

## National PBM Drug Monograph Nelarabine (Arranon®)

January 2007

**VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel**

*The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

### **Executive Summary**

#### **Mode of Action:**

Nelarabine is a pro-drug of the deoxyguanosine analogue 9-β-D-arabinofuranosylguanine (ara-G). Nelarabine is demethylated by adenosine deaminase to ara-G, which is subsequently converted to the active 5'-triphosphate, ara-GTP. The leukemic blasts gather the active form allowing for the incorporation into the deoxyribonucleic acid (DNA) which results in inhibition of DNA synthesis and eventual cell death.

#### **FDA-Approved Indication:**

Nelarabine was approved by the FDA in October of 2005 for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma who have not responded to or have relapsed following treatment with at least two chemotherapeutic regimens.

#### **Dosage and Route:**

The recommended dose of nelarabine in **adults** is 1,500 mg/m<sup>2</sup> intravenously over 2 hours on days 1, 3 and 5 repeated every 21 days. The recommended dose of nelarabine in **pediatric patients** is 650 mg/m<sup>2</sup> intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. The duration of therapy with nelarabine has not been established. During clinical trials, treatment was continued until there was evidence of disease progression, intolerable toxicity, or the patient became a candidate for bone marrow transplantation.

#### **Efficacy:**

The FDA fast-track approval of nelarabine was based on complete and partial response data observed in clinical trials. There are currently no trials addressing survival as an endpoint. The only published trial in adults is a pilot protocol involving the use of nelarabine in combination with fludarabine. The patients received a 1,200 mg/m<sup>2</sup> dose of nelarabine on days 1, 3, and 5 in combination with 30 mg/m<sup>2</sup> fludarabine on days 3 and 5 four hours prior to the nelarabine every 21-28 days. The mean duration of therapy was not provided. Seven of the thirteen patients achieved a complete or partial response. There are two trials in adults that are currently not published. Both trials are looking at nelarabine for monotherapy in refractory T- and B-cell malignancies. Nelarabine had shown a 31.6% and a 54.5% total response rate in each trial prior to publication.

#### **Safety:**

Nelarabine contains a “black-box” warning regarding severe neurological events that occurred in clinical trials, including severe somnolence, CNS effects including convulsions, and peripheral neuropathies ranging from numbness and paresthesias to motor weakness and paralysis. Over 60% of the patients who received nelarabine had some nervous system event (e.g. headache, somnolence, and peripheral neuropathy). Providers should closely monitor for signs and symptoms of neurological events. Other common adverse effects include fatigue, hematologic disorders (e.g. anemia, thrombocytopenia and neutropenia), gastrointestinal (GI) disorders (e.g. diarrhea, vomiting, and nausea), pulmonary disorders (e.g. cough and dyspnea) and fever. A small percentage of patients (4%) have complained of experiencing blurred vision while receiving nelarabine. Fatal opportunistic infections have also been reported periodically in patients receiving nelarabine.

**Recommendations:**

- Limited for use in hematology-oncology.
- Patients must have a history of at least 2 treatment failures and a diagnosis of either T-cell acute lymphoblastic leukemia or T-cell lymphoblastic lymphoma.

**Introduction**

Lymphomas and leukemias involving T cells (e.g. T-cell acute lymphoblastic leukemia [T-ALL], T-cell lymphoblastic lymphoma [T-LBL]) are highly uncommon, but extremely aggressive malignancies.<sup>1</sup> In recent years, treatment of these cancers has vastly improved. Unfortunately, like many cancers, failure to respond to the standard treatment options or disease relapse is often associated with a poor prognosis.<sup>2</sup> Because of this, research into second- and third-line treatment options is essential. Agents such as nucleoside analogs have been recognized to have efficacy in various hematologic malignancies.<sup>3</sup> Nelarabine is a 6-methoxy derivative of the active nucleoside metabolite ara-G.<sup>4</sup> Although discovered during the 1960s, ara-G was never medically used due to its lack of solubility.<sup>5</sup> With the discovery of the soluble nelarabine, ara-G's known toxicity to T-cells could be utilized. Nelarabine's data demonstrate complete responses in T-ALL and T-LBL patients who have failed two or more prior inductions.<sup>6-10</sup> The activity of nelarabine led to its FDA fast-track approval status in October of 2005. Nelarabine recently gained Orphan Medical Product Status in Europe and is currently undergoing the complete drug filing process there.

**Pharmacology/Pharmacokinetics<sup>11</sup>**

The mechanism of action for nelarabine involves the transformation of the pro-drug into the deoxyguanosine analogue 9-β-*D*-arabinofuranosylguanine (ara-G). Adenosine deaminase (ADA) demethylates nelarabine to ara-G, followed by the mono-phosphorylation and the final modification to the active 5'-triphosphate, ara-GTP. The leukemic blasts gather the active drug allowing for the incorporation into the deoxyribonucleic acid (DNA). This results in inhibition of DNA synthesis and eventual cell death. Other mechanisms of cytotoxicity and systemic toxicity may contribute to the cytotoxic effects of nelarabine.

The majority of the clinical trials with nelarabine were completed in Caucasians. The clearance and volume of distribution appear to be higher in Caucasians than in African-Americans by about 10%. It appears the opposite is true regarding the active metabolite, ara-G. Safety and effectiveness do not appear to be compromised despite these differences. There is no discrepancy among gender pharmacokinetics for nelarabine. Use in patients age 65 years and older appears to be associated with increased rates of neurological adverse events.

Nelarabine and ara-G had minimal effect on the liver cytochrome P450 enzyme system.

**Table 1-Pharmacokinetics<sup>11</sup>**

	<b>nelarabine</b>	<b>Ara-G</b>
<b>V<sub>ss</sub>(adults)</b>	197 +/- 216 L/m <sup>2</sup>	50 +/- 24 L/m <sup>2</sup>
<b>Metabolism</b>	O-demethylation to ara-G	Hydrolyzed to guanine
<b>Protein Binding</b>	< 25%	< 25%
<b>Half-Life</b>	30 minutes	3 hours
<b>Elimination</b>	5-10% renally	20-30% renally

There is no specific data in hemodialyzed patients or patients with renal impairment. The mean clearance of ara-G in patients with mild to moderate renal impairment was about 15% -40% lower. No differences in safety or efficacy were observed. Patients with severe renal impairment (CrCl <30 mL/min) should be monitored closely for toxicities while receiving nelarabine.

The role of hepatic impairment on the pharmacokinetics of nelarabine has not been studied. Patients with severe hepatic impairment (bilirubin >3.0mg/dL) should be closely monitored for toxicities while receiving nelarabine.

**FDA Approved Indication(s) and Off-Label Uses<sup>11</sup>**

Nelarabine is FDA-approved for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma who have not responded to or have relapsed following treatment with at least two chemotherapeutic regimens. Increased survival and other clinical benefits have not been established. The approvals are based on response data during clinical trials. There is currently no off-label use information available.

**Current VA National Formulary Alternatives**

Nelarabine is the first third-line FDA-approved medication to treat this limited patient population. Current alternatives are limited to clinical trial data involving combination chemotherapy regimens.

**Dosage and Administration<sup>11-12</sup>**

The recommended dose of nelarabine in **adults** is 1,500 mg/m<sup>2</sup> intravenously over 2 hours on days 1, 3 and 5 repeated every 21 days.

The recommended dose of nelarabine in **pediatric patients** is 650 mg/m<sup>2</sup> intravenously over 1 hour daily for 5 consecutive days repeated every 21 days.

The duration of therapy with nelarabine has not been established. During clinical trials, treatment was continued until evidence of disease progression, intolerable toxicity, or the patient became a candidate for bone marrow transplantation.

The appropriate UNDILUTED dose of nelarabine is transferred into polyvinylchloride infusion bags or a glass container prior to administration. The intravenous product should be inspected for particulates and discoloration prior to administration. To prevent hyperuricemia of tumor lysis syndrome, appropriate hydration, urine alkalinization, and preventative allopurinol must be given prior to administration.

Nelarabine has not been studied in patients with renal or hepatic impairment. Dosing adjustments for patients with a creatinine clearance  $\geq 50$  mL/min are not recommended. There are inadequate data supporting dosing modifications with  $CL_{cr} < 50$  mL/min.

Nelarabine should be discontinued for neurological toxicities of NCI common toxicity criteria grade 2 or greater. Dosages may be delayed in patients who experience additional toxicities including hematological toxicities.

**Overdosage:** There is no antidote in the event of an overdose to nelarabine. It is expected that overdosage would cause severe neurotoxicity, involving paralysis, myelosuppression, and potential death. Doses up to 2,900 mg/m<sup>2</sup> of nelarabine have been given in clinical trials. Patients receiving 2,200 mg/m<sup>2</sup> of nelarabine in one trial developed grade 3 ascending sensory neuropathy.

**Efficacy Measures**

In the published trials involving nelarabine, no survival data were collected for evaluation. The FDA fast-track status is based on complete and partial response numbers observed. Phase III studies looking at improvement in survival and quality of life need to be completed in order to fully assess nelarabine's role in cancer treatment.

1. Published Trials<sup>7-8</sup>**A. Pediatrics**

- Patients with relapsed or refractory disease initially diagnosed as T-cell malignancy at 21 years of age or younger were evaluated in 4 separate treatment arms to determine the "early response" rate after treatment with nelarabine. The patients were assigned to different arms depending upon site of relapse and the number of prior relapses to the T-cell acute lymphoblastic leukemia (T-ALL) or T-cell non-Hodgkin's lymphoma (T-NHL).

- The initial dose of 1.2 g/m<sup>2</sup> IV daily for 5 consecutive days every 3 weeks was reduced after considerable neurotoxicity to 650 mg/m<sup>2</sup>/day and 400 mg/m<sup>2</sup>/day among the treatment arms.
- 106 patients out of 121 patients enrolled were eligible for evaluation of response rates.
- Arm 1 = ≥ 25% bone marrow blasts in 1<sup>st</sup> relapse, Arm 2 = ≥ 25% bone marrow blasts in ≥ 2<sup>nd</sup> relapse, Arm 3 = positive CSF, Arm 4 = extramedullary (non-CNS) relapse.
- Complete + Partial response at the adjusted dose levels were: 55% in arm 1; 27% in arm 2; 33% in arm 3; and 14% in arm 4.
- 18% of the patients experienced grade 3 or greater neurological adverse events.
- The authors concluded that nelarabine is an active agent for recurrent T-cell leukemia.

## B. Adults

- A pilot protocol was completed to test the efficacy of nelarabine in combination with fludarabine in 13 adult patients with T-cell acute lymphoblastic leukemia, chronic myelogenous leukemia, and mycosis fungoides.
- Patients received a 1.2 g/m<sup>2</sup> nelarabine IV infusion over 1 hour on days 1, 3 and 5. They also received 30 mg/m<sup>2</sup> IV fludarabine on days 3 and 5 four hours prior to the nelarabine infusion. The treatment course was completed every 21 to 28 days.
- 7 of the 13 patients (54%) were characterized as having a complete or partial response.
- Grade 3 or 4 myelosuppression was seen in 31% of the patients.
- The authors concluded that combination therapy of nelarabine with fludarabine is an effective and well-tolerated regimen against leukemias with further investigation needed.

*Further data regarding the published clinical trials can be found at the end of the document.*

## 2. Unpublished Trials<sup>9-11, 13</sup>

### A. Adults

#### 1. Cancer and Leukemia Group B (CALGB) trial<sup>9</sup>

- The efficacy of nelarabine was examined in 38 patients with T-cell malignancies who had relapsed or were refractory to at least 2 prior induction regimens.
- A dose of 1,500 mg/m<sup>2</sup> IV infusion was given on days 1, 3, and 5 during a 21-day cycle. The length of treatment ranged from 10 to 136 days with a mean of 56 days.
- The overall response rate was 31.6% (CR 26.3% + PR 5.3%) with a median disease-free survival rate of 9.8 months for the 10 patients who achieved a complete response.
- The one-year overall survival rate was 32% and the one-year disease-free survival rate was 40%.

#### 2. National Cancer Institute Phase II study<sup>10</sup>

- Nelarabine treatment was studied in 16 patients who had failed 1-3 previous treatment regimens for T-cell and B-cell lymphoma.
- Nelarabine 1,500 mg/m<sup>2</sup> IV infusion was given on days 1, 3, and 5 every 28 days for 6 cycles. Treatment was discontinued for toxicity and disease progression.
- At the time of reporting, only 11 patients were eligible for evaluation. Two patients (18.2%) had achieved a complete response and 4 (36.4%) a partial response. Three patients had just recently begun treatment and 2 patients died unrelated to nelarabine treatment.
- The full trial with results has not yet been published.

### Serious Adverse Events<sup>11, 12</sup>

Nelarabine labeling contains a “black-box” warning pertaining to neurotoxicity seen in clinical trials. During Phase I and Phase II trials, nervous system events were reported in 64% of the patients. Common signs and symptoms associated with neurotoxicity include somnolence, convulsions, ataxia, confusion, and paresthesias. Patients may be at greater risk for neurologic events if they have received intrathecal chemotherapy or craniospinal irradiation. Providers are strongly recommended to monitor patients for neurological events. The following tables convey the data observed in clinical trials regarding neurological events.

**Table 2. Neurological adverse reactions occurring in pediatrics<sup>12</sup>**

Nelarabine Neurologic Adverse Reactions ( $\geq 2\%$ ) in <b>Children</b>					
Neurologic adverse reaction	Percentage of patients; n = 84				
	Grade 1	Grade 2	Grade 3	Grade 4+ <sup>a</sup>	All grades
Ataxia	1%	0	1%	0	2%
Headache	8%	2%	4%	2%	17%
Hypesthesia	1%	1%	4%	0	6%
Motor dysfunction	1%	1%	1%	0	4%
Nervous system disorder	1%	2%	0	0	4%
Paresthesia	0	2%	1%	0	4%
Peripheral neurologic disorders, any event	1%	4%	7%	0	12%
Peripheral motor neuropathy	1%	0	2%	0	4%
Peripheral neuropathy	0	4%	2%	0	6%
Peripheral sensory neuropathy	0	0	6%	0	6%
Somnolence	1%	4%	1%	1%	7%
Seizures	0	0	0	6%	6%
Convulsions	0	0	0	3%	4%
Generalized tonic-clonic convulsions	0	0	0	1%	1%
Status epilepticus	0	0	0	1%	1%
Tremor	1%	2%	0	0	4%

<sup>a</sup>Grade 4+ = Grade 4 and Grade 5

There were 3 deaths in pediatric patients, with only one from status epilepticus likely to be related to the treatment of nelarabine. Other neurological events reported include third and sixth nerve paralysis, dysarthria, encephalopathy, hydrocephalus, hyporeflexia, lethargy, mental impairment, paralysis, and sensory loss.

**Table 3. Neurological adverse reactions in adults<sup>12</sup>**

Nelarabine Neurologic Adverse Reactions ( $\geq 2\%$ ) in <b>Adult Patients</b>					
Neurologic adverse reaction	Percentage of patients; n = 103				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Amnesia	2%	1%	0	0	3%
Ataxia	1%	6%	2%	0	9%
Balance disorder	1%	1%	0	0	2%
Depressed level of consciousness	4%	1%	0	1%	6%
Dizziness	14%	8%	0	0	21%
Dysgeusia	2%	1%	0	0	3%
Headache	11%	3%	1%	0	15%

Hypesthesia	5%	10%	2%	0	17%
Paresthesia	11%	4%	0	0	15%
Peripheral neurologic disorders, any event	8%	12%	2%	0	21%
Neuropathy	0	4%	0	0	4%
Peripheral motor neuropathy	3%	3%	1%	0	7%
Peripheral neuropathy	2%	2%	1%	0	5%
Peripheral sensory neuropathy	7%	6%	0	0	13%
Sensory loss	0	2%	0	0	2%
Somnolence	20%	3%	0	0	23%
Tremor	2%	3%	0	0	5%

There were five deaths in adult patients being treated with nelarabine. An adult patient died following cerebral hemorrhage/coma/leukoencephalopathy that was thought to have been caused by treatment with nelarabine. The others were not considered to be related to treatment.

The majority of other neurological events could be classified as grade 1 or 2. Grade 3 or 4 events included aphasia, convulsion, hemiparesis, loss of consciousness, cerebral hemorrhage, coma, intracranial hemorrhage, leukoencephalopathy, and metabolic encephalopathy. Additional reports have linked demyelination and ascending peripheral neuropathies similar to Guillain-Barré syndrome with nelarabine treatment. This will cause patients to experience symptoms similar to multiple sclerosis. Full recovery from this has not always occurred following cessation of nelarabine therapy.

### **Common Adverse Events**<sup>11, 12</sup>

The most frequent adverse effects seen in adults receiving nelarabine were fatigue, hematologic disorders (e.g., anemia, thrombocytopenia and neutropenia), gastrointestinal (GI) disorders (e.g., diarrhea, vomiting, and nausea), nervous system disorders (e.g., dizziness and somnolence), pulmonary disorders (e.g., cough and dyspnea) and fever. In pediatrics, the most common adverse events included hematologic disorders, headache, hypokalemia, decreased albumin, vomiting, hyperbilirubinemia and increased transaminase levels. Table 4 represents the adverse effects seen in the adult population.

**Table 4. Common adverse reactions in adults**<sup>12</sup>

Nelarabine Adverse Reactions in Adult Patients (≥ 5%)			
Adverse reaction	Percentage of patients; n=103		
	Toxicity grade		
	Grade 3	Grade 4+ <sup>a</sup>	All grades
<b>Cardiovascular</b>			
Hypotension	1%	1%	8%
Sinus tachycardia	1%	0%	8%
<b>CNS</b>			
Abnormal gait	0%	0%	6%
Asthenia	0%	1%	17%
Confusional state	2%	0%	8%
Depression	1%	0%	6%
Fatigue	10%	2%	50%
Insomnia	0%	0%	7%
Rigors	0%	0%	8%
<b>Dermatologic</b>			

Petechiae	2%	0%	12%
<b>GI</b>			
Abdominal distension	0%	0%	6%
Abdominal pain	1%	0%	9%
Anorexia	0%	0%	9%
Constipation	1%	0%	21%
Diarrhea	1%	0%	22%
Nausea	0%	0%	41%
Stomatitis	1%	0%	8%
Vomiting	1%	0%	22%
<b>Hematologic/ Lymphatic</b>			
Anemia	20%	14%	99%
Febrile neutropenia	9%	1%	12%
Neutropenia	14%	49%	81%
Thrombocytopenia	37%	22%	86%
<b>Hepatic</b>			
AST increased	1%	1%	6%
<b>Metabolic/Nutritional</b>			
Dehydration	3%	1%	7%
Edema	0%	0%	11%
Edema, peripheral	0%	0%	15%
Hyperglycemia	1%	0%	6%
<b>Musculoskeletal</b>			
Arthralgia	1%	0%	9%
Back pain	0%	0%	8%
Muscular weakness	5%	0%	8%
Myalgia	1%	0%	13%
Pain in extremity	1%	0%	7%
<b>Respiratory</b>			
Cough	0%	0%	25%
Dyspnea	4%	2%	20%
Dyspnea, exertional	0%	0%	7%
Epistaxis	0%	0%	8%
Pleural effusion	5%	1%	10%
Pneumonia	4%	1%	8%
Sinusitis	1%	0%	7%
Wheezing	0%	0%	5%
<b>Miscellaneous</b>			
Chest pain	0%	0%	5%
Chest pain, Non-cardiac	0%	1%	5%
Infection	2%	1%	9%
Pain	3%	0%	11%
Pyrexia	5%	0%	23%

<sup>a</sup>Grade 4+ = Grade 4 and Grade 5.

### **Other Adverse Effects**<sup>11</sup>

Four percent of adult patients have reported having blurred vision. Reports of fatal opportunistic infections have periodically been reported in patients receiving nelarabine as well. Progressive multifocal leukoencephalopathy was confirmed in one adult patient during treatment of nelarabine.

### **Pregnancy/Lactation**<sup>11</sup>

Nelarabine is a pregnancy Category D. Patients should use effective contraceptive measures to avoid pregnancy. Mothers who are breast-feeding should also refrain from nursing infants while receiving nelarabine.

**Precautions/Contraindications**<sup>11</sup>

Nelarabine should be avoided in patients with a history of hypersensitivity to nelarabine or any of its components.

**General:** Patients receiving nelarabine should be managed for tumor lysis syndrome according to the standard medical practice for controlling hyperuricemia. Intravenous hydration and prophylaxis administration of allopurinol should be considered. Patients should be made aware that seizures have been known to occur in patients receiving nelarabine. Any health care professional administering the medication should be made aware of this precaution. If this should occur, the prescribing health-care professional should be immediately informed. Immunocompromised patients receiving nelarabine should avoid receiving live vaccines.

**Hematologic:** Neutropenia, anemia, thrombocytopenia, and leukopenia have also been associated with nelarabine therapy. Patient blood counts including platelets should be regularly monitored.

**Patient Information:** Patients may experience somnolence with nelarabine therapy and should avoid operating hazardous machinery, including motorized vehicles. A physician should be contacted if patients experience any peripheral neuropathy including numbness or tingling, difficulty with fine motor coordination, and abnormal weakness.

**Look-alike/Sound-alike Error Risk Potential**

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for nelarabine 250 mg (5 mg/mL) inj.	LA/SA for Arranon® 250 mg (5mg/mL) inj.
Nesacaine® 1.0 G inj.	Aranelle™ 0.035 mg tablet
clofarabine 1.0 mg IV solution	<b>Aromasin® 25 mg tablet</b>
fludarabine phosphate 50 mg inj.	Adagen® 250 unit inj.
<b>cytarabine 1.0 G inj.</b>	amrinone 5 mg inj.
cladribine 1.0 mg IV solution	Aramine® 10 mg inj.
<b>mepiridine hydrochloride 0.9 G IV solution</b>	Aranesp® albumin free 25 mcg inj.
NephrAmine® 3.0 mEq IV solution	Aredia® 30 mg powder for inj.
nevirapine 200 mg tablet	<b>Alkeran® 2 mg tablet</b>
<b>Navelbine® 10 mg inj.</b>	<b>Lupron® 5 mg solution</b>
gemcitabine 1.0 G powder for inj.	<b>Norcuron® 10 mg powder for inj.</b>
nicardipine hydrochloride 2.5 mg inj.	Albalon® 1.0 G ophthalmic solution

**The drugs highlighted in bold are considered “high risk” medications. Any confusion involving these medications would be severe.**

**Drug Interactions**<sup>11</sup>

There is *in vitro* evidence that pentostatin is a strong adenosine deaminase inhibitor, which may result in a decreased conversion of nelarabine to its active substrate. This may result in diminished efficacy and a potential change in the adverse event profile for either medication. The combination of nelarabine and adenosine deaminase inhibitors should be avoided. Patients should notify their provider before taking any over-the-counter medications, herbals or receive flu shots and other live vaccines while on nelarabine. It is recommended that patients receive live vaccines at least 2 weeks prior to initiating chemotherapy or during remission at least 3 months after chemotherapy has been completed.<sup>14</sup>

**Pharmacoeconomic Analysis**

No data are available regarding the pharmacoeconomics of nelarabine.

**Acquisition Costs**

FSS Price = Nelarabine 50mL vial (5mg/5mL) injection (6 vials) = \$2,537.88

BIG4 Price = Nelarabine 50mL vial (5mg/5mL) injection (6 vials) = \$1,791.99



<b>Cost Nelarabine per Unit</b>	<b>Average Dose (1.72 m<sup>2</sup> * 1500mg/m<sup>2</sup>)</b>	<b>Cost per Day per Patient</b>	<b>Cost per Cycle per Adult Patient*</b>	<b>Cost per Adult Patient</b>
\$1,791.99 (250mg X 6 vials)	2580 mg	\$3,285.37	\$9,856.11	\$19,712.22 (2 cycles) \$59,136.66 (6 cycles) \$78,848.88 (8 cycles) \$118,273.32 (1 year)

\*One cycle = Nelarabine on days 1, 3, and 5 of a 28 day cycle

### **Conclusions**

Nelarabine has minimal data regarding its use as monotherapy for treatment of T-cell malignancies in adult patients. Because of this, it is difficult to extrapolate the data to the majority of the VA's patient population. Nelarabine has shown activity against T-cell leukemias and lymphomas in small treatment groups including both pediatrics and adults as a third-line agent for relapsed or refractory disease. Additional research is being done regarding its use in combination therapy with fludarabine in patients who have failed first-line treatment regimens. There are limited options available for the patients with T-cell malignancies who fail numerous chemotherapies. Nervous system events were reported in over half the patients who received nelarabine, including some serious neurologic events, leading to a black box warning. Providers must carefully monitor their patients for any signs of neurotoxicity. Nelarabine is a rather expensive medication, although cost analyses have not yet been completed.

### **Recommendation for Use:**

- Limited for use in hematology-oncology.
- Patients must have a history of at least 2 treatment failures and a diagnosis of either T-cell acute lymphoblastic leukemia or T-cell lymphoblastic lymphoma.

**Published Clinical Trials:**

<b>Citation</b>	Berg SL, Blaney SM, Devidas M, Lampkin TA, Murgo A, Bernstein M, et al. Phase II study of nelarabine in children and young adults with refractory t-cell malignancies: a report from the children's oncology group. <i>J Clin Oncol</i> 2005 May;23(15): 3376-82.																				
<b>Study Goals</b>	Define the response rate of nelarabine in children and young adults with refractory or recurrent T-cell disease.																				
<b>Methods</b>	<p><b>Study Design</b> The patients were stratified into 4 treatment arms. Arm 1: ≥25% bone marrow blasts in 1<sup>st</sup> relapse, Arm 2: ≥25% bone marrow blasts in ≥2<sup>nd</sup> relapse, Arm 3: positive CSF, Arm 4: extramedullary (non-CNS) relapse. Complete response (CR) was considered no evidence of disease while partial response (PR) was measured as &gt;50% decrease in all measurable lesions with no disease progression.</p> <p><b>Data Analysis</b> The study was declared "active" if 8 of the 33 recruited patients for strata 1 and 2 achieved an early PR or CR. Study arms 3 and 4 had no statistical goals for the enrolled patients. Fisher's exact test was used to compare response rates across strata.</p>																				
<b>Criteria</b>	<p><b>Inclusion criteria</b> Life expectancy ≥ 8 weeks, patients younger than 21 years old at time of initial diagnosis with refractory T-cell malignancies, performance status &gt;50%, ALT &lt; 5X the upper limit of normal, normal creatinine for age, no concurrent anticancer therapy, and recovery from toxicity of prior therapy.</p> <p><b>Exclusion criteria</b> Patients with isolated CNS relapse, pregnant and lactating women, and patients with history of ≥grade 2 neurotoxicity.</p>																				
<b>Results</b>	<table border="1"> <thead> <tr> <th></th> <th>Total # Patients</th> <th>Response Rate % (CR+PR #)</th> <th>95%CI</th> </tr> </thead> <tbody> <tr> <td>1. Arm 1</td> <td>33</td> <td>55% (16+2)</td> <td>38 to 72</td> </tr> <tr> <td>2. Arm 2</td> <td>30</td> <td>27% (7+1)</td> <td>11 to 43</td> </tr> <tr> <td>3. Arm 3</td> <td>21</td> <td>33% (5+2)</td> <td>13 to 53</td> </tr> <tr> <td>4. Arm 4</td> <td>22</td> <td>14% (0+3)</td> <td>0 to 28</td> </tr> </tbody> </table>		Total # Patients	Response Rate % (CR+PR #)	95%CI	1. Arm 1	33	55% (16+2)	38 to 72	2. Arm 2	30	27% (7+1)	11 to 43	3. Arm 3	21	33% (5+2)	13 to 53	4. Arm 4	22	14% (0+3)	0 to 28
	Total # Patients	Response Rate % (CR+PR #)	95%CI																		
1. Arm 1	33	55% (16+2)	38 to 72																		
2. Arm 2	30	27% (7+1)	11 to 43																		
3. Arm 3	21	33% (5+2)	13 to 53																		
4. Arm 4	22	14% (0+3)	0 to 28																		
<b>Conclusions</b>	The authors concluded that nelarabine is an active single agent for the treatment of recurrent T-cell leukemia. Further trials need to be completed to determine survival data associated with the use of nelarabine.																				
<b>Critique</b>	<p><b>Strengths:</b> The patients in this trial were divided into 4 treatment arms based on clinical features that could conceivably affect treatment outcomes.</p> <p><b>Limitations:</b> There is no survival data evaluated and the patient population assessed makes it difficult to extrapolate across a VA setting. There was no statistical information available prior to the trial for treatment arms 3 and 4. The clinicians have also not yet agreed upon an appropriate dosing regimen for nelarabine.</p>																				

<b>Citation</b>	Gandhi V, Plunkett W, Weller S, Du M, Ayres M, Rodriguez C, et al. Evaluation of the combination of nelarabine and fludarabine in leukemias: clinical response, pharmacokinetics, and pharmacodynamics in leukemia cells. <i>J Clin Oncol</i> 2001 April;19(8):2142-52.
<b>Study Goals</b>	To evaluate the efficacy of nelarabine combined with fludarabine in treatment of hematologic malignancies. The pharmacokinetics were also evaluated to discover a relationship between ara-G concentrations and clinical response.
<b>Methods</b>	<p><b>Study Design</b> A pilot protocol involving thirteen patients began with treatment of nelarabine (1.2G/m<sup>2</sup>) on days 1, 3 and 5. They also received fludarabine (30mg/m<sup>2</sup>) on days 3 and 5. Plasma and cellular pharmacokinetic measurements were collected during the first 5 days.</p> <p><b>Data Analysis</b> Linear regression analysis was completed for the <i>r</i> value with F-ara-ATP and ara-GTP. Comparison of the plasma pharmacology was done through a Wilcoxon signed rank two-tailed <i>t</i> test. The clinical response was evaluated using a Mann-Whitney two-tailed <i>t</i> test.</p>
<b>Criteria</b>	<b>There were no inclusion/exclusion criteria discussed in the published trial.</b>
<b>Results</b>	<b>Seven patients (54%) had an evident response. Five patients had a complete or partial response, while one patient had stable disease.</b>
<b>Conclusions</b>	The authors concluded that combination treatment with fludarabine and nelarabine was an effective and well-tolerated treatment against leukemias. They also recommended further research of nelarabine use in fludarabine-refractory illnesses.
<b>Critique</b>	<p><b>Strengths:</b> While this trial demonstrates patients having a response, there is limited information regarding patient characteristics and their definition of a response.</p> <p><b>Limitations:</b> This trial failed to discuss any inclusion or exclusion criteria with the patient's studied. They also included both patients who had previously received fludarabine and those who were refractory to prior treatment. This may affect treatment outcomes. Again it's important to reiterate that there are no patient characteristics available for this trial throughout the literature and monograph. More trials need to be completed in order to apply this to a clinical practice setting.</p>

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