434 trial. During the efficacy phase of COG AALL0434, patients with intermediate- and high-risk T-ALL (N = 659) were randomized to 1 of 4 treatment arms after completion of induction therapy as follows:

- Arm A: aBFM with C-MTX without nelarabine (n = 151)
- Arm B: aBFM with C-MTX with nelarabine (n = 147)
- Arm C: aBFM with HD-MTX with leucovorin rescue and without nelarabine (n = 185)
- Arm D: aBFM with HD-MTX with leucovorin rescue and nelarabine (n = 176).

The primary efficacy end point in the efficacy phase of COG AALL0434 was DFS; the secondary efficacy end points were OS and CNS relapse. The safety outcomes of the efficacy phase of COG AALL0434 included central neurotoxicity, peripheral motor neuropathy, and peripheral sensory neuropathy. Patients with low-risk T-ALL did not participate in the nelarabine randomization in either the safety or efficacy phases of the COG AALL0434 trial. Treatment duration with nelarabine was 2 years from the start of the interim maintenance phase for females, and 3 years for males.

Baseline characteristics were well balanced between the treatment groups. Half of the patients (49.9%) were younger than 10 years, 33.4% of patients were aged between 10 and 15 years, and 16.7% were aged 16 years or older. A total of 74.8% of patients were male, and 25.2% were female. A total of 70.6% of patients had CNS1, 20.8% had CNS2, and 8.6% had CNS3 at diagnosis. Bone marrow M1 at the end of induction was determined in 95.3% of patients, and M2 marrow was determined in 4.7% of patients. A total of 83.3% of patients did not have allogeneic hematopoietic stem cell transplant (alloHSCT), whereas 3.2% underwent alloHSCT.

Efficacy Results

Table 3 presents a summary of key results from the efficacy phase of the COG AALL0434 trial.

Overall Survival

The 5-year OS rate was 90.3% (SE ± 2.2%) in patients who were randomly assigned to receive nelarabine compared with 87.9% (SE ± 2.3%) in those who did not receive nelarabine (P = 0.168). In patients with intermediate-risk T-ALL who were randomly assigned to receive nelarabine or not receive nelarabine, the 5-year OS rates were 91.3% (SE ± 2.7%) and 92.4% (SE ± 2.4%), respectively (P = 0.617). In patients with

high-risk T-ALL who were randomly assigned to receive nelarabine or not receive nelarabine, the 5-year OS rates were 88.5% (SE ± 3.8%) and 79.2% (SE ± 4.6%), respectively (P = 0.051).

Disease-Free Survival

A total of 97 (14.7%) patients experienced any DFS events, including 39 patients who received nelarabine compared with 58 patients who did not receive nelarabine. Of the 97 patients, 70 (10.6%) had relapse, 12 (1.8%) had secondary malignant neoplasm, and 15 (2.3%) died during remission. The 5-year DFS rate was 88.2% (SE ± 2.4%) in patients who were randomly assigned to receive nelarabine compared with 82.1% (SE ± 2.7%) in patients who did not receive nelarabine (P = 0.029). The analysis by treatment arms showed that 5-year DFS rates were 91.4% (SE ± 3.1%) in patients who received C-MTX regimen with nelarabine (n = 147), 87.2% (SE ± 3.5%) in those who received C-MTX regimen without nelarabine (n = 151), 85.5% (SE ± 3.6%) in those who received HD-MTX regimen with nelarabine (n = 176), and 78.1% (SE ± 4.0%) in those who received HD-MTX regimen without nelarabine (n = 185) (P = 0.01).

In patients with intermediate-risk T-ALL who were randomly assigned to receive nelarabine or not receive nelarabine, the 5-year DFS rates were 90.8% (SE ± 2.8%) and 86.3% (SE ± 3.1%), respectively (P = 0.077). In patients with high-risk T-ALL who were randomly assigned to receive nelarabine or not receive nelarabine, the 5-year DFS rates were 83.5% (SE ± 4.4%) and 74.1% (SE ± 4.8%), respectively (P = 0.106). The 5-year DFS rates in patients with CNS3 disease who were assigned to receive HD-MTX with nelarabine or HD-MTX without nelarabine were 93.1% (SE ± 6.5%) and 67.9% (SE ± 12.2%), respectively (P = 0.014).

CNS Relapse

The 5-year cumulative incidence rate of CNS relapse (isolated and combined) was 1.3% (SE ± 0.6%) in patients who received nelarabine compared with 6.9% (SE ± 1.4%) in patients who did not receive nelarabine (P = 0.0001). Among patients with CNS3 disease, CNS relapse occurred in 1 (3.4%) patient who was assigned to receive HD-MTX regimen with nelarabine compared with 6 (21.4%) patients who were assigned to receive HD-MTX regimen without nelarabine.

Health-Related Quality of Life

HRQoL was not measured or reported in the COG AALL0434 trial.

Harms Results

In the efficacy phase safety analysis of the COG AALL0434 trial, the rates of nontargeted toxicity of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher were 41.2% in patients who received nelarabine compared with 46.1% in patients who did not receive nelarabine. The targeted neurotoxicity and overall toxicity rates were slightly higher among patients who received nelarabine compared with those who did not. Of 323 patients who received nelarabine, 11 (3.4%) experienced central neurotoxicity of CTCAE grade 3 or higher, 26 (8.0%) experienced peripheral motor neuropathy of CTCAE grade 3 or 4, and 29 (9.0%) experienced peripheral sensory neuropathy of CTCAE grade 3 or 4. Of 336 patients who did not receive nelarabine, 7 (2.1%) patients experienced central neurotoxicity of CTCAE grade 3 or higher, 19 (5.7%) experienced peripheral motor neuropathy of CTCAE grade 3 or 4, and 27 (8.0%) experienced peripheral sensory neuropathy of CTCAE grade 3 or 4.

Table 3: Summary of Key Results of the Efficacy Phase of COG AALL0434, ITT

Detail	Nelarabine N = 323	No nelarabine N = 336	Arm A C-MTX without nelarabine N = 151	Arm B C-MTX with nelarabine N = 147	Arm C HD-MTX without nelarabine N = 185	Arm D HD-MTX with nelarabine N = 176
Efficacy						
Overall survival						
5-year OS rate[a] (SE), %	90.3 ± 2.2	87.9 ± 2.3	NR	NR	NR	NR
P value[b]	0.168		NR			
Disease-free survival						
5-year DFS rate[c] (SE), %	88.2 ± 2.4	82.1 ± 2.7	87.2 ± 3.5	91.4 ± 3.1	78.1 ± 4.0	85.5 ± 3.6
P value	0.029		0.01			
Relapse, n (%)	27 (8.4)	43 (12.8)	11 (7.3)	10 (6.8)	32 (20.2)	17 (9.7)
CNS relapse	1 (0.3)	14 (4.2)	1 (0.7)	0 (0)	13 (7.0)	1 (0.6)
Bone marrow relapse	12 (3.7)	14 (4.2)	5 (3.3)	2 (1.4)	9 (4.9)	10 (5.7)
CNS and bone marrow relapse	2 (0.6)	8 (2.4)	1 (0.7)	1 (0.7)	7 (3.8)	1 (0.6)
CNS relapse						
5-year CNS relapse rate[d] (SE), %	1.3 ± 0.63	6.9 ± 1.4	NR	NR	NR	NR
P value[b]	0.0001		NR	NR	NR	NR
Second malignancy,[e] n (%)	4 (1.2)	7 (2.1)	3 (2.0)	5 (3.4)	2 (1.1)	2 (1.1)
Remission death, n (%)	5 (1.5)	10 (3.0)	4 (2.6)	0 (0)	6 (3.2)	5 (2.8)
Harms[f]						
Central neurotoxicity,[g] n (%)	11 (3.4)	7 (2.1)	NR	NR	NR	NR
Peripheral motor neuropathy,[h] n (%)	26 (8.0)	19 (5.7)	NR	NR	NR	NR
Peripheral sensory neuropathy,[h] n (%)	29 (9.0)	27 (8.0)	NR	NR	NR	NR

C-MTX = Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase; CNS = central nervous system; DFS = disease-free survival; HD-MTX = high-dose methotrexate with leucovorin rescue; ITT = intention to treat; NR = not reported; OS = overall survival; SE = standard error.

[a]Percentage (SE) of patients alive from the Kaplan-Meier estimates.

[b]P value has not been adjusted for multiple testing.

[c]Percentage (SE) of disease-free events from the Kaplan-Meier estimates.

[d]Cumulative incidence rate.

[e]Included Ewing sarcoma, acute myeloid leukemia, mucoepidermoid carcinoma, malignant melanoma, Langerhans cell histiocytosis, myelodysplastic syndrome, malignant histiocytosis histiocytic medullary reticulosis, lymphoproliferative disease, and malignant lymphoma.

[f]Safety analyses of the efficacy phase of COG AALL0434.

[g]CTCAE grade 3, 4, or 5.

[h]CTCAE grade 3 or 4.

Source: Dunsmore et al. (2020).

Critical Appraisal

The COG AALL0434 trial was an open-label, phase III, 2 × 2 pseudofactorial, randomized trial comparing nelarabine and an aBFM backbone in pediatric, adolescent, and young adult patients with newly diagnosed intermediate- and high-risk T-ALL. Detailed information on randomization and treatment allocation is not available. The open-label design of the trial was most likely due to the nature of treatment administration, which made blinding infeasible. Knowledge of the assigned treatment could have led to bias in the reporting of subjective adverse events; however, the extent and direction of bias due to treatment knowledge is uncertain. There is no information available regarding the treatment discontinuation rates and the proportion of protocol deviations. The study utilized 2 × 2 pseudofactorial randomization to compare 2 separate treatments, including C-MTX versus HD-MTX, and nelarabine versus no nelarabine. Since there was no interaction between the 2 randomized treatments, the trial was powered to examine the main effects of the 2 randomized comparisons separately. However, it is unclear whether the study was powered to provide a statistically rigorous evaluation of the 2-stage procedure, including methotrexate and nelarabine randomizations. In addition, no adjustments for multiple comparisons were made in the trial. The primary (DFS) and secondary outcomes (OS and CNS relapse) were considered appropriate for the disease setting and were conducted using the ITT population, which maintains randomization and minimizes the risk of bias by comparing groups with similar prognostic factors. The median DFS was not reported in either treatment group, thus the longer-term efficacy of nelarabine for DFS is unknown for upfront therapy of newly diagnosed T-ALL. The clinical experts consulted noted that the results of the DFS analysis were clinically meaningful based on the absolute event rate reduction within the selected study population; however, there is no known or accepted minimally important difference for DFS rates in this population. There is no information available regarding the dropout rates and how missing values in the trial were handled in the trial. Although HRQoL has been identified as an important outcome by both clinicians and patients, it has not been evaluated or reported in the COG AALL0434 trial.

In general, the clinical experts consulted for this review confirmed that the population of the COG AALL0434 trial was similar to patients seen in clinics, and there is no concern generalizing the findings from the trial to the Canadian clinical setting. A total of 373 patients were not eligible for postinduction therapy, including 353 patients who discontinued protocol therapy at the end of induction therapy mainly due to refusal of further protocol therapy by patient, parent, or guardian (61.7%), which further reduces the generalizability of the trial results. The clinical experts indicated that the failure to continue protocol therapy after induction may be related to the fact that some patients may already have neurotoxicity events and are reluctant to take more medication that could cause more neurotoxicity events. Another reason mentioned by the clinical experts is that all patients in the trial received prophylactic cranial radiation, which may cause more harm to the patient, especially in children younger than 5 years of age.

The COG AALL0434 trial included patients aged 1 year to 30 years, and most patients were younger than 15 years. The clinical experts consulted indicated that this is reflective of Canadian clinical practice. The clinical experts further noted that nelarabine can be prescribed to patients with T-ALL older than 30 years because the older the patient, the higher the risk of the disease. The clinical experts consulted emphasized that nelarabine is currently considered the SOC in addition to aBFM backbone therapy for patients with

newly diagnosed T-ALL and is reimbursed in some formularies (i.e., nelarabine may be funded through a hospital budget). The clinical experts consulted mentioned that patients with low-risk T-ALL did not receive nelarabine in the trial due to concerns about neurotoxicity; however, neurotoxicity rates reported in the study were minimal. They also highlighted that some centres across Canada are successfully prescribing nelarabine to all patients with T-ALL, including those at low risk. All patients in the COG AALL0434 trial received prophylactic cranial radiation therapy at a dose of 12 Gy, and patients with CNS3 disease received cranial radiation therapy at a dose of 18 Gy. However, the clinical experts consulted for this review stated that attempts should be made to prevent radiation exposure in young children and adolescents because of late cognitive effects that can be associated with radiation therapy.

Long-Term Extension Studies

No long-term extension studies were identified for this review.

Indirect Comparisons

No studies with indirect evidence were identified for this review.

Studies Addressing Gaps in the Pivotal and RCT Evidence

No studies addressing gaps in the pivotal and randomized controlled trial evidence were identified for this review.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Microsimulation model
Target population	Children, adolescents, and young adults (aged 1 year to 30.99 years) with newly diagnosed, intermediate- or high-risk T-ALL
Treatment	Nelarabine in addition to SOC
Dose regimen	Nelarabine as an add-on therapy to aBFM for which dosing is expected to be aligned with the COG AALL0434 trial (i.e., 650 mg/m^2 on days 1 to 5 and 43 to 47 of the consolidation phase, days 29 to 33 of the delayed intensification phase, and days 29 to 33 for the first 3 cycles of the maintenance phase)
Submitted price	$545.42[a] per 50 mL vial
Treatment cost	Course cost as an add-on to aBFM[b]: • Consolidation: $17,386 • Delayed intensification: $8,693 • Maintenance: $8,693
Comparator	SOC, defined as aBFM multidrug chemotherapy protocol
Perspective	Canadian publicly funded health care payer

Component	Description
Outcomes	QALYs, LYs
Time horizon	Lifetime (90 years)
Key data source	COG AALL0434
Key limitations	• Long-term efficacy of nelarabine + SOC for the first-line treatment of children, adolescents, and young adults with newly diagnosed intermediate- or high-risk T-ALL is unknown. Although data in the COG AALL0434 trial suggest nelarabine is associated with a modest but clinically meaningful benefit in 5-year OS rates compared with SOC, clinical expert feedback received by CADTH noted the duration of treatment and follow-up period were likely too short to observe the beneficial effect of nelarabine on OS. Similarly, nelarabine was associated with a 5-year DFS benefit in the trial (between-group difference of 6.1%); however, because median DFS was not reported the long-term DFS benefit remains unknown. • The reimbursement-requested population excludes low-risk patients and adult (30 years and older) patients. Clinical expert feedback received by CADTH noted that nelarabine, as an add-on to first-line therapy, is already prescribed to low-risk pediatric patients in some centres across Canada and that a patient's age should not exclude a patient from being eligible for nelarabine. The cost-effectiveness of nelarabine + SOC in low-risk T-ALL and in adult patients aged 30 years or older is unknown. • Drug costs may be underestimated due to incorrect drug pricing and BSA assumptions because the dosing of nelarabine is based on the patient's BSA, which was assumed to be aligned with that of a 9-year-old, over the entire treatment duration (i.e., ranging from 2 to 3 years, based on sex). • Clinical efficacy data comparing nelarabine + aBFM SOC to Hyper-CVAD, in newly diagnosed adult patients with intermediate- or high-risk T-ALL, is not available; therefore, the comparative cost-effectiveness of nelarabine + aBFM SOC to Hyper-CVAD is unknown.
CADTH reanalysis results	• CADTH revised the unit price for several drugs, including nelarabine, to address 1 of the identified key limitations as part of its reanalysis. • In the CADTH reanalysis, the ICER for nelarabine + SOC was $26,362 per QALY gained compared with SOC alone. Therefore, no price reduction is required for nelarabine + SOC to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained at current list prices. • CADTH was unable to address the limitation pertaining to uncertainties in the long-term efficacy of nelarabine + SOC. Should a smaller OS difference be observed for nelarabine + SOC vs. SOC as a first-line treatment for children, adolescents, and young adults with newly diagnosed intermediate- or high-risk T-ALL, then a smaller QALY benefit would be expected, leading to a higher ICER for nelarabine + SOC vs. SOC alone. In the absence of available data, the magnitude of long-term OS efficacy remains unknown.

aBFM = augmented Berlin-Frankfurt-Munster; BSA = body surface area; COG = Children's Oncology Group; DFS = disease-free survival; Hyper-CVAD = cyclophosphamide-vincristine-doxorubicin-dexamethasone-methotrexate-leucovorin-cytarabine; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; QALY = quality-adjusted life-year; SOC = standard of care; T-ALL = T-cell acute lymphoblastic leukemia.

[a]Model uses the price of $582.49 based on applying an inflation adjustment to derive 2022 values.

[b]Costs calculated using a $579.54 per 50 mL vial of nelarabine wholesale price from IQVIA Delta PA (accessed April 2023).

Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: the market share for nelarabine was likely underestimated, drug costs may be underestimated due to utilization of incorrect drug unit costs, and patient budget impact analysis dependent assumptions. The CADTH base case updated unit drug costs. In the CADTH base case, the estimated incremental budget impact of reimbursement for nelarabine as an add-on therapy to the first-line treatment of patients (aged 1 year to 30 years) for intermediate- or high-risk T-ALL is $1,888,641 in year 1, $2,340,039 in year 2, and $2,358,411 year 3. Therefore, the 3-year budget impact is $6,587,091.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: August 9, 2023

Regrets: 3 expert committee members did not attend.

Conflicts of interest: None

ISSN: 2563-6596

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.